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Coagulopathic Patients With Traumatic Intracranial Bleeding: Defining the Role of Recombinant Factor VIIa

Carmi Bartal, MD, John Freedman, MD, FRCPC, Kim Bowman, RN, and Michael Cusimano, MD, PhD, FRCSC, FACS

Background: The combination of coagulopathy and intracranial bleeding (ICB) is a well-recognized cause of morbidity and mortality in the neurosurgical patient because of the risk of hematoma expansion. Although recombinant factor VIIa (rFVIIa) has been shown to be useful in intracerebral hemorrhage, its use in other forms of ICB such as subdural hematomas (SDHs) has rarely been described.

Methods: The clinical and laboratory features of a prospectively followed case-series of 15 patients with traumatic ICB (mainly isolated SDHs) and coagulopathy international normalized ratio (INR) >1.3 treated with rFVIIa in our institution are presented, along with a review of the literature regarding the role of rFVIIa in neurosurgical patients with ICB.

Results: All 15 patients suffered a SDH (4 of 15 had a combined ICB) and coagulopathy (mean INR, 2.34 ± 0.83; thrombocytopenia rate, 20%), which was attributed to anticoagulants in 46.7%. The mean INR decreased to 1.5 ± 0.14 after standard therapy and 0.92 ± 0.1 after rFVIIa therapy. There was no evident progression of bleeding in any patient treated with rFVIIa. In three patients, neurosurgery was obviated by rFVIIa therapy, whereas the other 12 patients underwent neurosurgery safely and successfully. None required subsequent surgery for continuing hemorrhage, and no adverse events secondary to rFVIIa administration were observed.

Conclusions: rFVIIa is an inducer of hemostasis, which successfully controlled potentially devastating bleeding in all of 15 coagulopathic neurosurgical patients with ICB. The use of rFVIIa lowered the INR into the operable range in all patients, allowing surgery, and in some cases, obviated the need for surgery. Randomized, placebo-controlled clinical trials are needed to further assess the efficacy and cost-effectiveness of this approach in this setting.

Key Words: Factor VIIa, Subdural hematoma, Intracranial bleeding, Neurosurgery, Coagulopathy.

with an annual patient volume of approximately 1,400 cases. We prospectively followed up 15 consecutive patients admitted to our institution during a 1-year period, who had traumatic ICB, coexistent coagulopathy, and an indication for urgent neurosurgery. All patients had a brain CT scan within the first hour of admission or of clinical deterioration. Patients with chronic SDH or other chronic brain processes who had been found to have an acute bleeding as evident by CT scan were excluded.

Patients with acute traumatic brain injury were deemed to require urgent surgery when fulfilling at least one of the following criteria: (a) hematoma >1 cm in diameter; (b) midline displacement; (c) significant clinical deterioration, as evident by deterioration in the Glasgow Coma Scale (GCS) score of >2 points or occurrence of seizures or focal neurologic signs. Further, patients with a predisposition to bleeding (coagulopathy) were deemed at risk for hematoma expansion in the presence of (a) an international normalized ratio (INR) >1.3; (b) thrombocytopenia; (c) anticoagulant therapy.

rFVIIa was administered when an INR >1.3 was present even after administration of standard therapy (vitamin K and or fresh-frozen plasma [FFP]). When significant thrombocytopenia was present, platelets transfusions were given. The administered dose of rFVIIa was 40 g/kg to 90 g/kg; dosage was at the discretion of the treating physician and initially followed the recommended dose for use in hemophilia, but subsequently was generally at the lower dose of 40 μg/kg.

The following data were collected for each patient: age, gender, comorbid conditions, ICB type, use of anticoagulants per indication, GCS score at admission, INR and platelet count, INR measurements 1 hour after administration of vitamin K, FFP, and rFVIIa, clinical deterioration, time until surgery, thromboembolic and other complications, and outcome including crude and attributable mortality rates.

Data were analyzed using EpiInfo version 2004 (CDC, Atlanta, GA). Mean values are presented as average ± 1 SD. Means were compared using the paired-sample t test and nonparametric Wilcoxon test as appropriate. A p value <0.05 was considered statistically significant.

RESULTS

The clinical and laboratory characteristics of the 15 study patients are presented in Table 1. The mean age of patients was 61 years ± 11 years and 53.3% were male. All patients suffered from a SDH, either as an isolated (73.3) or combined (26.7%) injury involving ICH, epidural hematoma (EH), or subarachnoid hemorrhage. Underlying comorbidities were present in 66.7% of patients, the most common of which were heart diseases (90%).

All patients were coagulopathic at presentation with INR >1.3; the mean admission INR was 2.34 ± 0.83 (median, 2.6; range, 1.4–3.7), and 20% had thrombocytopenia. There was no evidence for disseminated intravascular coagulopathy in any patient. The distribution of INR values at admission and after standard therapy and rFVIIa administration is presented in Figure 1. Seven patients (46.7%) were receiving anticoagulants before injury, because of atrial fibrillation, either isolated or with a prosthetic valve. Anticoagulated patients had a significantly higher admission INR (3.1 ± 0.38 vs. 1.67 ± 0.4, p = 0.0012). All patients received FFP (mean, 6 ± 2 units per patients) and vitamin K was given to 10 patients (66.7%) including all 7 anticoagulated patients. After FFP and vitamin K therapy, the mean INR was 1.5 ± 0.14 (median, 1.48; range, 1.34–1.8), and INR values were slightly higher among anticoagulated patients 1.57 ± 0.18 versus 1.44 ± 0.7, p = 0.16. Thus, after standard therapy, all patients still had an inoperable INR >1.3 (Fig. 1).

rFVIIa was given at a dose of 40 μg/kg to 66.7% of patients and at a dose of 90 μg/kg to 33.3% of patients. One patient received two doses of rFVIIa. There was no difference between anticoagulated and nonanticoagulated patients in the prevalence of INR >1.3. After therapy, the mean INR was 0.92 ± 0.1 (median, 0.91; range, 0.8–1.2) and all patients were thus operable (Fig. 1). Neurosurgery was performed in 12 patients (80%), whereas in 3 others, rFVIIa therapy halted ICB progression and obviated the need for surgery. All surgical procedures were performed <24 hour after admission (mean, 6 ± 2.5 hours; range, 1.5–14). Among anticoagulated patients, the mean paired INR difference (net decrease) attributed to standard therapy was 1.53 (p < 0.0001) and that attributed to rFVIIa was 0.6 (p < 0.0001), and among nonanticoagulated patients, the mean paired difference (net decrease) was 0.23 after standard therapy (p = 0.1) and 0.56 after rFVIIa therapy (p < 0.0001). There was no difference later in the hospital course between anticoagulated and nonanticoagulated patients in the prevalence of coagulopathic disturbances.

All bleeding episodes were controlled for the next 7 days and 14 of 15 patients improved clinically (93.3%), and 1 patient remained with severe disability with no change from the predmissant state. One patient developed pulmonary edema because of volume overload during FFP administration (patient no. 5), and one patient who improved after treatment subsequently died from sepsis complications 35 days after rFVIIa administration (patient no. 14). There were no adverse events, either thromboembolic or other complications attributed to rFVIIa therapy, and no complications related to withholding anticoagulation during the course of therapy or during follow-up.

Anticoagulants with subcutaneous unfractionated heparin for prophylaxis of deep vein thrombosis was administered to all 15 patients within 1 week after surgery and anticoagulation. Furthermore, warfarin therapy was re instituted in five of seven chronically anticoagulated patients (within 2 weeks after surgery in 3 patients and within 4 weeks in the remaining 2 patients). Anticoagulants were not given again for patients 1 and 9 because of their age (>80 years), atrial fibrillation, and occurrence ICB. No difficulty in reaching a
Table 1 Clinical and Laboratory Characteristics of 15 Patients with Traumatic Intracranial Bleeding Treated with rFVIIa

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>ICB Type</th>
<th>GCS Score at Admission</th>
<th>Deterioration</th>
<th>Comorbidity</th>
<th>Anticoagulated*</th>
<th>INR1†</th>
<th>Vitamin K</th>
<th>FFP Units</th>
<th>rFVIIa Dose (µg/kg)</th>
<th>INR2‡</th>
<th>INR3§</th>
<th>Platelet Count (×10⁹/l)/Units Transfused</th>
<th>Neurosurgery</th>
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<td>7</td>
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<td>Yes</td>
<td>6</td>
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<td>No</td>
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<td>1.80</td>
<td>Yes</td>
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<td>No</td>
<td>3</td>
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* Indication for anticoagulation in parentheses.
† INR at admission.
‡ INR after standard therapy.
§ INR after rFVIIa therapy.
| 2 doses of rFVIIa were given.

ICB, intracranial bleeding; SDH, subdural hematoma; ICH, intracerebral hemorrhage; EH, epidural hematoma; SAH, subarachnoid hemorrhage; GCS, Glasgow Coma Scale; CAD, coronary-artery disease; DM, diabetes mellitus; HTN, arterial hypertension; AF, atrial fibrillation; CA, carcinoma of prostate; CVA, cerebrovascular accident; MVR, mitral valve replacement; FFP, fresh-frozen plasma; INR, international normalized ratio.
steady state after the fVIIa administration was encountered among patients requiring chronic anticoagulation.

**DISCUSSION**

The neurosurgical management of patients with ICB (e.g., SDH), and especially warfarin-induced ICB has a poor outcome, and necessitates urgent reversal of anticoagulation for a rapid surgical intervention. There are no definitive data regarding the threshold INR value according to which surgery for intracranial pathologic finding may be safely performed. In a retrospective analysis of patients who had urgent craniotomy for ICH, Yasuda found a high mortality index in the postoperative period in patients with preoperative INR values >1.25 or thrombocytopenia (platelet count <100 × 10^9/L). According to Matheison et al., an INR of 1.2 to 1.5 is sufficient for neurosurgical hemostasis, and Boulis et al. chose an INR of 1.3 to be the goal of preoperative Warfarin reversal. An INR of 1.25 to 1.3 is thus accepted as a safe value for craniotomy and is used by many neurosurgeons as a threshold value for performing neurosurgery.

Standard modalities for correction of Warfarin coagulopathy have included FFP and vitamin K. The main disadvantage of this therapy is a slow rate of INR correction. Kawamata et al. reported that they were unable to obtain sufficient reversal of anticoagulation using vitamin K alone in any of their patients with Warfarin-related acute SDH and cerebral contusions. It has been observed that the rate of INR correction was approximately 0.18 INR/h for patients treated with FFP and vitamin K. Furthermore, treatment with FFP for rapid preoperative reversal of anticoagulation requires infusion of relatively large volumes of FFP, which can precipitate pulmonary edema in a group of patients who are often elderly with previous cardiac disease. Moreover, there might be further elevation of the intracranial pressure in patients with already compromised brain function.

Alternative strategies for urgent warfarin reversal include prothrombin complex concentrate and factor IX complex, which have been shown to reverse anticoagulation more rapidly than FFP in patients with Warfarin-related intracranial hemorrhage, although the reported time to INR correction (8 hours for prothrombin complex concentrate and about 3 hours for factor IX complex) seems to be much longer than that required in urgent neurosurgical settings. In addition, these agents can also induce thromboembolic complications. Although used in Europe, these modalities have not generally been used in North America. Importantly, a common but as yet unexplained observation in traumatic and nontraumatic ICB is the difficulty in correcting the INR. Sorensen has shown that the traditional treatment with FFP and vitamin K may not achieve the desired correction of coagulopathy sufficiently to avoid progression of ICB. Small doses of rFVIIa, however, may reverse an elevated

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**Fig. 1.** A scatter graph of INR measurements of study patients (n = 15) at three different time points. For each patient, three INR values are depicted: INR1, on admission; INR2, after “standard therapy” with vitamin K and fresh frozen plasma therapy; and INR3, after rFVIIa administration. The x- and y-axes intersect at INR = 1.3, which is the acceptable cutoff for operability of intracranial bleeding. All patients had an INR >1.3 at admission (INR1). Standard therapy resulted in a significant decrease in INR values (INR2) but all patients still had INR >1.3. Operability (INR <1.3), however, was achieved only after rFVIIa administration (INR3), thus showing an additive effect of the two treatment modalities.
Coagulopathic Patients With Traumatic Intracranial Bleeding

INR to a level below 1.25, which allows subsequent surgery.26,27

rFVIIa acts in a tissue factor-dependent manner, binding with high affinity to the surface of activated platelets and enhancing thrombin formation after direct rFVIIa activation of factors IX and X on the surface of the activated platelets. Although its widespread use has been constrained by its high cost and by reports of thrombotic events,28–36 rFVIIa has been evaluated in many areas of medicine. In regard to spontaneous ICH, Mayer et al. recently reported a randomized controlled trial evaluating the efficacy and safety of three dosing regimens of rFVIIa (40, 80, and 160 μg/kg) versus placebo.35 In a large cohort of patients (n = 399) rFVIIa significantly reduced mortality and morbidity in patients with ICH.35 Adverse events were similar in the rFVIIa-treated and placebo groups. Mayer has also shown the safety and efficacy of the “ultra-early hemostatic therapy” with rFVIIa for spontaneous ICH.17,18,35 Other than for ICH, rFVIIa has been successfully used in both spontaneous and traumatic ICB; however, this observation currently relies only on anecdotal reports,25,37,38 and ICH is at present the only generally approved indication for rFVIIa administration in neurology and neurosurgery patients.

We are unaware of any large series documenting the use of rFVIIa in the setting of SDH.12–14 In patients with SDH, urgent craniotomy, especially within 2 hours of patient arrival, has been shown to result in decreased recurrence rates and improved prognosis.39–41 Because ICB, either spontaneous or traumatic, is a common lethal complication of warfarin treatment,42,43 such patients in particular may benefit from rFVIIa, which can provide urgent and rapid reversal of anti-coagulation if surgical intervention is indicated.44,45 Our experience shows 100% success in achieving rapid operability, and no complications or deaths were related to rFVIIa treatment. Our series consisted of two major groups: one with coagulopathy related to anticoagulant treatment (7 patients) and one with coagulopathy related to unspecified causes, mainly trauma (8 patients). No difference in outcome or adverse reaction was evident between these two groups. Apparently, standard and rFVIIa therapy had an additive and significant effect on the coagulopathy. Vitamin K and FFP had a more pronounced effect on warfarin-related coagulopathy when compared with patients with other causes of coagulopathy. However, rFVIIa had a similar significant effect in both groups. Although our series represents only a small patient cohort, it adds to the accumulating data in the literature that support a benefit with rFVIIa in patients with traumatic ICB, in preventing expansion of the bleeding and optimizing clinical outcome by facilitating urgent surgical intervention, or obviating the need for surgery in some cases.

We used a dose ranging between 40 μg/kg and 90 μg/kg of rFVIIa. The dosing of rFVIIa in the literature has been variable, and the optimal dose has yet to be found.46 Although a dose-response relationship has been documented, a clear relationship with efficacy and adverse events has not been established. Furthermore, higher doses may be required for surgical coverage. This may be because higher doses are required for a full thrombin burst to occur. Several studies support these conclusions;47,48 The Hemophilia Research Society study found that doses higher than 200 μg/kg were of greater efficacy;46 overall there was 97% effectiveness in the high-dose group, compared with 84% efficacy in lower-dose groups. At the same time that there is a call for higher dosing regimes, it should be remembered that a single small dose of rFVIIa is often very effective in controlling even serious hemorrhage.19 and phase III rFVIIa trials are studying doses of 20 μg/kg and 80 μg/kg.

The Role of rFVIIa in Coagulopathic Intracranial Hemorrhage—A Suggested Approach

The development of potential management schemes of coagulopathic patients with traumatic ICB is an evolving process, which progresses as evidence is accumulated during time. However, neurosurgeons, anesthetists, and intensivists are called on to treat such patients on a daily basis and decision-making surrounding the use of rFVIIa in this context is complex given the limited data regarding its hemostatic capabilities, cost, and safety. On the basis of our experience and the data available to date, we propose the following initial treatment algorithm for coagulopathic patients with intracranial hemorrrhages.

We recommend that rFVIIa therapy be considered to halt bleeding expansion and optimize the condition of patients with ICB and coagulopathy requiring an emergency craniotomy. Patients who require intracranial surgery within 2 hours after admission and who have a coagulopathy are candidates for immediate rFVIIa administration along with vitamin K and FFP; patients requiring surgery within 2 hours to 24 hours in the presence of coagulopathy that cannot be corrected (target INR <1.3) with 10 mg of vitamin K and four to eight units of FFP should be considered as candidates for rFVIIa treatment.39 Nevertheless, one may choose to treat such patients in a way similar to the treatment of patients who require emergency surgery, especially if available resources support such an approach. For those cases in which fluid volume should be limited (e.g., patients with impaired left ventricular function and pulmonary congestion), rFVIIa should be considered even earlier.

The decision to administer rFVIIa should be based on the answers to two main questions:

1. What is the type of bleeding and what is the risk for expansion of the hematoma?
   a. EH has the highest risk of expansion as a result of arterial bleeding;
   b. SDH has the worst prognosis, especially in the elderly because of the accompanying brain ischemia and the high recurrence rate of postoperative bleeding;
   c. ICH have an expansion risk of 18% to 38% in the first 4 hours;35
d. expanding hematomas with clinical deterioration are at the highest risk.

2. How urgent is the indicated surgery (timing)?

Based on 30 years of trials showing significantly better outcomes, surgical intervention within 2 hours of admission is recommended for EH or acute SDH with prominent clinical impairment or deterioration. Many patients with subacute and chronic SDH, if not deteriorating rapidly (decrease of GCS score by more than 2 points, development of focal signs, seizures), can however be operated on within 2 hours to 24 hours.44,47

Our algorithm (Fig. 2) thus provides a stratified approach to the patient with ICB, which is based on allocation of patients into one of four groups according to the need for surgery and its timing as well as the presence of coagulopathy. The surgical group is divided into (a) an “immediate” subgroup, requiring surgery within 2 hours, and (b) an “early” subgroup, requiring surgery within 2 hours to 24 hours. The

Fig. 2. Flow chart of a proposed stratified approach to the management of coagulopathic patients with intracranial bleeding. The algorithm is discussed in the text.
nonsurgical group is divided into (c) possible use of rFVIIa to prevent surgery, and (d) a subgroup that has no indication for rFVIIa administration.

For the “immediate” or ultra-early surgical group (need for surgery no later than 2 hours from admission), rFVIIa should be given promptly, along with the traditional management by FFP and vitamin K, to patients with acute SDH or acute EH with mass effect or with clinical instability requiring urgent craniotomy and surgery within 2 hours, when a coagulopathy is present that precludes surgical intervention. FFP should be given after rFVIIa, to correct the coagulopathy after the effect of rFVIIa diminishes, thereby reducing the need for repeated doses of rFVIIa. Although patients with acute spontaneous ICH may not require surgery, there is evidence to support the ultra early use of factor rVIIa in these patients because of the early risk of hematoma expansion.17,35

The early surgical group includes clinically stable patients with coagulopathy and subacute or chronic SDH and EH who are not progressing rapidly, but require surgery within 2 hours to 24 hours after admission.48,49 These patients often have a coagulopathy that cannot be corrected with four to eight units of FFP or platelet transfusion, or may have factors that preclude fluid administration to the patient (e.g., congestive heart failure, pulmonary edema).

The first nonsurgical group is the “watchful waiting group”. This includes patients with SDH or EH small enough to require only clinical observation. In such patients rFVIIa should be considered only when the accompanying coagulopathy cannot be corrected in the first few hours after admission, or when other factors preclude fluid administration as stated above. There are few reports in the literature using rFVIIa in EH, and our suggestion is based on the pathophysiology of this condition.

For the second nonsurgical group, the “No indications” group, there is currently no evidence to support rFVIIa administration in traumatic SAH without coagulopathy.12 Traumatic SAH usually has a favorable outcome and only conservative treatment is indicated. There are only a few case reports of spontaneous SAH treated with rFVIIa,50 but results have been disappointing.

A Note of Caution

There are several theoretical concerns regarding the use of rFVIIa in neurosurgical patients. These patients are often subject to prolonged immobility or paralysis, increasing their risk for thrombotic events. Microvascular thrombi in the brains of patients with traumatic brain injury may hypothetically be made worse, but here too, supporting data are lacking.50 Furthermore, release of tissue thromboplastin, a procoagulant released from damaged brain, is a theoretical concern. The large trial of rFVIIa use in ICH by Mayer et al. also raised concerns of interest to neurosurgeons that are based on Level I evidence rather than theory. Although the rate of thromboembolic serious adverse events possibly or probably related to treatment, and that were fatal or disabling, occurred at an equal rate of 2% among patients on placebo and rFVIIa, serious thrombotic events were seen in 7% of rFVIIa-treated patients versus 2% of those treated with placebo. This is a significantly higher adverse event rate than has previously been reported.35 Further data on the use of rFVIIa in neurosurgical patients is needed to refine its evolving role in the management of these patients.

CONCLUSION

In recent years, rFVIIa therapy has emerged as an efficacious treatment modality for bleeding disorders. ICB, particularly in the setting of coagulopathy, is common, and improved outcome can be potentially achieved with rapid and effective care. Through a review of the literature and our own experience with ICB, we discuss an algorithm for the use of rFVIIa in coagulopathic patients with ICB. Given the unresolved issues surrounding the potential efficacy, complications, and cost-effectiveness of rFVIIa, randomized controlled trials of rFVIIa are needed to validate the suggested treatment approach.

REFERENCES


Alveolar Interleukin-10 Regulates Neutrophil Apoptosis in Severely Traumatized Patients

Matthias Turina, MD, PhD, J. Jason Hoth, MD, Ryan M. Turpen, BA, Melanie J. Scott, PhD, and William G. Cheadle, MD

Background: The lung produces a localized immunologic response to systemic trauma, characterized by an initial proinflammatory period with production of interleukin (IL)-8 and IL-18, followed by an anti-inflammatory phase with elevated levels of IL-10. Recent studies have shown a correlation between alveolar IL-10 and the rate of local neutrophil apoptosis. The aim of the present study was to further characterize the association of alveolar IL-8 and IL-10 after trauma with neutrophil activation, apoptosis, and phagocytic capacity.

Methods: Bronchoalveolar lavage fluid (BALF) was obtained from 17 trauma patients with an Injury Severity Score ≥16 who required mechanical ventilation. Neutrophils from venous blood of healthy volunteers were incubated in either (1) cell culture media (control), (2) culture media + BALF, (3) culture media + BALF + anti-IL-8 neutralizing antibody, or (4) culture media + BALF + anti-IL-10. Surface CD11b expression, ability to phagocytose fluorescent bacteria, and neutrophil apoptosis were determined by flow cytometry.

Results: Phagocytosis and CD11b expression were both augmented on postinjury day 1 when compared with controls. Neutralization of IL-10 or IL-8 produced no significant differences in phagocytosis or CD11b expression. However, neutralization of IL-10 significantly decreased the rate of apoptosis in samples from postinjury day 1.

Conclusion: Phagocytosis and CD11b expression on neutrophils are IL-8 and IL-10 independent. However, our data indicate that alveolar neutrophil apoptosis is dependent on IL-10 at early time points after injury. Elucidation of this pathway may allow novel interventions to prevent posttraumatic pulmonary dysfunction.

Key Words: Interleukin-10, Neutrophil, Apoptosis, Acute respiratory distress syndrome, Trauma.

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TNF-α, interferon-γ, and the granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor are all known to decrease neutrophil apoptosis.\textsuperscript{11–15} In addition, bacterial products such as lipopolysaccharide (LPS) are strong inhibitors of apoptosis, presumably by activation of inhibitors of apoptosis proteins, which inhibit the activity of caspase-3, a key effector enzyme in the apoptosis pathway.\textsuperscript{16} On the other side, the anti-inflammatory cytokine IL-10 has been described to counteract the LPS-induced inhibition of neutrophil apoptosis, leading to a more rapid apoptotic turnover of PMNs, as previously demonstrated in circulating PMNs from both septic patients and healthy controls.\textsuperscript{17} This antagonizing effect of IL-10 is thought to be mediated through an inhibition of the extracellular signal-related kinase (ERK) pathway in neutrophils.\textsuperscript{18}

A previous study from our laboratory has shown that alveolar levels of IL-10 are directly proportional to the percentage of neutrophils undergoing apoptosis, both increasing after an initial posttraumatic decline as time from injury increased.\textsuperscript{5} The reduction in apoptosis that was observed immediately after injury returned to control levels within 72 hours, when alveolar IL-10 reached its peak concentrations. IL-10 may therefore be critical in regulating the rate at which PMNs are removed from the alveolar space in ALI. In the present study, we have tested the hypothesis that IL-10 directly increases the levels of neutrophil apoptosis in bronchoalveolar lavage fluid (BALF), and that the experimental blockade of IL-10 reverses these changes. To correlate the results of these experiments with data on the functional activity of neutrophils, we have also evaluated the effects of blocking IL-10 and IL-8 on neutrophil phagocytosis and cell surface expression of CD11b.

The CD11b antigen (integrin α M, Mac-1α), a 165 kDa adhesion glycoprotein, is part of the CD11b/CD18 heterodimer and belongs to the family of β2-integrin adhesion molecules.\textsuperscript{19} CD11b in conjunction with CD18 serves as an adhesion molecule mediating the diapedesis of leukocytes across the endothelium through interaction with CD54 [intracellular adhesion molecule (ICAM)-1], CD102 (ICAM-2), and CD50 (ICAM-3). It is also a receptor for the iC3b fragment of complement.\textsuperscript{20} Integrin activation has further been shown to delay apoptosis and prolong survival of transendothelial-migrated PMN in the presence of TNF-α and LPS, illustrating the functional interdependence between cell adhesion/transmigration and PMN apoptosis.\textsuperscript{21}

To test our hypothesis, we have incubated bronchoalveolar lavage supernatants from severely injured patients with neutrophils from healthy volunteers in the presence or absence of human anti-IL-10 and anti-IL-8 antibodies. Our data indicate that alveolar IL-10 may play a pivotal role in determining the rate at which alveolar neutrophils undergo apoptosis, an essential step in the resolution of ALI after trauma.

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Average age (yr)</th>
<th>Female (%)</th>
<th>ISS</th>
<th>Admission GCS</th>
<th>Ventilation (d)</th>
<th>Hospital stay (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (yr)</td>
<td>36.7 ± 3.4</td>
<td>42</td>
<td>22.5 ± 1.5</td>
<td>8.6 ± 1.0</td>
<td>9.3 ± 2.1</td>
<td>23 ± 4</td>
</tr>
</tbody>
</table>

Patient characteristics of all 17 enrolled patients.

**ISS**, Injury Severity Score; **GCS**, Glasgow Coma Scale.

**PATIENTS AND METHODS**

To separately assess the effects of BALF from trauma patients on extravasated neutrophils, our model was set up to incubate circulating neutrophils from healthy volunteers (taken by venous blood sampling) together with BALF of severely traumatized patients. This set-up enabled us to study the bronchoalveolar cytokine milieu separate from other simultaneous cellular effects likely present in traumatized patients, as PMNs taken from healthy volunteers do not underlie any activation changes before entering the incubation period.

**Patient Population**

Approval by the University of Louisville Human Studies Committee (189-02) was obtained as required by local Institutional Review Board regulations. The study population, described in greater detail in our preliminary report on alveolar effector cell apoptosis,\textsuperscript{5} comprised 17 patients with multiple injuries between the ages of 18 and 55 (Table 1). All patients required mechanical ventilation for significant pulmonary dysfunction within 2 hours of injury, and had an Injury Severity Score of 16 or greater. Clinically significant pulmonary dysfunction was defined as partial pressure of oxygen in arterial blood (PaO₂)/fractional inspired oxygen (FiO₂) < 200 by postruma day 3 (Table 2). Patients with documented aspiration or pre-existing infection were excluded. The majority of patients (n = 16; 94%) suffered from blunt injuries, predominantly closed head injuries (n = 12; 71%) and thoracic injuries (n = 11; 64%), followed by extremity fractures (n = 9; 53%) and abdominal injuries (n = 5; 29%), occurring alone or in combination.

**Sample Collection and Preparation**

BALF samples from trauma patients were obtained through the endotracheal tube using a flexible, fiberoptic bronchoscope (3.8 mm, Olympus LF2; Olympus Corporation, Center Valley, PA). Samples were collected at two separate intervals after injury: 12 to 24 hours postinjury (day 1) and 72 to 84 hours postinjury (day 3). The bronchoscope was wedged into the right lower lobe and 10 mL of sterile saline (0.9% NaCl, 37°C) was instilled, aspirated with suction, and discarded. Next, a total of 60 mL of sterile saline was instilled and aspirated into a sterile mucus specimen trap (BARD, Covington, GA). The fluid recovery rate was 50%.
Table 2  PaO2/FIO2 Ratio and Bronchoalveolar Lavage Cell Count and Differentials

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FIO2 ratio</td>
<td>—</td>
<td>282 ± 47</td>
<td>185 ± 18</td>
</tr>
<tr>
<td>Cell count (10⁶/mL)</td>
<td>0.23 ± 0.06</td>
<td>5.1 ± 2.0*</td>
<td>5.0 ± 1.6*</td>
</tr>
<tr>
<td>Polymorphonuclear cells (10⁶/mL)</td>
<td>0.11 ± 0.0</td>
<td>3.7 ± 1.4*</td>
<td>3.9 ± 1.0*</td>
</tr>
<tr>
<td>Polymorphonuclear cells (%)</td>
<td>48</td>
<td>73*</td>
<td>78*</td>
</tr>
<tr>
<td>Monocytes (10⁶/mL)</td>
<td>0.11 ± 0.0</td>
<td>1.0 ± 0.4*</td>
<td>0.8 ± 0.3*</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>48</td>
<td>20*</td>
<td>16*</td>
</tr>
</tbody>
</table>

Patient characteristics of all 17 enrolled patients. * p < 0.05 versus controls undergoing elective general surgery operations without signs of pulmonary or systemic infection.

PaO2, partial pressure of oxygen in arterial blood; FIO2, fraction of inspired oxygen.

All samples were processed within 60 minutes of collection. Samples were stained through three layers of fine mesh gauze to remove mucus and then centrifuged at 1,400 rpm for 15 minutes at 4°C. The cell pellet was resuspended to a final concentration of 20 × 10⁶ white blood cells/mL in phosphate buffered saline (PBS) without calcium (Sigma, St. Louis, MO). Viability was determined by trypan blue exclusion, and all samples were >90% viable. Cyto-spin samples were prepared for each specimen. The percentage of PMN cells and monocytes for each sample were calculated based on the assessment of at least 200 cells.

In Vitro Manipulation of Neutrophils

Two milliliters of venous blood, drawn from healthy volunteers using ethylenediamine tetra-acetic acid Vacutainers (Becton Dickinson, Franklin Lakes, NJ), were layered onto an equal volume of Histopaque 1.077 (Sigma Chemical Co.). The gradients were centrifuged at room temperature for 30 minutes at 400g. The mononuclear layer and all liquid above the bottom layer were discarded, leaving red blood cells and granulocytes. Red blood cells were removed by hypotonic lysis with ice-cold ammonium chloride, potassium bicarbonate, and ethylenediamine tetra-acetic acid (Sigma Chemical Co.). The granulocytes were pelleted by centrifugation and washed once with Dulbecco’s PBS (Sigma Chemical Co.). After assessment of viability, the cells were then either resuspended in 400 µL of normal saline (NS), 400 µL of BALF taken from trauma patients as described above, or 400 µL of trauma BALF supplemented with 1 µg/mL of human monoclonal anti-IL-8 or anti-IL-10 antibody. The samples were cultured for 24 hours at 37°C in 5% CO₂. This length of incubation was chosen according to previous experiments in our laboratory, in which we found that a maximum of >40% of PMNs in vitro undergo apoptosis after 24 hours of incubation. The percentage of apoptotic PMNs also responds best to experimental stimuli such as endotoxin at this time point.²²

After 24 hours of incubation, the cells were recounted by hemocytometer and viability assessed by trypan blue exclusion. The samples were then centrifuged at 1,500 rpm for 14 minutes at 4°C. After washing twice with PBS, the cell pellet was resuspended in PBS to a final concentration of 20 × 10⁶ white blood cell/mL. Measurement of CD11b expression, phagocytosis, and apoptosis were performed as described below.

Measurement of Cell Surface CD11b

Neutrophils were identified using fluorescein-isothiocyanate (FITC)-conjugated human anti-CD16b (FcγRIIIb) monoclonal antibodies (Immunotech, Beckman Coulter, Marseille, France), with CD11b counterstaining using phycoerythrin (PE)-conjugated human anti-CD11b (Immunotech) to identify the population of activated neutrophils. Of the neutrophil cell suspension, 10⁶ cells were stained with 20 µL of PE-conjugated human anti-CD11b and 20 µL FITC-conjugated human anti-CD16b monoclonal antibodies. Negative controls consisting of appropriate nonhuman isotype-matched monoclonal antibodies were used to control for nonspecific binding. Samples were incubated with the antibodies for 25 minutes and fixed in 300 µL of 1% paraformaldehyde.

Data analysis was performed on a flow cytometer (FACSCalibur, Beckton Dickinson Co., San Jose, CA) equipped with CELLQuest software (Becton Dickinson). Neutrophil CD11b expression was measured by gating on CD16b positive cells in the granulocyte region of the forward and right scattergram. Results are expressed as CD11b mean channel fluorescence units of the gated CD16b positive cells.

Measurement of Apoptosis: The Annexin V Assay

Apoptosis was assessed using the annexin V and propidium iodide (PI) technique (BD Biosciences, San Diego, CA).²³ Apoptotic cells express phosphatidylserine, a membrane phospholipid usually only present on the inner side of the bilipid membrane, on the outer side of the cell membrane, allowing recognition and phagocytic clearance by tissue macrophages.²⁴ The assay was performed according to the manufacturer’s instructions. Briefly, cells were stained with 3 µL FITC-annexin V and 10 µL PE-PI for 15 minutes in the dark after resuspension in 150 µL of calcium-rich binding buffer (BD Biosciences). Flow cytometric analysis of the percentages of cells binding to Annexin V and PI was performed within 1 hour of staining.

Phagocytosis Assay

Phagocytosis was assessed by flow cytometry using FITC-labeled E. coli (Molecular Probes, Eugene, OR). FITC-labeled E. coli (10⁶) were opsonized with 5 µL of human serum for 30 minutes at 37°C in a shaking water bath. A total of 10⁶ neutrophils were then incubated with the opsonized, FITC-labeled E. coli at a 1:25 cell to bacteria ratio in a shaking water bath at 37°C for 30 minutes. Samples were washed twice with PBS, fixed in 300 µL 1%
formaldehyde, and stored at 4°C until further analysis. The percentage and mean fluorescence intensity of FITC-labeled cells were determined by flow cytometry, recording the uptake of FITC-labeled bacteria by individual cells. Appropriate negative controls were used to adjust for background autofluorescence.

Statistical Analysis

Data are presented as mean ± SEM, unless otherwise specified. According to the distribution of data, the unpaired t test was used for single comparisons and one-way analysis of variance was used to detect differences among three or more groups, followed by the Dunn’s or Holm-Sidak test to isolate the group or groups that differ from the others. For data that were not normally distributed, the Kruskal-Wallis statistic (multiple comparisons) or the Mann-Whitney U test (two groups) was applied. All statistical computations were performed using SigmaStat 3.01.0 software (Systat Software, Inc., Richmond, CA). Results were considered significant at p < 0.05.

RESULTS

Effects of BALF, Anti-IL-8, and Anti-IL-10 on Neutrophil Apoptosis

After 24 hours of incubation in NS, a mean 47.3% ± 3.3% of neutrophils undergo apoptosis as assessed by the total percentage of neutrophils binding to Annexin V (Fig. 1; control bars on left). Incubating neutrophils in the presence of BALF was associated with a lower percentage of apoptotic neutrophils (42.5% ± 5.5%), but this difference did not reach statistical significance. Coincubating neutrophils with anti-IL-8 in the presence of BALF did not affect the percentage of apoptotic neutrophils on day 1 or day 3 when compared with BALF alone. Samples that were incubated with BALF and anti-IL-10, however, showed a significantly lower percentage of apoptotic neutrophils on day 1 when compared with BALF alone (p = 0.01). On day 3, the percentage of apoptotic neutrophils was again smaller in the presence of anti-IL-10 (38.6% ± 4.2%), but the difference was no longer statistically significant when compared with BALF alone (p = 0.36).

Effects of BALF, Anti-IL-8, and Anti-IL-10 on Neutrophil Phagocytic Capacity

The effects of BALF, anti-IL-8, and anti-IL-10 on neutrophil phagocytosis are shown in Figure 2. A mean 62.5% ± 3.5% of neutrophils stained positive for phagocytosed FITC-labeled E. coli when incubated in NS (controls). In samples incubated with BALF alone, a significant increase in the percentage of phagocytic neutrophils to 81.3% ± 3.7% was noted on day 1 (p < 0.01). However, no differences were observed between samples incubated with BALF and anti-IL-8 (p = 0.75) or BALF with anti-IL-10 (p = 0.87) when compared with BALF alone. On day 3 posttrauma, phagocytic activity was lower in all treatment groups when compared with day 1, but remained significantly elevated compared with controls. Again, no differences in phagocytic activity were noted in samples incubated with either anti-IL-8 or anti-IL-10 antibodies.

Effects of BALF, Anti-IL-8, and Anti-IL-10 on Neutrophil CD11b Expression

The effects of BALF, anti-IL-8, and anti-IL-10 on neutrophil CD11b expression are shown in Figure 3. A mean 62.5% ± 3.5% of neutrophils expressed 617 ± 73 CD11b mean channel fluorescence when incubated in NS (controls). In samples incubated with BALF alone, a significant increase in the percentage of phagocytic neutrophils to 81.3% ± 3.7% was noted on day 1 (p < 0.01). However, no differences were observed between samples incubated with BALF and anti-IL-8 (p = 0.75) or BALF with anti-IL-10 (p = 0.87) when compared with BALF alone. On day 3 posttrauma, phagocytic activity was lower in all groups compared with corresponding samples from day 1 (p < 0.05), but remained significantly elevated when compared with samples incubated with NS alone (p < 0.01).
on circulating neutrophils,17 alveolar IL-10 may serve to support our hypothesis that, similar to the effects of systemic IL-10 on circulating neutrophils of septic patients.17 Although the precise pathway of this counteraction has yet to be elucidated, potential mechanisms generally would have to interfere with either the death-receptor–related extrinsic or the mitochondrial intrinsic apoptosis pathway, both of which ultimately lead to the activation of caspase enzymes, a family of intracellular proteases critical for the subsequent cleavage of cell proteins and DNA.35 In fact, Ward et al.18 have recently demonstrated an IL-10-mediated inhibition of ERK activation in purified human neutrophils. ERK inhibits the activation of caspase-8, a central enzyme in the extracellular apoptosis pathway, and thus overrides proapoptotic stimuli by TNF, Fas, and TNF-related apoptosis-inducing ligand.

Similar to day 1, samples treated with BALF from posttrauma day 3 with anti-IL-8 or anti-IL-10 did not differ from those treated with BALF alone.

**DISCUSSION**

Pulmonary dysfunction resulting from direct or indirect ALI remains a leading cause of mortality in severely injured patients. Previous studies have elucidated several immunologic factors that are associated with this phenomenon, including a bimodal cytokine response consisting of high alveolar levels of the chemokine IL-8, followed by increasing levels of the anti-inflammatory cytokine IL-10 at later time points.5 Alveolar IL-8 contributes to the diapedesis and intra-alveolar accumulation of neutrophils,25,26 and IL-8 levels have been shown to parallel the severity of ALI.27 Although initially necessary to combat bacterial contamination and infection, high numbers of persisting neutrophils can lead to local tissue damage through the uncontrolled release of reactive oxygen species and proteases such as elastase.28

We have previously shown that the rate of alveolar neutrophil apoptosis inversely correlates with the levels of alveolar IL-10 in surviving trauma patients at 36 hours and later time points.5 It is also known that neutrophils express small numbers of IL-10 receptors on their surface, which increases with exposure to LPS.29 In the present study, we have examined whether the increase in IL-10 in BALF from trauma patients directly relates to the higher rate of neutrophil apoptosis in the alveolar compartment of such patients. It was our hypothesis that, similar to the effects of systemic IL-10 on circulating neutrophils,17 alveolar IL-10 may serve to counteract the inhibition of neutrophil apoptosis brought upon by proinflammatory mediators such as TNF-α or IL-6.14,15 A higher rate of alveolar neutrophils undergoing apoptosis after the initial proinflammatory phase as a result of IL-10 may benefit the host by preventing excessive neutrophil-induced lung tissue damage. To test this hypothesis, we have measured the percentage of apoptotic neutrophils from healthy donors, which were incubated for 24 hours in BALF from trauma patients in the presence or absence of anti-IL-10 or anti-IL-8 antibodies. Our results indicate that alveolar IL-10 may indeed increase alveolar neutrophil apoptosis at early time points after injury, as shown by reduced percentages of apoptotic neutrophils in samples incubated with anti-IL-10 antibodies (Fig. 1). Incubation in BALF without anti-IL-10 did not reduce the overall levels of PMN apoptosis per se, when compared with that of control samples incubated in NS. However, samples that were incubated in trauma BALF with the addition of anti-IL-10 antibodies showed significantly lower levels of PMN apoptosis. This finding implies that BALF IL-10 affects the levels of PMN apoptosis because its experimental blockade led to significantly lower percentages of apoptotic PMNs on day 1. A possible reason why the overall levels of PMN apoptosis in the trauma BALF groups are not different from the control group is that other soluble factors in BALF may counteract the effects of IL-10, which may include cytokines such as IL-2, IL-6, TNF-α, or even granulocyte-macrophage colony stimulating factor, all of which were shown to increase the levels of PMN apoptosis in a local inflammatory response.11–15

On day 3, however, the reduction of neutrophil apoptosis in the presence of anti-IL-10 was no longer significant in our experiments. This is notable in that IL-10 levels were shown to be higher on day 3 than day 1 in our previous study.5 Potentially, this may be because of a need for more anti-IL-10 blocking antibody on day 3, as higher concentrations of unblocked IL-10 may have contributed to the increased levels of neutrophil apoptosis. Alternatively, other mediators in BALF such as the ones described above may potentially augment the rate of apoptosis at later time points, and thus override the effects of IL-10.

IL-10 is found in high concentrations in BALF at 18 to 72 hours after injury.5 It is synthesized by T cells, macrophages, monocytes, and B cells and dampens many inflammatory responses,30 e.g., attenuating TNF-α, IL-1β, or IL-6 release from LPS-activated monocytes and macrophages.31–34 Similar to the results of our study, IL-10 has been shown to counteract the LPS-induced inhibition of apoptosis in circulating neutrophils of septic patients.17 Although the precise pathway of this counteraction has yet to be elucidated, potential mechanisms generally would have to interfere with either the death-receptor–related extrinsic or the mitochondrial intrinsic apoptosis pathway, both of which ultimately lead to the activation of caspase enzymes, a family of intracellular proteases critical for the subsequent cleavage of cell proteins and DNA.35 In fact, Ward et al.18 have recently demonstrated an IL-10-mediated inhibition of ERK activation in purified human neutrophils. ERK inhibits the activation of caspase-8, a central enzyme in the extracellular apoptosis pathway, and thus overrides proapoptotic stimuli by TNF, Fas, and TNF-related apoptosis-inducing ligand.
The suppression of ERK would then in turn remove its inhibitory effect on caspase-8, and subsequently lead to a higher rate of apoptosis in affected PMNs.

Interestingly, neither the phagocytic capacity of remaining neutrophils (Fig. 2) nor the expression of CD11b (Fig. 3), both significantly augmented in BALF as opposed to NS, were affected by exposure to anti-IL-10 antibodies, demonstrating the independence of the apoptosis signaling pathway from the functional activity of PMNs in vitro. Both parameters were found to be significantly higher on day 1 posttrauma than on day 3, indicating an early normalization of the functional activity of these cells after injury. Potentially, this may be because of an IL-10-mediated decline of TNF-α or IL-1β levels in BALF, both known to activate alveolar neutrophils after trauma.

Our data are in agreement with an earlier study by Cox, in which the author could show that IL-10 helped facilitate the resolution of pulmonary inflammation induced by intratracheal LPS administration in rats. IL-10 did not affect the initial onset or extent of alveolar neutrophil sequestration in animals receiving LPS, but the degree of alveolar neutrophilia was markedly decreased at 18 hours and later. This finding is even more significant in that alveolar neutrophil transmigration in ALI usually peaks around 24 hours after the initial insult. Interestingly, the authors at the time concluded with good hindsight that the effect of IL-10 in their model may lie in a prevention of (LPS-) stimulated increases in neutrophil survival.

The limitations of our study, however, should be noted. We have chosen to investigate the effects of alveolar IL-8 and IL-10 on neutrophils collected by peripheral venipuncture from healthy volunteers, as opposed to either systemic or alveolar neutrophils from injured or otherwise immunologically challenged patients. This was performed to control for the potential changes in neutrophil function in patients after trauma, as it has been shown that even the transmigration of neutrophils across a membrane can potentially trigger the sequence of caspase activation. Therefore, PMNs extracted directly from the alveolar space may react differently to the stimuli used in our model. We plan to examine systemic and alveolar PMNs taken from trauma patients in subsequent experiments, to account for these potential systemic effects, and to further characterize the biological behavior of extravasated PMNs in the alveolar space.

In summary, our study shows that the blockade of alveolar IL-10 from severely injured patients leads to a lower apoptotic turnover of incubated human neutrophils. These data suggest that, similar to its effects in the systemic circulation, IL-10 may be able to counteract the initial proinflammatory inhibition of neutrophil apoptosis in the lung. This finding may be of therapeutic relevance, as the presence of large numbers of activating neutrophils in the alveolar space has repeatedly been associated with the development of ALI and acute respiratory distress syndrome in trauma patients. Potentially, increasing the apoptotic turnover and removal of alveolar neutrophils by topical IL-10 may benefit the host by preventing excessive neutrophil-induced tissue damage during the later phase of local inflammation. Future in vivo studies are necessary to better delineate this pathway as a therapeutic approach to reduce pulmonary dysfunction and the high mortality in affected trauma patients.

REFERENCES


Toll-Like Receptor 2 and 4 Expression After Severe Injury is Not Involved in the Dysregulation of the Innate Immune System

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Background: Severe injury after trauma is associated with a diminished production of different proinflammatory cytokines after stimulation with bacterial cell wall components. The cellular mechanisms, leading to a decreased responsiveness especially of monocytes after multiple injuries have not yet been elucidated in detail. The expression of Toll-like receptors (TLR) on leukocytes is essential for recognition of bacterial components. We investigated the expression of TLR2 and 4 in correlation with gram-negative and gram-positive stimuli-dependent cytokine liberation after severe injury in comparison with that in healthy volunteers.

Methods: In a prospective clinical experimental study, 12 trauma patients with an Injury Severity Score above 21 points and 14 healthy volunteers were analyzed. Heparinized whole blood samples of patients were collected within 48 hours after trauma and incubated in vitro with or without lipopolysaccharide (LPS) and peptidoglycan (PGN). TLR2 and TLR4 expression on monocytes was analyzed by flow cytometry. LPS- and PGN-induced tumor necrosis factor alpha (TNFα) and interleukin-8 production was measured by means of enzyme-linked immunosorbent assay.

Results: Both LPS- and PGN-induced TNFα liberation were significantly reduced in severely injured patients. The surface expression of TLR2 was also significantly decreased on monocytes collected from trauma patients, whereas the expression of TLR4 remained unchanged. There was only a negative correlation between TLR2 expression and the liberation of TNFα after stimulation with LPS or PGN.

Conclusions: We conclude that diminished cytokine production after trauma cannot be explained simply by changes in TLR2 or TLR4 expression and that subsequent signaling cascades or additional receptors are involved in the blunted cytokine response after trauma.

Key Words: Toll-like receptor 2, Toll-like receptor 4, CD14, Sepsis, Trauma, Endotoxin.


Severe injury influences the adaptive and innate immune response, which renders severely traumatized patients highly susceptible to infectious complications. A common feature of the immune response of multiply injured patients is the hyporesponsiveness of circulating leukocytes to bacterial stimuli. Whole blood as well as isolated mononuclear cells show a diminished production of a variety of proinflammatory cytokines after stimulation with the gram-negative cell wall component endotoxin (lipopolysaccharide [LPS]) within the first 24 hours after trauma.\(^1\)\(^2\) However, concerning the responsiveness to gram-positive stimuli, some authors also report an unchanged responsiveness after severe injury in human mononuclear leukocytes.\(^3\)

In contrast, in animal models of burn injury, a decreased production of the proinflammatory cytokine interleukin (IL)-12 after stimulation with Staphylococcus aureus lysates has been reported,\(^4\) whereas the synthesis of the anti-inflammatory mediator IL-10 was increased in the same burn injury model.\(^4\)

In general, the diminished cytokine response is commonly regarded as an expression of a disturbed “first line” immune defense and has been titled with phrases such as “immunoparalysis” or “immune incompetence”. The action of anti-inflammatory cytokines,\(^5\) prostaglandins,\(^6\) and substances such as ubiquitin\(^7\) have been discussed as a causative factor for the change in leukocyte reactions. However, the cellular mechanisms leading to a decreased responsiveness especially of monocytes after multiple injuries have not yet been elucidated.

Recently, a novel family of receptors—the Toll-like receptors (TLRs)—has been characterized. This receptor family—also referred to as “pattern recognition receptors”—consists of by now 13 different proteins that are expressed in or on the surface of various leukocytes.\(^8\) TLRs play a central role in the innate immune response, because their expression is essential for the reaction of leukocytes to gram-positive membrane substances such as lipoteichoic acid (LTA), peptidoglycan (PGN), or LPS derived from gram-negative bacteria.
Because CD14 is either present as a membrane receptor lacking an intracellular signaling domain or soluble in serum, a transmembrane coreceptor has been postulated for LPS- or, e.g., LTA-responsive cells.

Recently, it could be shown that TLR2 is essential for the reaction of macrophages or monocytes to stimuli such as LTA or PGN. Binding of PGN or LTA is mediated by an assembling of TLR2 with TLR6 on the cell surface.

Gram-negative bacterial stimuli such as endotoxin bind to TLR4 together with the surface protein CD14. Upon ligand binding, TLRs transfer their signal intracellularly via a sequential action of receptor-associated kinases including the association of myeloid differentiation primary-response protein 88 (Myd88), which in turn recruits IL-1R-associated kinase 4 (IRAK4), thereby finally leading to the activation of IRAK1. IRAK1 in turn leads to the phosphorylation of further downstream-located kinases, resulting in the activation of transcription factors such as nuclear factor κB and subsequent gene activation of, e.g., tumor necrosis factor alpha (TNFα). Because the TLRs are crucial for the cytokine production after bacterial stimulation, we speculated that a regulation of these receptors may be involved for the impaired cytokine response after trauma. Therefore, we studied the surface expression of TLR2 and TLR4 on circulating monocytes from severely injured patients and correlated the degree of TLR expression with the cytokine production after stimulation with PGN and LPS representing the respective stimulus derived from gram-positive and gram-negative bacteria.

**PATIENTS AND METHODS**

**Patients**

Severely injured patients aged between 18 years and 80 years, with an Injury Severity Score (ISS) >21 points, and with primary admission to our surgical intensive care unit within 8 hours after injury were included in the study. Heparinized blood samples were collected via central venous lines within 48 hours after injury. All patients were free of known pre-existing immunologic disorders or systemic steroid medication. No penetrating or burn injuries were observed in the patients’ collective. Sepsis was defined according to the consensus conference criteria published by Bone et al. The patients’ collective. Sepsis was defined according to the consensus conference criteria published by Bone et al.12

Gram-negative or gram-positive sepsis was defined on the basis of the first relevant microbial finding after onset of systemic inflammatory response syndrome. Organ failure was evaluated on a daily basis by applying the Sequential Organ Failure Assessment (SOFA) Score.13 Multiple organ failure was defined as SOFA Score >2 points of two organ systems persisting for more than 2 days excluding the evaluation of the central nervous system. Twelve consecutive patients were studied. All patients received standardized advanced trauma life support (ATLS)-adapted emergency department treatment and standardized intensive care unit therapy. Surgical treatment was performed according to damage control strategies. Fourteen individuals from the staff and healthy volunteers (mean age, 45 years; 8 men and 6 women) served as controls and declared their informed consent to donate blood for this study. The ethic committee of the University Hospital of Essen approved the study.

**Blood Stimulations and Cytokine Analysis**

Heparinized blood was diluted 1:1 vol/vol with RPMI 1640 medium, and blood cultures were set up in flat bottom 24-well plates in a total volume of 500 μL in triplicates. Blood samples were stimulated with either 10 ng/mL *Salmonella friedenau* LPS (protein-free phenol-extracted LPS, provided by H. Brade, Borstel, Germany) or 1 μg/mL PGN (LPS-free, consists of a glycan backbone with alternating β-1,4-linked residues of N-acetyl-d-glucosamine and muramic acid; Sigma-Aldrich, Munich, Germany) for 16 hours at 37°C. After centrifugation with 900g, supernatants were removed and stored at −20° until cytokine detection. TNFα and IL-8 were detected by means of enzyme-linked immunosorbent assay using specific monoclonal antibodies (Beckman Coulter, Marseille, France). The lower detection limit was 15 pg/mL.

**Flow Cytometry**

TLR2 and TLR4 expression of CD14+ monocytes was estimated by an indirect two-color labeling technique. In brief, 10 μL of mouse anti-TLR2 and anti-TLR4 antibodies from BioCarta Europe (Hamburg, Germany) were added to 250 μL phosphate-buffered saline (PBS). After addition of 100 μL of heparinized whole blood, cells were incubated for 15 minutes in the dark at room temperature. After a wash step, 200 μL of a 1:200 PBS-diluted fluorescein isothiocyanate isothiocyanate-labeled anti-mouse IgG H+L F(ab)2 (Coulter-Immunotech, Krefeld, Germany) was added and incubated as previously described. After washing, 200 μL of a 1:20 dilution in PBS of phycoerythrin-labeled anti-CD14 monoclonal antibody (mab) (Becton Dickinson, Heidelberg, Germany) was added and incubated as described. After lysis of erythrocytes (Becton Dickinson lysing solution) and washing, cells were measured using a FACSCalibur (Becton Dickinson) and CELLQuest software. HLA-DR+ CD14+ monocytes were stained by two colors using the mab combination HLA-DR fluorescein isothiocyanate/CD14 phycoerythrin (Becton Dickinson, San Jose, CA) in whole blood lysing technique as described above. A total of 20,000 cells per sample were acquired. Monocytes were gated according to forward and side-scatter properties and CD14-staining. Mean fluorescence intensities (MFI) for the respective surface markers were determined.

**Statistics**

Statistical calculations were performed with the use of a standard statistical package (SPSS/PC; SPSS Inc., Chicago, IL). For analysis of independent parameters between each individual group, the Mann-Whitney U test was used.
Table 1 Onset of Sepsis and Characteristics of Infection

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset of Sepsis (First Day)</th>
<th>Bacteria</th>
<th>Focus</th>
<th>Gram Staining</th>
<th>TLR2*</th>
<th>TLR4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>E. coli</td>
<td>Lung</td>
<td>Negative</td>
<td>485</td>
<td>401</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Staphylococcus aureus</td>
<td>Lung</td>
<td>Positive</td>
<td>527</td>
<td>390</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Pseudomonas aeruginosa</td>
<td>Catheter</td>
<td>Negative</td>
<td>634</td>
<td>493</td>
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<tr>
<td>4</td>
<td>26</td>
<td>Staphylococcus epidermidis</td>
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<td>623</td>
<td>458</td>
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<tr>
<td>5</td>
<td>7</td>
<td>Staphylococcus epidermidis</td>
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<td>Positive</td>
<td>634</td>
<td>461</td>
</tr>
<tr>
<td>6</td>
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<td>Enterobacter cloacae</td>
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<td>466</td>
</tr>
<tr>
<td>7</td>
<td>No sepsis</td>
<td>No sepsis</td>
<td>Lung</td>
<td>Positive</td>
<td>551</td>
<td>401</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>Staphylococcus aureus</td>
<td>Lung</td>
<td>Positive</td>
<td>646</td>
<td>501</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
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<td>Negative</td>
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<td>475</td>
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<tr>
<td>10</td>
<td>3</td>
<td>Pseudomonas aeruginosa</td>
<td>Lung</td>
<td>Negative</td>
<td>597</td>
<td>422</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>Streptococcus group G</td>
<td>Lung</td>
<td>Positive</td>
<td>459</td>
<td>456</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>Haemophilus influenzae</td>
<td>Lung</td>
<td>Negative</td>
<td>552</td>
<td>419</td>
</tr>
</tbody>
</table>

Mean ± SD

- E. coli: 8.8 ± 9.7
- Gram-negative: 7.8 ± 5.4
- Gram-positive: 8.8 ± 9.7

Differences in TLR4 and TLR2 expression between those patients with gram-positive sepsis and those with gram-negative sepsis, differences were not significant (Mann-Whitney U test).

* Data are expressed as MFI (channels) ± SD.

Table 2 Correlation of Receptor Expression and Cytokine Synthesis After Trauma

<table>
<thead>
<tr>
<th></th>
<th>TNFα After LPS</th>
<th>IL-8 After LPS</th>
<th>TNFα After PGN</th>
<th>IL-8 After PGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR2*</td>
<td>−0.316 (0.317)</td>
<td>0.195 (0.544)</td>
<td>−0.625 (0.03)†</td>
<td>0.467 (0.126)</td>
</tr>
<tr>
<td>TLR4*</td>
<td>−0.55 (0.067)</td>
<td>0.195 (0.544)</td>
<td>−0.67 (0.018)†</td>
<td>0.175 (0.587)</td>
</tr>
<tr>
<td>CD14*</td>
<td>−0.08 (0.81)</td>
<td>0.317 (0.316)</td>
<td>−0.163 (0.613)</td>
<td>0.432 (0.161)</td>
</tr>
</tbody>
</table>

* MFI (channels) versus concentration of cytokines after stimulation with LPS/PGN in vitro.
† Bivariant analysis of Pearson.

RESULTS

Patients’ Characteristics

Twelve severely injured patients with a mean ISS of 42.5 were studied. The mean age of the study population was 37.2 years ± 17.3 years (range, 18–71 years). All blood samples were collected within 48 hours after injury, because during this period, the suppression of immune functions can be assumed to be present independently of septic complications. This assumption is supported by the fact that no positive blood cultures or other bacterial foci were identified within the first 48 hours. Arterial and central venous lines were used only if placed under sterile conditions in the emergency room. Central venous lines placed in the field were removed after admission to the intensive care unit. All patients had blunt trauma. There was no patient with perforating bowel injury or open fractures greater than second degree with major contamination. Eleven patients survived, and one patient died because of uncontrollable intracranial pressure after blunt brain injury. Possibly because of the extremely high ISS of the studied patient group, the remaining 11 patients all developed sepsis according to the criteria of bone in most cases followed by a form of multiple organ failure, usually pulmonary failure, which resulted in a long duration of respirator therapy with a mean of 29 ventilator days. No myocardial infarction occurred within the first 48 hours as confirmed by electrocardiogram evaluation. Patients’ characteristics are summarized in Table 3.

TNFα and IL-8 Production of Whole Blood Cultures After LPS and PGN Stimulation

LPS- or PGN-dependent cytokine production of blood samples in vitro can be assumed as a marker for the immune response in vivo during the respective infection. To evaluate the potential of trauma patients to cope with gram-positive or gram-negative bacteria, we analyzed the cytokine production of blood samples from these patients after stimulation with LPS and PGN. Ex vivo TNFα production after LPS stimulation was significantly reduced in blood samples collected from severely injured patients within 48 hours after trauma in comparison with those in samples from healthy volunteers.
Similarly, TNFα production upon in vitro stimulation with PGN derived from gram-positive bacteria was significantly lower in blood cultures from trauma patients in comparison with those from healthy donors (Fig. 1A). IL-8 synthesis showed a greater variance and was not significantly lower in the group of severely injured patients after neither LPS nor PGN stimulation, although the median values were lower in trauma patients after both stimuli (Fig. 1B). TNFα and IL-8 production was barely detectable in unstimulated blood samples from both trauma patients and healthy volunteers, with no differences between groups (data not shown).

The reduced TNFα liberation of the whole blood cultures after trauma cannot be attributed to a lower amount of monocytes. The amount of monocytes (both total number and percentage of leukocytes) after trauma is not different than the respective values of healthy volunteers (793 ± 533 monocytes/μL in trauma patients vs. 452 ± 116 monocytes/μL in healthy volunteers, both 7% of total leukocytes).

**TLR2 Expression on Human Monocytes After Trauma**

Response of human monocytes upon gram-positive stimuli such as PGN depends on the expression of TLR2. The MFI of TLR2 on the cell surface of monocytes was slightly but significantly reduced within 48 hours after injury in comparison to that of healthy donors (p = 0.032; Table 4). A lower expression of TLR2 on monocytes could be considered as a sign for a disturbed immune response against gram-positive bacteria. Therefore, we analyzed the data with respect to a possible correlation with the onset of gram-positive sepsis and the degree of TLR2 expression after injury. We observed five gram-positive and seven gram-negative septic events. The focus of septic disease was either pneumonia or a catheter-associated infection. The onset of sepsis was mainly at the end of the first week after trauma (Table 1). Patients with gram-positive sepsis in the later course had a mean TLR2 expression of 573 (±74), whereas those with gram-negative sepsis had a TLR2 expression on monocytes of 554 (±55), respectively. Differences in TLR2 expression were not significant. At least on the basis of this small sample size, no context between decreased TLR2 expression in the early phase after trauma and the development of specific septic complications could be demonstrated.
CD14 and TLR4 Expression on Human Monocytes After Trauma

Response and signaling of human monocytes upon LPS from gram-negative bacteria depends on the presence and function of both CD14 and TLR4. However, despite reduced TNFα production upon LPS stimulation after severe injury, we did not observe a downregulation of either CD14 or TLR4. CD14 remained completely unchanged, and TLR4 expression did not increase even slightly but statistically not significantly after severe injury (Table 4). Differences in TLR4 expression between those patients with gram-positive sepsis and those with gram-negative sepsis in the later course were not observed (MFI TLR4: 445 ± 72 for those with gram-positive sepsis vs. 446 ± 37 gram-negative sepsis).

Influence of Primary Surgical Intervention on TLR Expression

Because TLR2 and TLR4 expression has been reported to be decreased after elective gastrointestinal surgery,14 we further analyzed the expression of these receptors in dependence of the extent of initial surgery. Five of the patients could be primarily treated without surgical intervention, whereas the majority needed primary surgical therapy. This consisted of damage control surgery for abdominal bleeding control in one case and primary stabilization of unstable fractures by external fixation in three patients; three patients needed primary stabilization of fractures and abdominal bleeding control. In alignment with the damage-control surgery principle, all additional necessary procedures were postponed until the patients’ general situation stabilized. There was no difference in either TLR2 or TLR4 expression between those patients treated conservatively (TLR2: 531 ± 73, TLR4: 447 ± 45) and those with primary surgery (TLR2: 587 ± 46, TLR4: 444 ± 35).

Correlation Between TLR Expression and Ligand-Dependent Response After Trauma

Because both TLR2 surface expression and the TLR2-ligand-dependent TNFα synthesis were reduced in trauma patients, we analyzed the data for a possible correlation of the two observations. Generally, the correlation between receptor expression and cytokine production revealed only two statistically significant correlations (Table 2). We found a statistically significant negative correlation between TLR2 and TLR4 expression. In addition, TLR2 expression inversely correlated with PGN-induced TNFα synthesis, meaning a low TLR2 expression is associated with a high PGN-induced TNFα production. This fact definitively rules out that a downregulation of the TLR2 mechanismically contributes to the decreased PGN-stimulated TNFα liberation of monocytes from trauma patients.

HLA-DR Expression in Monocytes After Trauma

HLA-DR expression on monocytes represents an established marker for the disturbed immune function after severe injury. To compare TLR expression with other markers of monocytes activation, we analyzed HLA-DR expression on the surface of monocytes from trauma patients in comparison to those from healthy volunteers. HLA-DR expression of monocytes in whole blood of severely injured patients (464 ± 41 channels) was significantly diminished compared with the appropriate values of healthy volunteers (664 ± 33 channels). There was no significant correlation between monocytes’ HLA-DR expression with either TLR2 or TLR4 expression (data not shown).

DISCUSSION

In this study, we demonstrated a reduced cytokine synthesis of whole blood culture from trauma patients both after TLR2- and TLR4-dependent stimuli. However, we observed a decrease of TLR2 surface expression, whereas TLR4 remained unchanged. In addition, we were not able to demonstrate a context between TLR expression and TLR-dependent response. This suggests regulation of the hyporesponsiveness to gram-positive and gram-negative stimuli in terms of TNFα production in a TLR receptor-independent manner.

There exist a variety of recent reports in the literature with conflicting results on surface or mRNA expression of TLR2 and TLR4 in situations of an acute inflammatory response with and without infection. In contrast to our results, Adib-Conquy et al.3 report a reduced expression of TLR4 in severely injured patients early after trauma, whereas TLR2 remained unchanged in their study. In addition, they found a lower responsiveness to TLR4-dependent stimuli such as LPS, whereas the cytokine synthesis after stimulation with gram-positive bacteria as a TLR2-dependent stimulus was not altered.3 In contrast, another study with trauma patients shows a downregulation of both TLR2- and TLR4-positive monocytes.15 Although the degree of injury and the time frame of sample collection after trauma were the same in our study and in the latter reports, there are two possible explanations for these conflicting findings. First, the patients of Adib-Conquy et al. had a high mortality because of the sequelae of severe brain injury, suggesting that this injury pattern predominated in the investigated patients. The injury pattern of our patients was not dominated by severe blunt brain injuries as is indicated by a mean Abbreviated Injury Scale brain score of 2 ± 2.1 points. Possibly more important is the fact that we used whole blood lysing technique for analyses of TLR expression, without any further manipulation, whereas the other studies analyzed mononuclear cells after ficoll gradient centrifugation. It has been reported that human monocytes downregulate TLR4 mRNA after ficoll gradient separation and subsequent culture without any other stimuli.16 In addition, the importance of serum components in the regulation of monocytes’ function has been described by Majetschak et al.17 It could be shown that isolated monocytes from trauma patients in the absence of patient serum revealed only a minor suppression of LPS-dependent TNFα synthesis, whereas the impaired cytokine-production was more promi-
nent when monocytes were cultured with patient’s serum.17 In addition, in this and other studies, it could be demonstrated that the reduced cytokine synthesis after trauma can be at least partly attributed to a cytokine-inhibitory capacity in the sera of these patients. Therefore, the differential results between analyses with whole blood cultures and isolated mononuclear cells may be caused by the missing effects of serum components in the latter studies. In addition, interaction between different cells in both isolated peripheral blood mononuclear cell and whole blood cultures are known to cause relevant changes in the immune response of a whole organism. Of special interest in this context are the so-called regulatory T cells (Tregs), which occur in small numbers but are known to regulate the immune response toward a counterinflammatory status preventing the development of a TH-1 type immune response. So, an increase in the number of Tregs in human patients with severe sepsis.18 In addition, Tregs have also been identified as crucial regulators of the systemic inflammatory response after burn injury.19 In general, it may be speculated that studies with whole blood cultures rather than isolated cells could be more suitable to reflect the situation in the patient.

TLR expression has also been analyzed for patients undergoing cardiac surgery with cardiopulmonary bypass, which is known to cause a similar sequence of changes in the immune response as observed after trauma.20,21 In these patients, a very rapid and short-lasting downregulation of both TLR2 and TLR4 expression on monocytes has been demonstrated, which is followed by an upregulation of both TLRs on the first day after surgery.22 Reports about TLR2 and TLR4 expression on circulating leukocytes in septic patients are similarly conflicting. Although Haerter et al.23 demonstrated an augmented surface expression of TLR2 and TLR4 on both isolated neutrophilic granulocytes and monocytes of septic patients, Calvano et al.24 found only TLR4 to be upregulated and unchanged TLR2 expression on monocytes. Armstrong et al.25 found only an upregulated TLR4 mRNA expression without a significant change of surface expression in monocytes from septic patients. However, in the same study TLR2 was upregulated both on the levels of mRNA and protein expression.25

There is a growing body of evidence about the role of TLRs in the immune response after burn injury. In a mice model of burn injury, both TLR2- and TLR4-dependent response of spleen cells are augmented, which represents a contrary regulation of the immune response to the one described in this study in human monocytes after blunt trauma. However, also in the murine burn model there was not any hint for a regulation of the changed immune response by changes of TLRs because the surface expression of TLR2 and TLR4 was not influenced by the burn injury.26

Finally, on the basis of the actual literature, a clear statement about the regulation of TLR2 and TLR4 is possible for neither inflammatory states without infection such as trauma or cardiac surgery nor inflammation with infection such as sepsis. The conflicting data may raise speculation that a regulation of TLR expression is not relevant for the responsiveness of, e.g., monocytes in pathophysiologic situations. Indeed, we did not find any positive correlation between the receptor expression and the cytokine response. In fact, TLR2 expression after trauma was negatively correlated with the TLR2-dependent TNFα liberation. Possibly, signaling events downstream of the receptor are modulated in these pathophysiologic situations. Because TLR2 and TLR4 share a common signaling pathway that includes the formation of an intracellular complex of IRAK-1, IRAK-4, and MyD88, this complex could be a candidate for regulating processes. In fact, a new member of the IRAK family has been recently discovered, IRAK-M, that is exclusively expressed in monocytes and macrophages.27 This protein exerts an inhibitory function on the LPS-activated TLR4 complex.28 Human monocytes rendered tolerant to endotoxin in vitro showed a reduced activity of the IRAK-129 accompanied by an induction of IRAK-M mRNA.30 Interestingly, also in monocytes from septic patients, which are known to show a similar hyporesponsiveness to endotoxin, an increased expression of IRAK-M could be detected.30 Although the final experimental proof up to date is still missing, the enhanced expression of IRAK-M could explain the reduced responsiveness to endotoxin independently of a change in TLR expression. Contrary, results in a mice burn injury model observed unchanged levels of IRAK-M despite an augmented TLR4-dependent response. In this study, an involvement of p38 MAPK was suggested as regulatory kinase.31

TLR2-dependent ligand recognition and signaling on monocytes or macrophages also requires the coexpression of TLR6. The expression of TLR6 has been described on human blood monocytes and monocyte-derived dendritic cells at low levels.11 In addition, TLR6 expression has been identified as crucial receptor for PGN-dependent TNFα secretion.11 Little is known about the regulation of TLR6 in human monocytes in pathophysiologic situations. It cannot be automatically assumed that TLR2 and TLR6 are regulated in the same way. In contrast, in a mice model of systemic Salmonella infection, TLR2 is upregulated, whereas TLR6 expression decreases during the time.32 Because no data about TLR6 regulation after trauma or sepsis in humans are available, it remains speculative whether TLR6 downregulation is involved in the reduced PGN-response that we observed in our trauma patients.

In summary, we describe a reduced immune response to both TLR2 and TLR4 ligands without any clear evidence for a regulation on the level of the receptors itself. Despite their crucial role as receptors for stimuli of the innate immune response, TLRs seem not to be involved in regulatory processes of the immune response after trauma. Therefore, TLR analysis in addition to the expression of HLA-DR probably does not contribute to a more sophisticated characterization of monocytes functions after trauma.
ACKNOWLEDGMENTS

We thank Mrs. B. Nyadu for her brilliant technical assistance.

REFERENCES


B-Type Natriuretic Peptide Levels May Be Elevated in the Critically Injured Trauma Patient Without Congestive Heart Failure

David Stewart, MD, Kenneth Waxman, MD, C. Alan Brown, MD, Rob Schuster, MD, Lynn Schuster, MSN, Eva Marie Hvingelby, MSN, Kelly Kam, RN, and Salvador Becerra

Background: Rapid diagnosis of congestive heart failure (CHF) is essential to treatment. B-type natriuretic peptide (BNP) is a neurohormone secreted by the heart in response to fluid overload and has been shown to be elevated in medical patients with left ventricular dysfunction. However, BNP has not been evaluated in the critically ill patient with trauma.

Methods: Trauma patients of at least 18 years of age with an expected intensive care unit stay of at least 24 hours were studied. Patients had BNP measurements at admission and at 24 hours and 48 hours. Echocardiography was performed within 48 hours of admission. CHF was determined by echocardiographic findings of systolic or diastolic dysfunction. Elevated BNP levels were defined as those greater than 100 pg/mL. A Fisher’s exact test was performed to determine whether a relationship between BNP levels and echocardiographic findings existed. Linear correlation was used to determine whether BNP correlated with echocardiographic findings and initial Glasgow Coma Scores.

Results: Fifty patients were included in the analysis. There was no relationship between elevated BNP levels and echocardiographic evidence of CHF (p = 0.149). There was no threshold value above which CHF was present. There were 28 patients with head injuries, and no relationship between BNP levels and CHF could be found (p = 0.432) in this group.

Conclusion: Our data show no association between BNP and CHF in the critically ill patient with trauma. BNP levels may be elevated in patients with head injuries without echocardiographic evidence of CHF.

Key Words: B-type natriuretic peptide, Echocardiography, Heart failure, GCS.

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Nearly 500,000 Americans are diagnosed with congestive heart failure (CHF) each year, and over 5 million people in the United States live with this disease. Rapid, accurate diagnosis of heart failure is essential because misdiagnosis may be fatal. However, clinical diagnosis may be difficult because the signs and symptoms of CHF are similar to chronic obstructive pulmonary disease, atelectasis, and pneumonia. B-type natriuretic peptide (BNP) is a neurohormone primarily secreted by the cardiac ventricles in response to pressure overload and volume expansion. Levels of BNP have been shown to be elevated in patients with left ventricular systolic and diastolic dysfunction. In addition, a study by Maisel et al. showed that rapid measurement of BNP was useful in establishing or excluding a diagnosis of heart failure in medical patients with dyspnea. However, these studies did not involve surgical or trauma patients.

The usefulness of BNP in diagnosing heart failure in the critically ill trauma patient has not been studied. Dyspnea, hypoxia, and tachypnea are common problems in trauma patients, and a timely diagnosis of the cause is essential. Treatment of heart failure in these patients needs to be instituted immediately and differs greatly from the treatment of other problems such as atelectasis, pulmonary contusion, pneumothorax, hemorhox, pneumonia, pulmonary embolus, fat embolus, reactive airway disease, or pleural effusions. Echocardiography is considered the gold standard for the detection of heart failure, but it is expensive and may not always be immediately accessible. No information exists to determine whether an elevated BNP level correlates with heart failure in trauma patients. BNP is also present in the brain. No data exist to determine whether systemic BNP levels are elevated after brain injury.

We therefore conducted a prospective study to evaluate BNP measurements in critically ill trauma patients, and to observe whether a correlation with a diagnosis of heart failure determined by echocardiography could be made. We also wished to determine whether BNP levels were increased after brain injury, independently of CHF.

METHODS

This was a prospective trial consisting of 50 trauma patients over the age of 18 who were admitted to the intensive care unit (ICU) with an expected ICU stay of at least 24 hours. All patients were evaluated at admission by the trauma care unit (ICU) with an expected ICU stay of at least 24 hours were studied. Patients had BNP measurements at admission and at 24 hours and 48 hours. Echocardiography was performed within 48 hours of admission. CHF was determined by echocardiographic findings of systolic or diastolic dysfunction. Elevated BNP levels were defined as those greater than 100 pg/mL. A Fisher’s exact test was performed to determine whether a relationship between BNP levels and echocardiographic findings existed. Linear correlation was used to determine whether BNP correlated with echocardiographic findings and initial Glasgow Coma Scores.

Results: Fifty patients were included in the analysis. There was no relationship between elevated BNP levels and echocardiographic evidence of CHF (p = 0.149). There was no threshold value above which CHF was present. There were 28 patients with head injuries, and no relationship between BNP levels and CHF could be found (p = 0.432) in this group.

Conclusion: Our data show no association between BNP and CHF in the critically ill patient with trauma. BNP levels may be elevated in patients with head injuries without echocardiographic evidence of CHF.

Key Words: B-type natriuretic peptide, Echocardiography, Heart failure, GCS.

J Trauma. 2007;63:747–750.
service. Medical history, including heart failure, chronic obstructive pulmonary disease, coronary artery disease, hypertension, diabetes, cardiomyopathy, and medications for these conditions were recorded. In addition, injuries and mechanisms were noted, as were Injury Severity Scale (ISS) scores. Consented patients had BNP measurements at admission and at 24 hours and 48 hours after admission. These patients then underwent a transthoracic echocardiogram within 24 hours of admission. The same cardiologist (C.A.B.) interpreted all echocardiography studies; the individual who interpreted the studies was blinded to BNP results. CHF was determined by echocardiography findings of systolic or moderate to severe diastolic dysfunction (Table 1). BNP levels were also compared between patients with and without brain injuries. Linear correlation and regression analysis was performed between admission Glasgow Coma Scores (GCCs) and the highest BNP level measured. Data collected included mortality, severity of injuries (ISS score), mechanism of injury, length of hospital stay, and data from invasive hemodynamic monitoring if it was clinically indicated.

For the purpose of this study, systolic heart failure was defined as an ejection fraction less than 40%. Diastolic heart failure was diagnosed by applying the Canadian Consensus Guidelines to measure transmitral flow velocities (TMF) and pulmonary venous flow velocities (PVF). The diagnosis of diastolic heart failure by TMF included an E/A ratio (the ratio of peak early diastolic transmitral flow velocity to peak atrial systolic TMF) of <1 or >2, and a deceleration time of early diastolic TMF of at least 150 milliseconds. PVF measurements of diastolic failure included S/D ratios (peak systolic PVF to peak diastolic PVF) of <1 and elevated peak atrial systolic PVF reversal velocities ≥0.35 m/s.

A Fisher’s exact test was performed to compare the presence or absence of CHF by echocardiography with normal and elevated BNP levels. Additionally, linear correlation and regression analysis between BNP levels and ejection fraction as measured by echocardiography was performed. Linear correlation and regression analysis was also performed between BNP levels and ICU and hospital length of stay.

### RESULTS

Fifty patients were included in the analysis. These patients included the first 50 trauma patients who consecutively met the inclusion criteria and for whom consent could be obtained. There were 37 men (74%) and 13 women (26%) in this study with a mean age of 50 years (SD ± 23.8). There were 20 patients (40%) with evidence of CHF as determined by echocardiography. The mean age of the patients with CHF was 61 years (SD ± 27.4 years), whereas the mean age for patients with normal findings on echocardiograms was 30 years (SD ± 18.9 years). There were 23 patients (46%) with elevations in BNP levels during their hospital stay as defined by a value greater than 100 pg/mL on at least one of three samples. Five of these patients had normal initial BNP levels but on subsequent samples had elevated BNP levels. This group had a mean age of 61 years (SD ± 23.4 years), whereas the mean age of patients with consistently normal BNP levels was 40 years (SD ± 20.2 years).

There was no significant relationship between BNP levels and echocardiography results (r = 0.149). The sensitivity of BNP for detecting heart failure was 0.75, with a specificity of 0.73. The positive predictive value of a BNP level >100 pg/mL for diagnosing heart failure was 0.65, whereas the negative predictive value for a BNP level <100 pg/mL was 0.81. There was no significant correlation between BNP levels and ejection fraction as measured by echocardiography (R² = 0.001) as demonstrated in the scatter plot diagram of ordinary least squares in Figure 1. All BNP levels in patients with evidence of CHF by echocardiography were evaluated and there was no minimum value above which CHF was invariably present. Eight patients had normal BNP levels but had evidence of heart failure on echocardiography; two of these patients had undetectable BNP levels.

Elevated BNP levels did not correlate with the length of hospital stay (mean stay = 8.1 days; R² = 0.022) or ICU length of stay (mean stay = 3.8 days; R² = 0.019). BNP levels had no correlation with ISS scores (R² = 0.024). There was only one death in the 50 patients analyzed. This patient had significant pre-existing liver disease and experienced a severe intracranial hemorrhage from a motor vehicle colli-
The patient’s family withdrew care because of the severity of his brain injury and his poor prognosis.

No patient in the study had a pulmonary artery catheter placed. Four patients had central venous pressure monitoring through a central line. Two of these patients had BNP levels <100 pg/mL and had no evidence of CHF by echocardiography. The other two patients had evidence of diastolic dysfunction by echocardiography. One of these patients had a mean central venous pressure (CVP) of 6 with a mean BNP of 98 pg/mL. The other patient had a mean CVP of 13 with a mean BNP of 278 pg/mL.

Of the 50 patients in this study, 28 had an intracranial hemorrhage detected by computed tomography scan. The mean age of these patients was 58 years (SD 26 years). Of these 28 patients, 18 had elevated BNP levels and 15 had abnormal echocardiography results consistent with CHF. There was no significant relationship between BNP values and echocardiography findings of CHF (p = 0.432). There was no significant correlation between BNP levels and ejection fraction among patients with head injury (R² = 0.086). There was also no correlation between BNP levels and overall length of hospital stay (R² = 0.02) or ICU length of stay (R² = 0.024). There was no minimum BNP value above which echocardiographic evidence of CHF was always present in this group. Of the patients with head injury, seven had normal findings on echocardiograms but had elevated BNP levels (mean BNP level of 182 pg/mL). There was no correlation between the highest BNP level in patients with head injury and GCSs at the time of admission (R² = 0.006).

**DISCUSSION**

BNP is a neurohormone secreted primarily by the cardiac ventricles in response to increased wall tension. Numerous studies have shown that BNP levels cannot only identify the presence of CHF in medical patients, but can also correlate with the severity of CHF and prognosis. A possible role for BNP in assessing the trauma patient for CHF has not been studied. Our data indicate that BNP values do not have the same diagnostic accuracy as they do in emergency room patients with medical disorders. In this study, patients often had echocardiographic evidence of CHF with normal BNP levels. Conversely, elevated BNP levels did not always indicate an abnormal echocardiography result.

Few studies have attempted to define the normal value of BNP, and therefore to find the cutoff value that allows the best balance between sensitivity and specificity while maintaining cost effectiveness. There is evidence that a single cutoff value cannot be chosen for all patients, as age, gender, body mass index, and race seem to affect the normal range of BNP. Several studies have shown that BNP values <100 pg/mL are very specific for normal heart function, and the threshold value for systolic or diastolic failure is less certain. In our study, a cutoff of 100 pg/mL was chosen to have the greatest sensitivity in detecting heart failure. Although there is a lack of cost-effectiveness data supporting any single cutoff value, using 100 pg/mL errrs on the side of increased sensitivity to not miss the diagnosis of CHF. Five patients in this study had normal initial BNP values followed by elevated subsequent BNP levels. This indicates that serial BNP measurements may have value in monitoring patients for heart failure, although in this study the elevated subsequent BNP levels were not clinically significant as the patients had no evidence of CHF on echocardiography.

In medical patients presenting with acute symptoms of heart failure, BNP levels are not only useful for diagnosis but can also correlate with the severity of heart failure (ejection fraction) and prognosis. In this study, BNP levels did not correlate with echocardiographic findings of heart failure, nor was there any correlation with ejection fraction. There was no threshold value of BNP above which all patients had echocardiographic evidence of heart failure. There was also no predictive value between BNP and length of hospital or ICU stay and no relationship between BNP and 30-day mortality. The reason for this difference in the significance of BNP values between medical and surgical patients is not known at this time. It has been shown that hypovolemia can cause low levels of BNP, whereas others have postulated that the systemic inflammatory response syndrome state of multi-

![Fig. 1](image-url). A plot of ordinary least squares with the y axis representing “ejection fraction” as a percentage and the x axis representing “BNP values” in picograms per milliliter.
system trauma can produce cardiac ventricular dilation and vasodilatation with a subsequent elevation of the ejection fraction. These changes may explain why many patients in this study were observed to have normal or slightly elevated ejection fractions with normal or low BNP levels. What changes occur in the heart’s endocrine function because of multisystem injury requires further study.

Transesophageal echocardiograms were performed in this study because of their noninvasive nature and well-established consensus criteria for determining the presence of CHF. Transthoracic echocardiograms would have been another option for imaging the heart. Although more sensitive for determining the presence of thrombus in the left atrial appendage, they are not significantly more sensitive at detecting CHF compared with transesophageal echocardiograms to justify their increased risk. Transesophageal echocardiograms require sedation, which can be contraindicated in the critically injured trauma patient. All of the echocardiograms used in this study were considered by the cardiologist to be of good quality so that statistical analysis would be unaffected by technical considerations in obtaining echocardiograms.

Only 4 of the 50 patients in this study had penetrating injuries, all of which were stab wounds to the abdomen. Five of the 50 patients, including 2 of the 4 stab wounds, underwent emergent exploratory laparotomies, all of which revealed injuries. The remainder of the patients had blunt mechanisms of injury, with 60% of the patients having multiple injuries of different body regions. Approximately 40% of the patients in this study had chest trauma as indicated by at least one thoracic bony fracture. A larger study may have incorporated more patients with penetrating trauma. However, blunt mechanisms of injury, including isolated head injuries and significant chest injuries, are well represented in this study.

BNP is also produced in the brain, and seven patients in this study had head injuries with normal findings on echocardiograms but with elevated BNP levels. This may be because of trauma causing a systemic release of BNP from the brain rather than from the heart. BNP did not predict heart failure or correlate with ejection fraction, GCS, or hospital length of stay in this subgroup. Therefore, BNP was not a useful marker for CHF or patient outcome among patients with head injuries.

**CONCLUSION**

BNP values do not have the same significance or prognostic value in trauma patients as they do in medical patients.

**REFERENCES**

Continuous Hemofiltration in Hyperthermic Septic Shock Patients

David Pestaña, PhD, Elena Casanova, MD, María J. Villagrán, MD, Carolina Torno, MD, Hanna Pérez-Chrzanowska, MBBS, Javier Redondo, MD, María V. Caldera, MD, and Concepción Royo, MD

Background: Severe hyperthermia commonly accompanies septic shock. High body temperature in absence of infection activates the inflammatory response and is associated with a high mortality. Three years ago, our hypothesis that sustained fever is harmful in septic shock led us to the development of a protocol aiming at decreasing hyperthermia (≥39.5°C) by means of hemofiltration when the patients did not respond to antipyretics. We present a report of temperature and hemodynamic changes and the outcome of 19 consecutive hyperthermic septic shock patients with multiorgan system failure and compare them with a historical similar group of patients in whom hyperthermia was not treated with hemofiltration.

Methods: Depending on renal function, patients were treated with continuous low-flow hemofiltration (n = 8) or hemodiafiltration (n = 11). Core temperature was registered every hour. A hemodynamic index (HI) was defined (mean arterial pressure to noradrenaline dose) and used during the first 24 hours to describe the patients' hemodynamic profile by means of its percent variation starting 6 hours before instituting the hemofiltration.

Results: The patients' temperature decreased linearly from 39.8°C ± 0.5°C before hemofiltration to 37°C ± 1.2°C after 24 hours of treatment (p < 0.001). The HI decreased significantly from −6 hours to the onset of hemofiltration (p = 0.002) and increased significantly after 24 hours (p = 0.008). Twenty-eight-day mortality was 32% (6 of 19) when compared with 100% (11 of 11) in the historical group (p < 0.001).

Conclusions: Continuous low-flow hemofiltration decreased body temperature and vasopressor requirements in hyperthermic septic shock patients. The mortality was unexpectedly low.

Key Words: Hemofiltration, Hyperthermia, Sepsis.

Table 1 Hemofiltration Group: Demographics, Site of Infection, and Severity Scores Data

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<td>39.8</td>
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<td>40</td>
<td>—</td>
<td>159</td>
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</tbody>
</table>

In patients 7 and 8, hydrocortisone was withdrawn after 1 day of treatment. HI, Hemodynamic index (mean arterial pressure/noradrenaline dose) at the moment of institution of hemofiltration; RD, renal dysfunction at the moment of institution of hemofiltration; Cort., Corticoids; APC, activated protein C; Temp., temperature (°C) at the moment of institution of hemofiltration; Hours pre-HF, hours with hyperthermia (core temperature ≥39.5°C) before the institution of hemofiltration; HF time, duration of hemofiltration (h); Survival, hours of survival after the diagnosis of hyperthermic septic shock in those patients who died within the first 28 days.

(Gambro, USA) with an AN69 polyacrylonitrile filter (Hospital, France) was used. The hospital’s Ethics Committee approved the procedure. The treatment was explained to the next of kin of the patients, and verbal consent was obtained. Sterile bicarbonate-buffered solutions at room temperature were used as dialysate or reinfusate fluid. Following our unit’s common practice, blood flow was set at 100 mL/min⁻¹ and ultrafiltrate flow at 1 L/h⁻¹. In case of renal dysfunction (creatinine >2.5 mg/dL⁻¹ or >50% increase in case of previous renal dysfunction), continuous hemodialysis (dialysate flow 1 L/h⁻¹) was also provided (continuous venovenous hemodiafiltration [CVVHD]). Fluid balance was adjusted by the physician in charge of each patient aiming at systolic volume variation ≤10% (the unit’s common clinical practice based on the PiCCO system [Pulsion Medical, Germany]), or a capillary wedge pressure ≥12 mm Hg when the PiCCO was not available. The extracorporeal circuit was heparinized using an individualized anticoagulation regime based on the aPTT ratio from the blood of the filter (target, 1.5–1.9). Cartridges were changed at 48 hours or earlier in case of filter malfunction. CVVH was continued depending on the evolution of the patient (Table 1), independent of the temperature.

The noradrenaline dose was titrated to maintain a mean arterial pressure ≥60 mm Hg. The noradrenaline dose (μg/kg min⁻¹) was used. The diagnosis of septic shock was established, hydrocortisone (50 mg/6 hours), or activated protein C (APC, 24 μg/kg⁻¹ h⁻¹ for 96 hours) were administered in some cases (Table 1). The treatment was explained to the next of kin of the patients, and verbal consent was obtained. The treatment was explained to the next of kin of the patients, and verbal consent was obtained. Hydrocortisone administration was reevaluated at 24 hours, and maintained for 7 days in patients who responded (>25% increase of the HI). APC was not initially available when the above protocol was put into practice. It is likely that some of the earlier patients could have been candidates for its use.

We reviewed 140 consecutive patients admitted to our ICU with criteria of multiorgan dysfunction secondary to infection during the 3 years previous to our study (July 1999 to June 2002, overall mortality rate of 69%). We selected those (control group, n = 11) who presented criteria for hemofiltration according to our protocol, that is, septic shock in those patients who could have been candidates for its use.

None of these patients received renal replacement therapy. We studied the 28-day mortality rate and the time of survival after the diagnosis of hyperthermic septic shock in those patients who died within the first 28 days.

Statistical Analysis

Statistical analysis was performed with the SPSS for Windows system (Release 11.0; SPSS Inc., Chicago, IL). A statistical analysis was performed with the SPSS for Windows system (Release 11.0; SPSS Inc., Chicago, IL). A
Mann-Whitney test was used to compare the quantitative variables between both groups. A one-way analysis of variance with repeated measurements was used to study the variations of the temperature with time. A 95% confidence interval was adjusted by the Bonferroni method. In the hemofiltration group, differences of the percent variation of the HI with respect to the onset of CVVH were evaluated with the Wilcoxon signed rank test. A Kaplan-Meier curve with a log rank test and a Cox multivariate regression model were performed to analyze the differences between groups regarding survival.

RESULTS

Data from the hemofiltration and control groups are presented in Tables 1 and 2. No differences regarding age (\(p = 0.33\)), Acute Physiology and Chronic Health Evaluation II (APACHE II) (\(p = 0.73\)), Sequential Organ Failure Assessment (SOFA) score (\(p = 0.8\)) or HI at the moment of the diagnosis of hyperthermic septic shock (\(p = 0.9\)) were observed between the both groups. All patients had multiorgan system failure involving, at least, the cardiovascular and respiratory systems. In the hemofiltration group hydrocortisone was empirically administered to 15 patients after septic shock was diagnosed, and withdrawn after 24 hours of treatment in two cases (7 and 8) as no hemodynamic improvement was observed after its administration. APC was administered to nine patients. None of the patients in the control group received hydrocortisone or APC. Following our common practice, a tidal volume $\leq 10$ mL/kg (ideal body weight) was used in all cases (both groups).

Renal dysfunction was present in 11 patients in the hemofiltration group, although initially the CVVH was not indicated because of this cause. In all cases the temperature was $\geq 39.5^\circ$C when the patient was included in the protocol. In patient 2, the temperature decreased to $39.1^\circ$C by the time the CVVH actually started. A linear decrease of temperature (from $39.8^\circ \pm 0.5^\circ$C before hemofiltration to $37^\circ \pm 1.2^\circ$C after 24 hours of treatment, \(p < 0.001\)) was observed (Fig. 1). Temperature dropped to $\leq 38^\circ$C in less than 24 hours in all but two patients (7 and 17). Temperature did not vary in the control group (\(p = 0.98\)).

In the hemofiltration group, the HI decreased significantly from -6 hours to the onset of CVVH (\(p = 0.002\)) and increased significantly at $+18$ hours and $+24$ hours (\(p = 0.043\) and 0.008 respectively). In the case of patient 17, a laparotomy as a result of peritonitis secondary to a suture failure was performed after 18 hours of hemofiltration. CVVHF was maintained for 36 hours after the relaparotomy. Hemodynamic data from this patient have not been included as the surgical problem was not resolved at the moment when hemofiltration was instituted. The 28-day survival rate was 68% (13 of 19) when compared with 0% (11 of 11) in the control group. The mean survival time (limited to 28 days) was $505 \pm 59$ hours after the institution of hemofiltration, compared with $38 \pm 29$ hours in the control group (\(p < 0.001\) in respect to time 0).

![Fig. 1. Time course of core temperature (mean ± SD) in the hemofiltration group after the institution of hemofiltration (time 0). \(p < 0.001\) in respect to time 0.](image_link)
may be present in up to 51% of cases of septic shock, and upon different pathogenic mechanisms. Acute renal failure sepsis independent of renal replacement needs.”

Continuous venovenous hemofiltration for the treatment of state that “there is no current evidence to support the use of temperature and with the literature. The presence of hyperthermia (temperature was rarely monitored and never used as a study endpoint. In fact, most of the studies even use heaters to prevent the cooling of the patient. To our knowledge, the only study in which an effect of the temperature on the outcome is apparent was published recently by Yekebas et al. In a porcine model which an effect of the temperature on the outcome is apparent. An additional explanation for the benefits of CVVH is the reduction of the core temperature in severely hyperthermic patients. Preconditioning with thermal stress reduced organ damage and enhanced survival in a model of sepsis, possibly because of the induction of heat-shock proteins, which are part of a natural protection mechanism. Lung edema, however, was accentuated by increased temperature in rabbits subjected to injurious ventilator settings. Timing of hyperthermia in respect to the injury seems crucial for the efficacy of the stress response in providing protection. In our patients, high temperature appeared after the injury (surgery and infection) had become established, so our clinical model would resemble that of the latter study. Besides, the increase in cardiac output, oxygen consumption, CO₂ production and energy expenditure that accompany high fever may be badly tolerated by patients with a limited cardiopulmonary reserve, and a core temperature >39.5°C was included by Bellomo and Ronco among their criteria for initiating continuous renal replacement therapy in the ICU. In absence of infection, sustained high temperature is associated with the heat stroke syndrome, characterized by an intense inflammatory response and high mortality. A “critical thermal maximum” (temperature of 41.6°–42°C maintained for 45 minutes to 8 hours) has been defined in marathon runners, healthy subjects and oncologic patients, although the onset of the inflammatory response (“subclinical critical thermal maximum”) occurs at lower temperatures. An increase in circulating endotoxin has been observed in experimental and human studies when temperature rose to 40°C.

An effect of lowering core temperature by means of hemodialysis or hemofiltration on hemodynamic variables has been reported previously, although in none of these studies were hyperthermic septic shock patients included. When CVVH has been evaluated in ICU patients, temperature was rarely monitored and never used as a study endpoint. In fact, most of the studies even use heaters to prevent the cooling of the patient. To our knowledge, the only study in which an effect of the temperature on the outcome is apparent was published recently by Yekebas et al. In a porcine model of pancreateogenic sepsis, the authors evaluated the impact on outcome and immunologic derangements of different modalities of CVVH modifying the flow and the period of filter changes. Both the initial elevation of the body temperature and hyperthermia in the late course of the experiment were ameliorated by CVVH, especially when high volume was studied.

The beneficial effects of hemofiltration on survival were still present when the administration of hydrocortisone and APC were taken into account (hazard ratio, 0.14; CI 95%, 0.03–0.7; p = 0.017).

No adverse effects related to hemofiltration (hemodynamic, hemorrhagic, infection of the central venous access) were observed.

**DISCUSSION**

The introduction of the CVVH was accompanied by a reversal of the worsening hemodynamic trend in hyperthermic septic shock patients and was associated with an unexpected increase in the survival rate (68%) when compared with our previous experience (0% survival in similar cases) and with the literature. The presence of hyperthermia (temperature ≥39.5°C) for, at least 6 hours in a historical group of septic shock patients (11 of 140 patients detected in a 3-year period) was associated with a 100% mortality.

The potential benefits of hemofiltration as part of the management of sepsis remain controversial. Recent guidelines for management of severe sepsis and septic shock state that “there is no current evidence to support the use of continuous venovenous hemofiltration for the treatment of sepsis independent of renal replacement needs.”

Hypothetically, CVVH may be useful in sepsis by acting upon different pathogenic mechanisms. Acute renal failure may be present in up to 51% of cases of septic shock, and an early introduction of hemofiltration might improve its outcome. According to our definition of renal dysfunction, 11 patients fulfilled these criteria and might have benefited from CVVH(D)F.

The elimination of inflammatory mediators through a convective and adsorptive mechanism has been studied in the last years in experimental and clinical settings. Animal studies have shown that CVVH improves hemodynamic and pulmonar...
used and filters were changed frequently. The normalization of temperature, although not formally studied, coincided with a better hemodynamic profile and survival, even though the authors attribute these results to an attenuation of the sepsis-related immunoparalysis. The authors also raise the question of whether the results could be caused by an improvement in splanchnic perfusion, protecting the bloodstream from bacterial invasion. This final remark coincides with our hypothesis concerning the potential beneficial effects of CVVH in hyperthermic human sepsis.

The present study has some important limitations as it is noncontrolled, and many unknown confounding factors may be present. Recent advances in the treatment of septic shock (small-dose corticoids and APC) may have contributed to a better outcome in some of the patients. However, these new therapies do not fully explain the dramatic reduction in mortality (from 100% to 32%) observed in our study. Published trials attribute an absolute decrease in mortality of 14% to treatment with corticoids and 6% to the use of APC, and a synergistic effect on decreasing mortality has not been demonstrated for concurrent use of both agents.\(^{32,33}\) According to the multivariate regression model, the risk of death was still 7.2 times higher in the control group after adjusting for the administration of both drugs. Clearance of inflammatory mediators by means of hemofiltration might have contributed to the better outcome of our patients. Based on results from previous clinical studies, this hypothesis however seems unlikely, as low-flow hemofiltration has to date not proved valuable in this setting, and in fact has been excluded from recent guidelines. The 6-hour period of severe hyperthermia in the control group was chosen with the intention of including only patients with sustained hyperthermia who did not respond to antipyretics, and to exclude patients with only a spike of fever. An arbitrary cutoff point had to be defined. As can be seen in Table 1, the mean time of hyperthermia before the institution of HF in the treatment group was 11 hours, although great variability can be observed among the patients. In the early cases, we waited for longer periods of time (more than 24 hours). However, as improvement in the hemodynamic status became more evident, we decided to institute HF earlier. At present, we do not wait more than 3 hours once lack of response to antipyretics is demonstrated. We are aware that many authors would be reluctant to implement such a protocol as the one described in the present article. However, based on our data, we consider that our hypothesis should be tested prospectively. To our knowledge, the first clinical report in which the reduction of tidal volume showed a positive effect on mortality in adult respiratory distress syndrome (ARDS) was also a noncontrolled study,\(^ {34}\) whose conclusions have been validated subsequently and contributed to improve our daily practice.

**CONCLUSIONS**

The presence of sustained (≥6 hours) core hyperthermia (≥39.5°C) in a historical group of septic shock patients was associated with an unacceptable 100% mortality rate. The institution of hemofiltration in severe hyperthermic septic shock patients was followed by a reduction in body temperature and vasopressor requirements and an apparent reduction in the mortality rate. The role of severe hyperthermia in sepsis needs to be reevaluated. Although the recommendation for the use of CVVH in hyperthermic septic shock patients cannot be changed based solely on our study, we consider it to represent a valuable contribution to the discussion of the role of CVVH in the management of sepsis. Temperature should be taken more seriously into account in the future. In view of our results, CVVH is not deleterious, and seems promising in this subgroup of septic patients. Further research in this field might be of interest.

**ACKNOWLEDGMENTS**

We are grateful to Rosario Madero and Belén San José for their help with the statistical analysis.

**REFERENCES**


The Value of Indicated Computed Tomography Scan of the Chest and Abdomen in Addition to the Conventional Radiologic Work-up for Blunt Trauma Patients

Jaap Deunk, MD, Helena M. Dekker, MD, Monique Brink, MD, Raoul van Vugt, Michael J. Edwards, MD, PhD, and Arie B. van Vugt, MD, PhD

Background: Multidetector computed tomography (CT) is more sensitive and specific in detecting traumatic injuries than conventional radiology is. However, still little is known about the diagnostic value and the therapeutic impact of indicated thoracoabdominal CT scan when it is performed in addition to the complete conventional radiologic work-up for blunt trauma patients.

Methods: Clinical and radiologic data from 106 consecutive blunt trauma patients were reviewed. Diagnoses revealed by conventional work-up of the chest, abdomen, pelvis, and thoracolumbar spine were compared with that detected by CT scan of the chest and abdomen. Unexpected findings by CT scan and rejected diagnoses by CT scan were collected. Therapeutic consequences of these diagnoses were determined both theoretically and collected from the medical records.

Results: In 74% (95% confidence interval [CI] 65–82) of the 106 patients, 1 or more diagnoses were demonstrated by chest or abdominal CT scan, whereas they had not been revealed by preceding conventional work-up. This resulted in an actual change of treatment in 34% (95% CI 25–43) of the patients. CT scan of the chest resulted in a change of treatment in 33% (95% CI 23–44) and abdominal CT scan in 16% (95% CI 9–24).

Conclusions: CT scan of the chest and abdomen has a high diagnostic value in the evaluation of blunt trauma patients, when it is selectively performed in addition to the early conventional radiologic work-up. Unexpected pathologic findings are detected by CT scan in the majority of the patients. These findings result in an adaptation of treatment in a substantial number of the patients.

Key Words: Computed tomography, Blunt trauma, Conventional radiography, Value.

abdomen. Exclusion criteria were penetrating injury, unstable hemodynamics, pregnancy, age <16 years, and patients with CT scanning after laparotomy or thoracotomy. Primary survey and secondary survey were performed according to the Advanced Trauma Life Support principles. Conventional radiologic work-up consisted of a supine chest radiograph, abdominal sonography, and cervical spine radiographs. Thoracic or pelvic radiographs were performed depending on the mechanism of trauma and clinical findings. Deviation from the radiologic work-up could be instructed by the senior trauma surgeon in case of hemodynamic instability or unstable cerebral injury. Additional CT scan of the chest or abdomen was requested by the senior trauma surgeon and performed only if certain abnormalities in physical examination or in conventional radiographs were present. These indications for additional CT scan are listed in Table 1.

Abdominal sonography was used primarily to exclude or detect intra-abdominal free fluid. Radiologists or radiology residents with a 24/7 availability performed it. Every operator was well trained by at least a specific ultrasound traineeship.

All CT scans were performed on a four-slice CT scanner (Volume Zoom, Siemens, Earlangen, Germany) with intravenously administered contrast. Transport time to the CT room was approximately 5 minutes.

The information collected from the medical records included patient demographics, mechanism of trauma, intubation status, arterial blood gas analysis, pulse-oxygen saturation, systolic blood pressure, pulse rate, and Glasgow Coma Scale score on arrival at the emergency department. Injury Severity Scores (ISSs) were calculated from the final diagnoses as noted in the medical records.

A senior trauma radiologist who was blinded to the clinical data and the original diagnoses reviewed for this study all conventional radiology and CT scans. Soft tissue and lung window settings of the chest and abdominal CT scan were used as appropriate. Bone window settings were used to evaluate the thoracic and lumbar spine. Radiology of the cervical spine was not taken into account for this study. After re-evaluation, findings on conventional radiography and sonography were compared with CT findings. An unexpected CT “diagnosis” was defined as pathologic findings detected only by CT scan, but not by conventional radiographs or abdominal sonography. Diagnoses on conventional radiology that formed the indication for additional CT scan (Table 1) were not considered unexpected. Intra-abdominal injuries on CT scan were considered as unexpected when sonography showed no free intra-abdominal fluid. When free intra-abdominal fluid was detected by sonography, parenchymal and mesenterial injuries on abdominal CT scan were considered as expected and retroperitoneal injuries or perforations of hollow organs were considered as unexpected.

An excluded diagnosis was defined as a diagnosis that was detected by or highly suspected based on conventional radiology, but rejected by CT scan. Diagnoses by conventional radiography that were subsequently confirmed by CT scan were not taken into account for this study.

The therapeutic value of the CT findings was determined in every patient by two different methods. First, the theoretical change of treatment, defined as the change of treatment dictated by our current trauma protocols, was determined as follows: one senior trauma surgeon decided which therapy would have been necessary based on the current protocols and all clinical data, but without CT findings. This person was blinded for the actually applied therapies. Two months later, the same trauma surgeon randomly evaluated the same cases, but now including the CT findings. The theoretical change of treatment was subsequently determined as the difference between the first and second proposal for therapy. In the second method, we determined the therapeutic changes that had actually been made as a direct result of the CT findings, as noted in the medical records. In both methods of assessing the therapeutic value of CT, we looked at changes in chest-tube placing, mechanical ventilation, laparotomy, thoracotomy, pelvic fixation, spine fixation, changes in care level needed, and additional diagnostic imaging. Results from this study are presented as means and frequencies. Ranges, standard deviations (±SD) or 95% confidence intervals (CIs) are given in parentheses.

### RESULTS

We included 106 consecutive blunt trauma patients for this study. The mean age of the study population was 41 (±19) years. Seventy-one percent of the patients were men. The mean ISS was 25 (range, 1–50). The mean Glasgow Coma Scale score was 10.8 (±5.0). One hundred and two of 106 patients had been hospitalized because of their injuries, 14 (13.2%) of them died during hospital stay, 9 of which as a result of their neurologic injuries. The mechanisms of injury are outlined in Figure 1.

In 63 patients, both chest CT scan and abdominal CT scan were performed in addition to the conventional radiologic work-up. In 28 patients, only additional abdominal CT scan was performed, and in 15 patients only additional chest CT scan. The radiography that was performed in the study population is outlined in Table 2.
Overall, a total of 236 unexpected diagnoses were found by CT scan when compared with the conventional work-up in 78 of the 106 patients (74%, 95% CI 65%–82%). In 28 patients, no unexpected diagnoses were found by CT scan. Chest CT scan revealed a total number of 163 unexpected diagnoses in 62 of the 78 patients (79%, 95% CI 71%–88%), of which 121 diagnoses were located in the chest and 42 in the thoracic spine. Abdominal CT scan revealed 73 unexpected diagnoses in 36 of the 91 patients (40%, 95% CI 30%–50%), of which 49 diagnoses were located in the abdomen, 12 in the bony pelvis, and 12 in the lumbar spine.

In 17 patients, hemoperitoneum was found by abdominal CT scan, whereas this had not been demonstrated by preceding abdominal sonography. In 13 patients, this hemoperitoneum was accompanied by parenchymal or bowel injury. A total of 54 unexpected spine diagnoses were imaged in 29 patients by abdominal or chest CT scan. Twenty-five stable vertebral fractures were unexpectedly found in 14 patients. Ten unstable vertebral fractures were only demonstrated by chest CT scan, not by conventional radiographs. Five vertebral fractures had been classified as stable by conventional radiographs, whereas they were classified as unstable by chest CT scan.

Twelve unexpected diagnoses were found in the pelvis in 10 of the 91 patients by abdominal CT scan. In four patients, the posterior pelvic ring seemed to be fractured, whereas this was not demonstrated by pelvic radiograph. The unexpected diagnoses by chest and abdominal CT scan are outlined in Table 3.

Unexpected Diagnoses

Eighteen diagnoses that had been diagnosed or highly suspected by conventional radiography were subsequently rejected by CT scan in 16 of the 106 patients (15%). The conventional chest radiograph had been highly suspicious for a thoracic aorta lesion in five hemodynamically stable patients, which could be rejected by chest CT scan. Abdominal sonography had detected a hemoperitoneum in five patients, which could not be confirmed by abdominal CT scan. The excluded diagnoses are outlined in Table 3.

Excluded Diagnoses

As theoretically dictated by our protocols, change of treatment would have resulted from the CT findings in 43 of the 106 patients (41%, 95% CI 31%–50%). Treatment actually changed in 36 of the 106 patients (34%, 95% CI 25%–43%) as a direct result of the findings by chest or abdominal CT scan. Chest CT scan resulted in a change of treatment in 26 of the 78 patients (33%, 95% CI 23%–44%) and abdominal CT in 15 of the 91 patients (16%, 95% CI 9%–24%). The changes of treatment actually performed according to CT findings are outlined in Figure 2.

Fourteen chest tubes were placed because of a substantial pneumothorax that was detected by chest CT scan, but not by conventional chest radiograph. One sternotomy was performed because of a tear of the right cardiac ventricle, which had not been suspected by chest radiograph. In five patients, a highly suspected aortic lesion was rejected by chest CT scan and therefore angiography was no longer indicated.

In three patients, aortic lesion was rejected by chest CT scan and therefore angiography was no longer indicated.

In three patients, laparotomy was performed because of intra-abdominal injury whereas abdominal sonography had been negative. One laparotomy was performed to treat multiple small hepatic lacerations, one to treat a lesion of the colonic serosa. In one intubated and sedated patient, laparotomy was performed because of a false-positive abdominal CT scan, which demonstrated free air and a suspicion of intestinal perforation. However, during laparotomy no abdominal injuries were found.

In three patients, screw fixation of the sacroiliac joint was performed because of a lumbar fracture that had been underestimated by conventional radiographs. One spondylodiscitis was performed because of a lumbar fracture, which seemed stable on radiographs, but was classified as unstable by abdominal CT scan. Because of unexpected thoracic spinal fractures, three patients were treated with a body cast and two with prolonged bed rest.

Ten patients were admitted to a higher level of care because of unexpected diagnoses by either chest or abdominal CT scan. Four of those ten patients were admitted to the intensive care unit instead of the medium care ward. Two

Table 2

<table>
<thead>
<tr>
<th>Examination</th>
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</thead>
<tbody>
<tr>
<td>Abdominal CT</td>
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<tr>
<td>Chest CT</td>
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<tr>
<td>Chest radiograph</td>
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<tr>
<td>Abdominal sonography</td>
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<tr>
<td>Pelvic radiograph</td>
<td>97</td>
</tr>
<tr>
<td>Lumbar spine radiographs</td>
<td>77</td>
</tr>
<tr>
<td>Thoracic spine radiograph</td>
<td>76</td>
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</table>

Fig. 1. The mechanisms of trauma of the 106 patients who met the inclusion criteria of our high-energy protocol18 are outlined.
were admitted to the medium care instead of the general ward, and four patients were admitted for clinical observation instead of being discharged from the hospital. Three patients were submitted to a lower care level because diagnoses were excluded by CT. One patient was admitted to the general ward instead of the medium care ward and two patients were discharged instead of being admitted to the general ward.

**DISCUSSION**

In this study, CT scan of the chest or abdomen revealed one or more unexpected diagnoses in 74% (95% CI 65%–82%) of the 106 patients, in addition to those of the conventional radiography and abdominal sonography. The findings of abdominal or chest CT scans actually resulted in a change of treatment in 34% (95% CI 25%–43%) of the patients. Most of these changes of treatment were according to the chest CT scan. CT scan of the chest found unexpected diagnoses in 79% of the patients, which resulted in an adaptation of treatment in 33% of the patients with a chest CT scan. Twenty-four unexpected pneumothoraces had been found by CT scan. Fourteen of those patients received tube thoracostomy. Tube thoracostomy for occult pneumothoraces that are evident on CT scan but not on chest radiographs is still an area of debate.16,20 In this study, tube thoracostomy was performed depending on the size of the pneumothorax and the state of ventilation. Small pneumothoraces did not receive tube thoracostomy in general. However, tube thoracostomy was performed more liberally in ventilated patients. CT scan of the abdomen found unexpected diagnoses in 40% of the patients, which resulted in a change of treatment in 16% of the patients. In this study, abdominal sonography was used primarily to detect free intra-abdominal fluid. Intra-

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**Table 3 Unexpected and Excluded Diagnoses by CT Scan**

<table>
<thead>
<tr>
<th>Unexpected Diagnoses</th>
<th>Excluded Diagnoses</th>
</tr>
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<tbody>
<tr>
<td><strong>Chest CT scan, N = 78</strong></td>
<td></td>
</tr>
<tr>
<td>Chest</td>
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<tr>
<td>46 Lung contusion</td>
<td>5 Aortic lesion</td>
</tr>
<tr>
<td>35 ≥1 rib fractures</td>
<td>1 Unilateral pneumothorax</td>
</tr>
<tr>
<td>24 Unilateral pneumothorax</td>
<td>1 Unilateral hemothorax</td>
</tr>
<tr>
<td>8 Unilateral hemothorax</td>
<td></td>
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<tr>
<td>4 Sternal fracture</td>
<td></td>
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<tr>
<td>3 Scapular fracture</td>
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<tr>
<td>1 Pericardial effusion</td>
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<tr>
<td>Total</td>
<td>In 61 patients</td>
</tr>
<tr>
<td>Thoracic spine</td>
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<tr>
<td>23 Stable vertebral fracture</td>
<td>1 Stable vertebral fracture</td>
</tr>
<tr>
<td>10 Unstable vertebral fracture</td>
<td>1 Unstable vertebral fracture</td>
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<tr>
<td>5 Reclassification: stable to unstable</td>
<td></td>
</tr>
<tr>
<td>4 ≥1 transverse process fractures</td>
<td>2 In 17 patients</td>
</tr>
<tr>
<td>Total</td>
<td>In 42 patients</td>
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<tr>
<td><strong>Abdominal CT scan, N = 91</strong></td>
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<tr>
<td>Abdomen</td>
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<td>17 Hemoperitoneum</td>
<td>5 Hemoperitoneum</td>
</tr>
<tr>
<td>6 Renal injury OIS 2</td>
<td>1 Renal injury</td>
</tr>
<tr>
<td>5 Retroperitoneal hematoma</td>
<td>1 Diaphragm injury</td>
</tr>
<tr>
<td>4 Bowel contusion</td>
<td>2 Free air</td>
</tr>
<tr>
<td>3 Splenic injury OIS 2</td>
<td>2 Renal injury OIS 3</td>
</tr>
<tr>
<td>3 Hepatic injury OIS 2</td>
<td>2 Splenic injury OIS 1</td>
</tr>
<tr>
<td>2 Free air</td>
<td>2 Hepatic injury OIS 1</td>
</tr>
<tr>
<td>2 Adrenal injury</td>
<td>2 Adrenal injury</td>
</tr>
<tr>
<td>1 Injury renal artery</td>
<td>1 Injury renal artery</td>
</tr>
<tr>
<td>Total</td>
<td>In 49 patients</td>
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<tr>
<td>Pelvis</td>
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<tr>
<td>4 Sacrum fracture</td>
<td>2 Acetabulum fracture</td>
</tr>
<tr>
<td>3 Acetabulum fracture</td>
<td>1 Ileac bone fracture</td>
</tr>
<tr>
<td>3 Pubic bone fracture</td>
<td>1 Femoral head fracture</td>
</tr>
<tr>
<td>1 Ileac bone fracture</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>In 12 patients</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td></td>
</tr>
<tr>
<td>10 ≥1 transverse process fractures</td>
<td>2 In 2 patients</td>
</tr>
<tr>
<td>2 Stable vertebral fracture</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>In 12 patients</td>
</tr>
</tbody>
</table>

OIS, Organ Injury Scale score, developed by the American Association for the Surgery of Trauma.
abdominal injuries on CT scan were only classified as unexpected in case sonography showed no free fluid. When sonography showed free fluid, intra-abdominal parenchymal and mesenterial injuries on CT scan were considered as expected. Our definition of unexpected abdominal CT findings, therefore, did not consider the specificity of the abdominal diagnoses. Consequently, the rate of unexpected injuries might be understated given the number that would have resulted if the specificity of the diagnoses had been considered.

Many authors have retrospectively and prospectively compared the diagnostic capacities of CT scan with conventional radiography and sonography. Most of these studies concern only a selected part of the body and did not investigate the value of thoraco-abdominal CT scan in addition to a complete conventional radiologic work-up. Karaaslan et al. and Trupka et al. both compared the unexpected diagnoses found by chest CT scan with the diagnoses found by chest radiographs. They found unexpected CT diagnoses in 30% and 65%, respectively, with a change of treatment in, respectively, 12.7% and 41% of the patients. However, they only focused on the chest and did not involve the abdomen, pelvis, or spine.

To our knowledge, only few studies investigated the therapeutic value of CT scan of the chest together with the abdomen in addition to a complete conventional radiologic work-up. In their study, Self et al. retrospectively evaluated all routinely made chest and abdominal CT scans for patients already undergoing cranial CT studies. They compared thoraco-abdominal CT findings with the preceding conventional radiography and determined the therapeutic consequences of the unexpected CT diagnoses. They found that in 38% of the patients, thoraco-abdominal CT scan demonstrated unexpected findings, which resulted in a change of treatment in 26% of the patients.

In contrast to our study, Self et al. did not use abdominal sonography in their conventional work-up, so they actually compared abdominal CT findings with physical examination of the abdomen. In many institutions, abdominal sonography is an important diagnostic screening tool to detect hemoperitoneum in patients after blunt abdominal trauma. It has a

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Fig. 2. The number of patients for whom treatment actually changed. The types of treatment are outlined. For some patients, there were multiple changes of treatment.
sensitivity of 42% to 88% in revealing intra-abdominal injury, a specificity of 98% to 100% and an accuracy of 99%. Abdominal sonography is used in many institutions to select patients who need further diagnostic work-up and patients who need immediate laparotomy. The use of sonography might decrease the likelihood that abdominal CT scan finds unexpected abdominal diagnoses after physical examination, because sonography might already have detected the hemoperitoneum. Therefore, Self et al. possibly would have found less unexpected abdominal diagnoses and less therapeutic consequences if they had used abdominal sonography in their conventional work-up. On the other hand, in 17 patients in our study, we found a hemoperitoneum on CT scan whereas abdominal sonography had been false-negative. An explanation for this might be, in addition to the known lower sensitivity of sonography to hemoperitoneum, that sonography was performed directly at admission, whereas CT scan was performed just after completion of the conventional work-up, and hemoperitoneum had more time to develop. Moreover, radiologists and radiology residents with different levels of experience performed sonography. Because it is known that results from sonography are operator and experience dependent, this might have influenced the results from the sonography in our study.

A second contrast to the study of Self et al. is that in their study, CT scan was performed routinely in every patient undergoing cranial CT scan, independent of physical examination or conventional radiography. In our study, however, additional CT scan was performed selectively, only when certain abnormalities in physical examination or preceding conventional work-up were present.

Some comments can be made to the results of our study. The first one is the selection bias, which is inherent to the fact that additional CT scans were performed only when indicated in a selected group of patients. The population in our study had a mean ISS of 25. Most patients were heavily injured, with a high incidence of traumatic chest, abdominal, and spine injuries. This makes the probability of finding unexpected injuries by CT scan higher than it would be in a less-injured population. Therefore, results from this study are only applicable to a heavily injured population. More studies are needed to determine the value of CT scan in a less-injured population. A second comment is that we did not have a comparison group. A policy for a more liberal use of CT scan in blunt trauma might be suggested by our results. However, no superiority or inferiority of any type of radiologic algorithm can be founded by this study. Another comment is that the determination of the therapeutic consequences remains susceptible to subjectivity and cannot be objectively measured. Whether results are therefore under- or overrated remains unclear.

Despite these concerns, results from this study are still very valuable and of clinical importance. Results show that additional CT scan reveals many unexpected diagnoses in the selected cases in which it has been performed. This raises the question how many times CT scan reveals clinically relevant unexpected diagnoses in the times another selection or no specific selection for additional CT scan is used. The latter is of great interest in the discussion about the value of routine CT scan in trauma patients.

Although CT scan of the chest and abdomen has gained wide acceptance in the evaluation of blunt trauma patients, controversy still remains about its most appropriate role in the early radiologic work-up. Radiologic work-up still differs from institution to institution. In some institutions, conventional radiography is omitted and CT scan is performed routinely, with the advantage of high diagnostic accuracy. However, this strategy of routine CT scan risks an increase of radiation exposure and healthcare costs. The radiation exposure risk is of special interest, because long-term consequences in terms of malignancy and mortality are based only on estimations. The exact consequences of radiation are still unclear and some authors therefore argue that exposure should be prevented as much as possible. Moreover, the strategy of routine CT scan implies a risk of a potential delay in intervention of acute problems while the patient is in the CT gantry and temporarily separated from the trauma team.

In contrast to a strategy with routine CT scan, in many other institutions, baseline radiologic work-up consists of conventional radiographs and abdominal sonography. Additional CT scan is selectively performed, only on indication in certain situations. This less-defensive strategy potentially implies less costs and lower radiation exposure, but risks an underestimation or even underdiagnosing of traumatic injuries. In terms of efficiency, containing reduction of healthcare costs, and radiation exposure, it is important to know whether a strategy with routine or selective CT scan should be followed. However, discussion about the most appropriate strategy still remains because of the lack of strong evidence about the right timing and indication of CT scan in trauma patients. Therefore, more prospective studies are needed to determine the most appropriate role of CT scan in the early work-up of blunt trauma patients.

From this study it can be concluded that CT scan of the chest and abdomen has a high diagnostic value in the evaluation of blunt trauma patients, when it is selectively performed in addition to the early conventional radiologic work-up. Unexpected diagnoses are found by CT scan in the majority of the patients. These findings actually result in an adaptation of treatment in a substantial number of the patients. Although chest CT scan dictates more changes of treatment, both CT scan of the chest and abdomen on indication have an important role in the early diagnostic evaluation of blunt trauma patients. More prospective studies are needed to evaluate the value and role of routinely performed CT scan in the early evaluation of blunt trauma patients and to determine its impact on treatment.
REFERENCES


The Increasing Use of Vena Cava Filters in Adult Trauma Victims: Data From the American College of Surgeons National Trauma Data Bank

Steven R. Shackford, MD, Alan Cook, MD, Frederick B. Rogers, MD, Benjamin Littenberg, MD, and Turner Osler, MD

Background: Vena cava filters (VCFs) have been advocated for prophylaxis of pulmonary embolism in trauma patients at high risk for venous thrombosis in whom anticoagulation is contraindicated or not feasible. We sought to determine the frequency of VCF insertion and patterns of use in trauma patients using a large database.

Methods: Retrospective analysis of data from the National Trauma Data Bank of the American College of Surgeons on patients over the age of 17 years from 1991 to 2002. We examined the annual frequency of VCF placement, the demographics and injury severity of patients receiving them, and the characteristics of the hospitals at which they were being placed.

Results: Of 614,349 patients, 6,282 received a VCF (1%); 86% were placed prophylactically (without an associated discharge diagnosis of either pulmonary embolism or venous thrombosis). Filter use increased significantly from 0.3% of patients in 1994 to 1.2% in 2002 (p < 0.001). There was substantial variation in clinical practice with regard to placement of VCF according to injury type and its perceived risk of venous thromboembolism. VCFs were placed significantly more frequently at hospitals verified as Level I trauma centers.

Conclusion: VCF insertion has increased significantly during the past 10 years in trauma patients reported to the National Trauma Data Bank. The lack of an evidence-based guideline for their use has resulted in a wide variation in practice. Such variation in practice indicates the need for a consensus conference or a multicenter prospective clinical trial to determine their role in trauma patients.

Key Words: Vena cava filters, Trauma.

Use of Vena Cava Filters

emboli. In selecting this time period, we hoped to eliminate a confounder in the reporting of PE produced by a change in technology. The NTDB currently receives data on trauma patients from 236 trauma centers in 36 states, territories, and the District of Columbia. NTDB data are subjected to quality screening for consistency and validity.20 The data are contained in nine related files, which have been purged of all identifying information to ensure confidentiality of patients, physicians, and hospitals.

We included all adults (at least 18 years of age) in the NTDB database with complete discharge status data. The presence of a VCF was determined by the procedure description field in the database: interruption of the inferior or superior vena cava (International Classification of Diseases-9 procedure code: 38.7). Additional data included information on the type of facility where the patients were treated (ACS verification status, teaching status, and number of beds), patient demographics, injury descriptors (mechanism of injury, Glasgow Coma Score,21 Revised Trauma Score,22 Injury Severity Score,23 TRISS Survival Probability,24) complications, length of hospital and intensive care unit stay, and outcome (discharge alive or dead). The complications of DVT and PE were abstracted from both the complications field and the discharge International Classification of Diseases-9 diagnostic codes. The contents of these two fields were matched for internal consistency. As others have done,11 we designated a patient’s VCF as “prophylactic” if neither DVT nor PE was found in either the complication or discharge diagnosis field. Conversely, the VCF was considered to be therapeutic if either DVT or PE was found in either the complication or discharge diagnosis field of a patient with a VCF. We examined the pattern of VCF insertion in terms of frequency of VCF placement per year, the facility type at which they were placed, and the frequency of DVT and PE.

Demographic characteristics were compared using $\chi^2$ analysis for categorical variables and Student’s $t$ test for continuous variables. Significance was attributed to a $p$ value of <0.05.

**RESULTS**

The ACS’ NTDB provided us with data on 764,215 patients. We excluded patients who were less than 18 years of age (148,798), and patients with records that were lacking the discharge status (1,068). In these two groups of excluded patients, 216 had a VCF. After these exclusions, there remained 614,349 patients, of which 6,282 received a VCF (1%).

Patients receiving a VCF were more severely injured, had longer hospital and intensive care unit stays, had a lower probability of survival (predicted by the TRISS methodology), and had a significantly higher mortality rate than patients who did not receive a VCF had (Table 1). Insertion of a VCF was most frequent in spinal cord injury (5.7%), pelvic fracture (4.7%), and vertebral fracture (4.1%), and was less common in head injury (1.8%) (Table 1).

Of patients reported to the NTDB, the percentage receiving a VCF increased substantially between 1994 and 2002. In 1994, 47 patients (0.3%) received a VCF and in 2002, 1,054 patients (1.2%) received a VCF; this is a significant increase ($p < 0.0001$). During the same time period, the reported prevalence of venous thromboembolism (VTE) (patients with either DVT or PE reported to the NTDB in a given year) increased from 0.2% to 0.5% ($\chi^2 p < 0.001$) (Fig. 1). Because the number of VCFs inserted increased at a greater rate than the number of reported pulmonary emboli or DVTs, it appears that more VCFs were being placed prophylactically. In fact, at least 86% of all VCFs inserted since 1994 were placed prophylactically (Fig. 2). The proportion of VCFs that were considered prophylactic is relatively uniform among the various high-risk diagnoses, ranging from a low of 85% for lower extremity fracture to a high of 94% for spinal cord injury.

There appears to be clinical practice variation with regard to the placement of VCF according to injury type and its perceived risk of VTE. For example, spinal cord injury is considered to be a significant risk factor for VTE and is thought to be a contraindication to anticoagulation. As such, patients with spinal cord injury would seem to be a strong impetus to the placement of a prophylactic VCF. Yet, only 5.7% of patients with spinal cord injury received a VCF. Similarly, pelvic fracture is also thought to be a major risk factor for VTE, and, because many have ongoing hemorrhage, it is thought to have a relative contraindication to anticoagulation. Despite being an optimal indication for a prophylactic VCF, only 4.7% of patients with pelvic fracture received a VCF. Conversely, vertebral fracture is not a consensus indication for prophylactic VCF, but 4.1% received them—most of which were placed prophylactically according to our definition.

There is great variation of clinical practice in the use of VCF between types of hospitals reporting data to the NTDB. Level I trauma centers25 insert VCFs into 1.3% of their patient population, whereas Level II centers insert VCFs into 0.6% of their patients. There is a similar disparity between university hospitals, community hospitals, and nonteaching hospitals (Table 2). Some of this disparity may be caused by variable distribution of high-risk injuries to the various classes of hospital. For example, Level I centers received 35% of all the high-risk injuries reported to the NTDB during the interval studied, whereas Level II hospitals received only 12% of the high-risk injuries. However, Level I centers inserted VCFs into 2.8% of their high-risk patients, whereas Level II centers inserted VCFs into 1.2% of their patients with high-risk injuries. Similarly, university hospitals received a greater proportion of high-risk patients and placed more filters in them (2.6%) than did community hospitals that received fewer high-risk patients and placed fewer filters in them (1.6%). These differences between Level I and Level II hospitals, and between university and community hospitals are significant ($p < 0.001$).
Venous thromboembolism is a frequent complication after trauma and remains a significant clinical problem affecting outcome. DVT occurs in up to 58% of severely injured patients, and PE causes up to 5% of deaths in trauma patients hospitalized for more than 48 hours.1,3,26,27 Clinical and epidemiologic factors associated with increased risk of VTE after trauma include the following: age $\geq 40$ years, Injury Severity Score $>9,23$ lower extremity fracture, pelvic fracture, severe head injury, venous injury, vertebral fracture, or spinal cord injury.2,7,9,10,28 The presence of more than one risk factor is associated with a significantly higher incidence of VTE.7,28 Currently, prophylaxis consists of anticoagulation with fractionated or unfractionated heparin or mechanical compression devices, such as foot pumps, pneumatic hose, or sequential compression boots.9,10 However, anticoagulant prophylaxis is not uniformly effective and is associated with a 3% to 30% risk of bleeding and a 0.5% to 1.9% incidence of thrombocytopenia, complications that can lead to significant morbidity in trauma patients.29–31 Because of the potential hemorrhagic complications, many surgeons think that the use of anticoagulation in trauma patients is relatively contraindicated.27,31

The ineffectiveness and complications of anticoagulant and mechanical prophylaxis have led to the “extended” or prophylactic use of VCFs.6,10 Prophylactic VCFs have been associated with a reduction in symptomatic and fatal pulmonary emboli when compared with historic controls.6,12–15

A single randomized prospective study in elderly trauma patients demonstrated that prophylactic partial caval interrup-

### Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>VCF</th>
<th>No VCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4,361 (1.1)</td>
<td>392,629 (98.9)</td>
</tr>
<tr>
<td>Female</td>
<td>1,916 (0.9)</td>
<td>214,494 (99.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>50 (0.7)</td>
<td>7,384 (99.3)</td>
</tr>
<tr>
<td>Black</td>
<td>1,217 (1.1)</td>
<td>107,589 (98.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>276 (0.7)</td>
<td>39,167 (99.3)</td>
</tr>
<tr>
<td>Native American Indian/Alaskan native</td>
<td>12 (0.4)</td>
<td>3,017 (99.6)</td>
</tr>
<tr>
<td>White</td>
<td>4,332 (1.1)</td>
<td>381,859 (98.9)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>97 (1.4)</td>
<td>7,047 (98.6)</td>
</tr>
<tr>
<td>Age, mean (95% CI)</td>
<td>46.1 (45.6–46.6)</td>
<td>45.7 (45.6–45.8)</td>
</tr>
<tr>
<td>Mean length of stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit, d (95% CI)</td>
<td>14.6 (14.2–15.0)</td>
<td>1.5 (1.4–1.5)*</td>
</tr>
<tr>
<td>Hospital, d (95% CI)</td>
<td>28.7 (28.0–29.3)</td>
<td>5.8 (5.8–5.8)*</td>
</tr>
<tr>
<td>Injury information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revised Trauma Score, mean (95% CI)</td>
<td>6.2 (6.1–6.2)</td>
<td>7.2 (7.2–7.2)*</td>
</tr>
<tr>
<td>Injury Severity Score,† mean (95% CI)</td>
<td>25.8 (25.4–26.1)</td>
<td>10.1 (10.0–10.1)*</td>
</tr>
<tr>
<td>TRISS Ps,† mean (95% CI)</td>
<td>0.80 (0.79–0.80)</td>
<td>0.90 (0.90–0.90)*</td>
</tr>
<tr>
<td>Head injury</td>
<td>2,713 (1.8)</td>
<td>145,008 (98.2)</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>216 (5.7)</td>
<td>3,581 (94.3)</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>2,671 (4.1)</td>
<td>63,112 (95.9)</td>
</tr>
<tr>
<td>Pelvic fracture</td>
<td>2,041 (4.7)</td>
<td>41,510 (95.3)</td>
</tr>
<tr>
<td>Femur fracture</td>
<td>1,428 (1.9)</td>
<td>73,796 (98.1)</td>
</tr>
<tr>
<td>Tibia fracture</td>
<td>1,138 (2.6)</td>
<td>42,850 (97.4)</td>
</tr>
<tr>
<td>Hospital (ACS verification level)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>2,985 (1.4)</td>
<td>218,793 (98.7)</td>
</tr>
<tr>
<td>Level II</td>
<td>473 (0.6)</td>
<td>73,586 (99.4)</td>
</tr>
<tr>
<td>Level III</td>
<td>1 (0.1)</td>
<td>1,291 (99.9)</td>
</tr>
<tr>
<td>Teaching status</td>
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<td>University</td>
<td>4,601 (1.3)</td>
<td>358,554 (98.7)</td>
</tr>
<tr>
<td>Community</td>
<td>1,443 (0.8)</td>
<td>175,441 (99.2)</td>
</tr>
<tr>
<td>Nonteaching</td>
<td>188 (0.5)</td>
<td>35,391 (99.5)</td>
</tr>
<tr>
<td>N/A or unknown</td>
<td>50 (0.1)</td>
<td>38,681 (99.9)</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT (lower extremity)</td>
<td>666 (37.9)</td>
<td>1,093 (62.1)</td>
</tr>
<tr>
<td>PE</td>
<td>228 (26.0)</td>
<td>650 (74.0)</td>
</tr>
<tr>
<td>Total N = 614,349</td>
<td>6,282 (1.0)</td>
<td>608,067 (99.0)</td>
</tr>
</tbody>
</table>

Values given are n (%) values unless indicated otherwise.

* $p < 0.001$.

† See text for details.

CI, confidence interval; Ps, probability of survival.
tion with an umbrella reduced the incidence of symptomatic and fatal PE.32 Although some work has implied that prophylactic VCFs are associated with a decrease in the incidence of fatal pulmonary emboli,12 there has been no comparison of survival between the treatment group and concurrent controls.

We found that VCFs were inserted in approximately 1% of patients reported to the NTDB and that the rate of insertion has been increasing during the past 10 years, from 0.3% in 1994 to 1.2% in 2002. We found that at least 86% of filters were placed for extended indications, and that this percentage was relatively constant among the various high-risk injuries (i.e., spinal cord injury, pelvic fracture, lower extremity fracture, etc.).

There was significant practice variation among hospitals in the insertion of VCFs into those patients considered to be at high risk by nature of their age or injury type. This insertion rate ranged from 1.2% at nonteaching hospitals to 2.6% at university hospitals. Kazmers et al.,33 in a retrospective analysis of VCF use in Veterans Affairs hospitals, also noted higher VCF use at medical centers associated with medical schools. A similar disparity in practice with regard to the patient with high-risk injury was seen between ACS Level I and Level II hospitals: Level I centers placed filters in 2.8% whereas Level II centers inserted them in 1.2%. A similar pattern of VCF use was found in pediatric trauma patients.34 We suspect that there are a number of reasons for the practice variation, but probably the most compelling is the lack of any Level I evidence documenting the efficacy of VCF in preventing fatal PE in high-risk trauma patients.

There are limitations to our analysis. First, this is a secondary analysis of an unvalidated multi-institutional database and we are only able to draw conclusions based on the data as they were entered into the NTDB. Second, the number of DVTs (1,759) is probably underreported based upon the numbers of reported pulmonary emboli (878). For example, if one assumes that 20% of proximal DVTs produce a PE, there should have been 4,390 DVTs reported, assuming that all reported DVT were proximal DVT. The underreporting is most likely because of either a lack of consistent surveillance or a low index of clinical suspicion. Reliable repeated surveillance is operationally difficult and costly and these two factors may encourage the placement of a VCF prophylaxis in a high risk patient with an absolute or relative contraindica-

![Fig. 1. Bar graph demonstrating the number of patients reported to the NTDB who had a VCF placed during the interval 1994–2002. Also shown are the number of patients reported to the NTDB who had either a DVT or a PE. When these numbers are divided by the total number of patients reported to the NTDB in each of the years shown, the number of VCF placed annually has increased 340% whereas the number of DVT or PE reported has increased 246%.](image1)

![Fig. 2. Bar graph demonstrating the total number of VCFs placed as reported to the NTDB during the interval 1994–2002. Also shown are the number placed in patients with a diagnosis or complication of either DVT or PE (considered to be a therapeutic filter) and the number placed in patients without DVT or PE as a complication or diagnosis (considered to be a prophylactic filter).](image2)
tion to heparin. Our proposed PE rates based on the reported DVT rates presume no treatment of established DVT. Third, our discussion of clinical practice variation in the placement of VCFs in patients with spinal cord injury and in patients with pelvic fracture is weakened because we were unable to determine from the NTDB the degree of paralysis associated with the cord injury and the complexity of the pelvic fracture. Paralysis with associated venous stasis is presumed to be the major pathophysiologic factor in DVT in patients with cord injury. Simple pelvic fractures are often associated with early walking and a much lower incidence of VTE. Thus, without the additional injury descriptors, it is possible to make inferences and not firm conclusions about practice patterns. Finally, we categorized patients with a VCF and a diagnosis of DVT or PE as having the filter placed therapeutically according to accepted guidelines. This categorization assumes that the filter was placed after the VTE event, but we had no way to verify this. This categorization would underestimate the number of prophylactic filters because any prophylactic filter that failed (i.e., the patient suffered a PE) or caused a DVT would be categorized as a therapeutic filter; conversely, the prevalence of therapeutic filters is overestimated.

Whether prophylactic or therapeutic, VCFs are being placed more frequently and some authors are questioning whether more should be inserted. VCFs are being placed more often at teaching hospitals and hospitals with ACS’ verification as Level I centers. This suggests that their use has been championed by centers that are involved in research (a prerequisite for Level I verification). It also appears that their frequency of use has prompted industry to develop the retrievable filter without strong evidence that permanent VCFs are effective.

The increased placement of VCFs coupled with the possible morbidity associated with their use and their cost demonstrate the need for a prospective randomized multicenter trial to examine the efficacy of VCFs in trauma patients who are at high risk for VTE. The platform for such a study exists within the various professional societies of trauma surgeons (i.e., American Association for the Surgery of Trauma, Western Trauma Association, Eastern Association for the Surgery of Trauma, and the ACS Committee on Trauma). These societies, through a consensus conference under the auspices of the National Institute of Health, could design this important trial to determine not only the effectiveness of VCFs and their complications, but also who might benefit most from their insertion.

**ACKNOWLEDGMENTS**

Data were supplied by the American College of Surgeons Committee on Trauma National Trauma Data Bank. We are grateful to Claudette Laplume who assisted in the preparation and editing of the article.

**REFERENCES**

The Effects of Ethanol on $\beta_2$-Integrin and L-Selectin on the Surface of Leukocytes in Human Whole Blood

Masayuki Ozaki, MD, Masanori Ogata, MD, PhD, Koichiroh Nandate, MD, PhD, Takashi Kawasaki, MD, PhD, and Takeyoshi Sata, MD, PhD

Background: Acute alcohol intoxication is associated with increased susceptibility to infection. In host defense, the expression of adhesion molecules such as $\beta_2$-integrin and L-selectin on leukocytes is involved in leukocyte migration to inflamed organ tissue. To elucidate the mechanisms underlying the immunosuppressive effects of ethanol, we investigated whether ethanol pretreatment may influence the changes in adhesion molecule expression induced by lipopolysaccharide (LPS) or interleukin (IL)-8 in human whole blood.

Methods: Ethanol was added to samples of human whole blood (final concentration: 0%, 0.2%, 0.4%, and 0.8%). Samples were assigned to an unstimulated group and an LPS-stimulated group. In another set of experiments, stimulation was induced by IL-8. After fluorescence labeling of $\alpha_4$-subunit of $\beta_2$-integrin (CD11b) and L-selectin (CD62L), the expression of CD11b and CD62L were measured using flow cytometry.

Results: Stimulation with LPS significantly upregulated CD11b expression (5.9 ± 0.9 to 16.3 ± 1.8, p < 0.05). Ethanol inhibited this LPS-induced upregulation of CD11b ($p < 0.001$). Stimulation with IL-8 significantly upregulated CD11b expression (5.3 ± 1.7 to 7.5 ± 2.7, $p < 0.01$) and this IL-8-induced upregulation of CD11b was also inhibited by ethanol pretreatment ($p < 0.001$). In contrast, ethanol did not modify CD62L expression in either unstimulated or stimulated groups.

Conclusion: The impairment of CD11b expression on leukocytes suggests that alcohol intake interferes with the migration of leukocytes to sites of inflammation, which may explain, in part, why alcohol intoxication increases susceptibility to infection.

Key Words: Ethanol, Adhesion molecules, $\beta_2$-Integrin, L-Selectin, Lipopolysaccharide, Interleukin-8.


Aacute alcohol intoxication has long been associated with an increased risk of trauma and burns. In these patients, an increased risk of infection has been reported. Although the underlying mechanism of the immunosuppressive effects of ethanol is not completely understood, one proposed mechanism is that ethanol impairs leukocyte migration to the site of inflammation. Recruitment of leukocytes consists of sequential steps: (1) rolling and tethering; (2) strong adhesion; and (3) extravasation to the site of inflammation. These steps are regulated by adhesion molecules such as selectins and integrins, involved in the adhesion cascade between leukocytes and endothelium. L-Selectin (CD62L) is expressed on most leukocytes and mediates a degree of adhesion that induces rolling along the vessel wall. Leukocyte rolling activates integrins, thereby, promoting firm adhesion of leukocytes to the vessel wall. Because integrins consist of an $\alpha$ and a $\beta$ subunit, they are grouped into subfamilies based on their interactions with ligands on the surface of other cells. One of the most important subfamilies of integrins is $\alpha_4\beta_2$-integrin, also known as C-receptor 3, Mac-1, or CD11b, which is expressed on neutrophils, monocytes, natural killer cells, and some subsets of T and B cells. CD11b and CD62L synergize for the transition of circulating leukocytes to binding at endothelium. After strong adhesion, leukocytes migrate into the inflamed tissue.

Bacterial lipopolysaccharide (LPS), a major component of the cell wall of gram-negative bacteria, is a highly biologically active molecule that activates leukocytes to express CD11b and shed CD62L. In the process of leukocyte recruitment, a potent chemokine, interleukin (IL)-8, plays a pivotal role, generating a chemotactic gradient that enables leukocytes to be activated and migrate from the systemic circulation toward sites of inflammation. IL-8 also activates leukocytes to express CD11b and shed CD62L.

The purpose of this study was to evaluate the effect of ethanol on expression of the adhesion molecules, CD11b and CD62L, in response to stimulation with LPS or IL-8 in human whole blood. The expression of adhesion molecules on the surface of leukocytes were assessed using flow cytometry.

MATERIALS AND METHODS

After obtaining approval from the institutional Human Investigations Committee, informed consent was obtained from seven healthy male volunteers. None of the volunteers had any infectious diseases, history of allergic reaction, and none were taking any medication.
Phenol-extracted *Escherichia coli* (serotype 0127:B8) LPS was purchased from Difco Laboratories (Detroit, MI). IL-8 was purchased from Sigma-Aldrich (St. Louis, MO). Antibodies against CD11b and CD62L were purchased from Beckman Coulter (Fullerton, CA).

Whole blood (10 mL) was collected into tubes that contained citrate (VT-050CWS; Terumo, Tokyo, Japan) from each individual by antecubial venipuncture. White blood cell counts were between 5,500 cells/μL and 8,500 cells/μL. Aliquots (100 μL) of whole blood were incubated in the absence and presence of ethanol (final concentration: 0%, 0.1%, 0.2%, 0.4%, and 0.8%) at 37°C in 95% air/5% carbon dioxide for 30 minutes. Each sample was assigned to an unstimulated group or an LPS-stimulated group. LPS was added to the samples of the LPS-stimulated group (final concentration: 10 ng/mL). The concentrations of LPS were determined according to our previous study. In another set of experiments, IL-8 was added to induce leukocyte activation. Samples in this experimental set were prepared with or without 10 ng/mL final concentration of IL-8, which was reported to be enough to induce CD11b expression. All samples were incubated for 90 minutes at 37°C in 95% air/5% carbon dioxide. Thereafter, whole blood samples were stained with fluorescein isothiocyanate-labeled monoclonal antibodies directed against CD11b (IMO530, Beckman Coulter) and phycoerythrin-labeled monoclonal antibodies directed against CD62L (IM2214, Beckman Coulter), and then incubated for 30 minutes in the dark room. Lysing medium was added to lyse erythrocytes. After confirmation of complete lysing, the samples were fixed with 0.2% paraformaldehyde and then washed twice. All samples were analyzed immediately by using a flow cytometer and XL software (EPICS-XL; Beckman Coulter) and then incubated for 30 minutes in the dark room. Lysing medium was added to lyse erythrocytes. After confirmation of complete lysing, the samples were fixed with 0.2% paraformaldehyde and then washed twice. All samples were analyzed immediately by using a flow cytometer and XL software (EPICS-XL; Beckman Coulter). Leukocytes were discriminated in terms of forward and side scatter. Forward scatter is correlated to cell size, whereas side scatter is related to cell granularity. The threshold was set properly in the forward scatter to exclude cell debris from measurements. To discriminate leukocytes from the other white blood cells, we used fluorescein isothiocyanate-labeled monoclonal anti-human CD14 antibody. For each sample, 10,000 cells were analyzed. The results were described as the mean fluorescence intensity (MFI).

The effect of ethanol on leukocyte viability was assessed by both the trypan blue exclusion test and assay with a cell counting kit (Cell Counting Kit-8, Dojindo, Tokyo, Japan). Different doses of ethanol (0%, 0.2%, 0.4%, 0.8%, and 1.0%) were added to diluted human whole blood and incubated for 2 hours at 37°C in a 95% air/5% CO₂ incubator. After incubation, the samples were centrifuged at 700g for 10 minutes. Buffy coats were isolated and NH₄Cl lysis of erythrocytes was performed. The white blood cells were resuspended in RPMI 1640 medium containing 5% fetal calf serum, and the cells were stained with 0.2% trypan blue, and the leukocyte viability was assessed by microscope. With Cell Counting Kit-8, the leukocyte viability was assessed according to the manufacturer’s directions. The cytotoxicity was assessed using a microplate reader (Bio-Rad Laboratories, Richmond, CA), after staining with Tetrazolium monosodium salt. The absorbance of each well was determined at a wavelength of 450 nm.

Data were analyzed using Sigma Stat v. 3.01 (SPSS, Inc., Chicago, IL). All data are presented as the mean ± SEM. The effects of LPS were analyzed with Wilcoxon’s signed rank test between LPS(+) groups and LPS(−) groups. Analysis for the effects of ethanol was performed with one-way repeated measures analysis of variance and Dunnett’s test in multiple comparisons with control group (without ethanol). Values of *p* < 0.05 were considered statistically significant.

**RESULTS**

Leukocytes were pretreated with saline or ethanol followed by LPS or IL-8 stimulation and then fluorescently labeled for flow cytometric analysis. Figure 1 shows the effects of ethanol on LPS-induced CD11b and CD62L expressions. In samples without ethanol, the unstimulated CD11b-positive leukocyte MFI was 5.9 ± 0.9. After LPS stimulation, CD11b expression increased to 16.3 ± 1.8 (*p* < 0.05 vs. LPS(−)) (Fig. 1A). Ethanol significantly inhibited the LPS-induced increase in CD11b expression in a concentration-dependent manner at concentrations of more than 0.2% of ethanol (*p* < 0.001). Ethanol did not affect CD11b expression significantly in unstimulated whole blood. Mean fluorescence intensities of CD62L on leukocytes decreased significantly in LPS-stimulated whole blood (*p* < 0.05 vs. LPS(−)) (Fig. 1B). This result demonstrates that LPS induces shedding of CD62L. As shown in Figure 1B, ethanol had no effect on LPS-induced shedding of CD62L expression. In addition, ethanol had no effect on CD62L expression in unstimulated samples.

Figure 2 shows the effects of ethanol on IL-8-induced CD11b and CD62L expressions. Without ethanol, the unstimulated CD11b-positive leukocyte MFI was 5.3 ± 1.7. After IL-8 stimulation, CD11b expression increased to 7.5 ± 2.7 (*p* < 0.01 vs. LPS(−)). When the ethanol concentration is more than 0.4%, IL-8-induced increase in CD11b expression decreased significantly (*p* < 0.05 vs. ethanol(−)) in a concentration-dependent manner. On the contrary, ethanol did not change significantly CD11b on leukocytes without IL-8 (Fig. 2A). IL-8 did not change significantly CD62L expression on leukocytes in whole blood, irrespective of whether they were exposed to ethanol. Ethanol had no effect on IL-8-stimulated or unstimulated CD62L expression (Fig. 2B).

To rule out the possibility that the effects of ethanol are induced by cellular toxicity of ethanol, we assessed cell viability. Assessment of leukocyte viability by trypan blue exclusion test revealed that 1.0% ethanol did not affect the viability of leukocytes (>95% cell viability). Examination using a cell counting kit also revealed that there was no significant difference in absorbance between each ethanol concentration sample and control sample.
DISCUSSION

Acute alcohol intoxication is associated with increased risk of infection, but the precise mechanism of the immunosuppressive effects of alcohol has not been well elucidated. In this in vitro study, we demonstrate that alcohol inhibits increase of CD11b expression induced by LPS or IL-8 stimulation in leukocytes. These results suggest that inhibition of CD11b expression of leukocytes is one of the mechanisms that underlie host susceptibility caused by alcohol intoxication.

The leukocyte-endothelial interactions are regulated by a cascade of molecular steps. CD62L is expressed on the surface of nonstimulated leukocytes, where it facilitates the adhesion of leukocytes to activated endothelial cells that are in close proximity to inflamed tissue. The binding affinity of the CD62L is relatively low, which causes leukocytes to decelerate by rolling on endothelial cells. Bacterial toxin such as LPS and chemokine IL-8 trigger leukocyte activation. When leukocytes are activated, CD11b is expressed, and CD62L is shed from the surface of the leukocytes. The firm attachment of leukocytes to the surface of endothelial cells is mediated by CD11b. Activated leukocytes adhere firmly to endothelial cells, and migrate toward the site of inflammation. Thus, the expression of CD11b and CD62L on the surface of leukocytes plays an important role in host immunity.

Fig. 1. Effects of ethanol on CD11b and CD62L expressions unstimulated and stimulated by lipopolysaccharide (LPS) in human whole blood. (A) LPS induced significant increase in CD11b expression on leukocytes compared with nonstimulated whole blood [p < 0.05 vs. LPS(–)]. At concentrations ≥0.2%, ethanol inhibited the increase in CD11b expression in a concentration-dependent fashion [p < 0.001 vs. ethanol(–)]. (B) LPS suppressed CD62L expression [p < 0.05 vs. LPS(–)]. Ethanol had no effect on CD62L expression in LPS-stimulated or nonstimulated leukocytes. Data are presented as mean ± SEM. *p < 0.05 versus the values of samples without ethanol; #p < 0.05 versus the values of samples with LPS.
Previous studies have shown that alcohol suppresses chemotactic functions that involve cytokines such as tumor necrosis factor-α and IL-1β and IL-6. Chemokines such as IL-8 and cytokine-induced neutrophil chemoattractant are also inhibited by acute ethanol intoxication. In addition to suppressing cytokine and chemokine production, ethanol intoxication inhibits leukocyte-endothelial interaction. It has been reported that ethanol inhibits adhesion molecule expression on the surface of neutrophils in rats during endotoxemia. Recently, Saeed et al. have shown that ethanol inhibits tumor necrosis factor-α-induced leukocyte-endothelial cell adhesion in vitro using isolated human leukocytes and human dermal microvascular endothelial cells.

In the present study, ethanol inhibited LPS- or IL-8-induced upregulation of CD11b on human leukocytes. Results of our in vitro study using human whole blood are compatible with previous findings about inhibitory effects of ethanol on adhesion molecule expression.

In addition to the role in adhesion to the endothelial cell, CD11b has another role in host defense. CD11b also functions as a receptor for the opsonic iC3b fragment of C3 that triggers phagocytosis or cytotoxicity. It has been reported that acute alcohol intoxication attenuates neutrophil bacterial activity. Our results suggest that decreased expression of CD11b in acute ethanol intoxication is related to impaired phagocytic activity.
We examined the effect of ethanol on the adhesion molecules expressed in human whole blood, stimulated not only with LPS but also with IL-8. IL-8 significantly increased the expression of CD11b, which is consistent with previous results. The increased expression of CD11b induced by IL-8 was also dose-dependently attenuated by ethanol, demonstrating that this is the direct effect of ethanol. LPS induced inflammatory cytokines such as TNF and IL-8. At a concentration of 0.2%, ethanol significantly inhibited LPS-induced CD11b expression. In the same concentration, however, ethanol could not suppress IL-8-induced CD 11b expression. This result suggested that the inhibitory effect of ethanol on LPS-induced CD11b expression include the secondary effect of suppression of inflammatory cytokines such as tumor necrosis factor and IL-8 as a part. Further study will be needed to clarify this problem.

CD62L also plays a crucial role in the first phase of recruitment of neutrophils: the shedding of CD62L increases the velocity at which cells roll, and as a consequence, affects the accessibility of sites of inflammation. Moreover, CD62L mediates chemokine signaling to the cytoplasm of neutrophils. Recruitment of leukocytes is regulated by signals that mediate CD62L. In the present study, LPS caused CD62L to be shed and this effect was not influenced by the presence of ethanol. These results suggest that ethanol does not influence L-selectin shedding. However, further examination will be needed; the experimental model of this study lacks leukocyte-endothelial interaction, which plays an important role in L-selectin shedding.

Previous studies have reported that ethanol intoxication increases the risk of infection in trauma patients. In such patients, infections are caused by bacterial contamination at the time of injury. Our finding that ethanol inhibited CD11b expression in human whole blood in vitro partly explains the immunosuppression in ethanol-intoxicated patients.

In conclusion, we found that ethanol inhibited the increase in CD11b expression induced by LPS or IL-8 on the surface of leukocytes in a dose-dependent manner, whereas it failed to affect LPS- or IL-8-induced expression of CD62L in human whole blood. These results that alcohol intake interferes with the adhesion molecule expression on leukocytes may explain, in part, why alcohol-intoxicated trauma patients have an increased risk of infection.

REFERENCES

Comparative Efficacy of Granular and Bagged Formulations of the Hemostatic Agent QuikClot

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Background: QuikClot is a zeolite-based dressing approved and deployed by military for the arrest of severe combat-induced hemorrhage. A novel formulation (bagged QuikClot [ACS]) of the original granular QuikClot (QC) has been proposed to facilitate the application of the hemostatic dressings under battlefield conditions. This study compares the hemostatic efficacy of ACS and QC in controlling blood loss and improving survival in a swine model of uncontrolled hemorrhage induced by complex groin injury.

Methods: After transsection of the femoral vasculature, anesthetized Yorkshire pigs (n = 32) were hemorrhaged for 3 minutes and randomized into four groups: no treatment (NONE) or application of standard dressing (SD), QC, or ACS. At 15 minutes, resuscitation was initiated by infusion of 500 mL Hextend during a span of 30 minutes. Vital signs were continuously recorded throughout the 4-hour experimental period. In addition, blood loss and temperature at the dressing and tissue interface were continuously recorded.

Results: After 3 minutes, average blood loss was 44.7% ± 11.9% estimated blood volume (EBV) for all animals (34.1 ± 3.2 kg). Posttreatment blood loss was significantly higher (p < 0.01) for NONE- and SD-treated animals (31.5% ± 21.8% and 22.3% ± 12.6% EBV, respectively) as compared with animals treated with QC and ACS (7.4% ± 7.1% and 10.3% ± 6.9%, respectively). All NONE animals died at approximately 60 minutes. Times until death were slightly greater for animals treated with SD (96.8 minutes) and significantly greater for animals treated with QC (188 minutes) and ACS (194 minutes). Overall survival to 4 hours for SD (1 of 8, 12.5%) was significantly lower (p < 0.02) than for QC (6 of 8, 75%) and for ACS (6 of 8, 75%) treatments. Elevated temperatures at the dressing and tissue interface were seen in animals treated with QC and ACS (average at 8 minutes was 58.1 ± 4.5°C and 58.2 ± 5.3°C, respectively) compared with SD treated animals (38.8 ± 2.7°C). Histologic examination revealed more edema in muscular tissue of animals treated with ACS as compared with in QC-treated animals.

Conclusions: ACS was as efficacious as original granular QC in inducing hemostasis and improving survival as compared with the efficacy of SD. Easier and more rapid application and complete removal of ACS may offer a distinct advantage in battlefield resuscitation efforts to enhance a clean wound site and eventual surgical repair.

Key Words: Uncontrolled hemorrhage, Hemostatic dressing, Bleeding, Survival.

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Massive bleeding reaching up to 45% of original blood volume has devastating effects that can be manageable only when action is taken rapidly after the onset of injury.1,2 It has been estimated that the lives of more than 30% of severe hemorrhage trauma victims could be saved if bleeding arrest is rapidly and effectively applied. Tourniquets, appropriate on extremity injuries, are of limited application in areas such as the neck, peritoneum, or groin, which are frequent sites of injury located at the edges of personal body armor. Zeolite, a mineral powder originating from volcanic rock, has remarkable physical and chemical properties that enhance the absorption of water and aqueous biologic materials through channels.3,4 It was previously shown that a synthetic version of zeolite, QuikClot (QC; Z-Medica Corp, Wallingford, CT), has powerful hemostatic properties that promote localized coagulation and bleeding arrest leading to increased (as compared with standard dressing) survival in severely hemorrhaged swine.5 Zeolite has been compared with other practical bandage dressings [e.g. HemCon (Hemcon, Portland, OR), Fibrin glue (American Red Cross, Rockville, MD), Quick relief (Biolife, Sarasota, FL), Trauma Dex (Medafor, Minneapolis, MN)] using various hemorrhage models (e.g. arterial and venous groin injury, punch arteriotomy, or liver injury).6–11 It has been reported to be most effective in the groin injury model.5,7 Zeolite is known to exhibit a significant exothermic reaction;5,11 this property is principally dependent upon the surface area, porosity, and

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residual moisture of the zeolite beads. It is noteworthy that the exothermic reaction resulting from water adsorption produces elevated temperatures that could be damaging to proximal tissue.\textsuperscript{1,12} When applied to an open, bleeding wound, it has been suggested by manufacturers that QC adsorbs aqueous components of the blood and thereby concentrates clotting factors and promotes bleeding arrest. QC has been used clinically in a few occasions for civilians, and reports of military use in the field indicate its benefit despite the thermal effects.\textsuperscript{13,14}

Adverse conditions including hazardous weather and darkness may have an influence on the application and efficacy of the original granular formulation of QC.\textsuperscript{13} Anecdotes from military users recount the dispersion of the product outside the wound as well as granules remaining in the wound even after saline washout.\textsuperscript{*} A modification in the presentation of the product was developed (Advanced Clotting Sponge [ACS]) to address these difficulties and improve the practical application (and removal) of QC. This novel ACS formulation consists of beads with chemical composition and residual moisture (1%) similar to the original powder but of slightly larger diameter. In addition, ACS beads are contained in mesh bags that are easier to handle and apply to the site of injury. The larger beads of ACS formulation could potentially reduce the thermal injury caused by attenuated heat formation by the smaller overall surface area.

The objective of the present study was to compare the efficacy of modified “bagged” ACS with the original granular QC in a groin model equivalent to the one described by Alam et al.\textsuperscript{7} To justify the practical advantage of the new bagged product, this study assessed the effect of both the bagged ACS and granular QC on (1) the survival, (2) hemostatic efficacy, and (3) temperature elevation (and tissue damage) when applied to a swine model of uncontrolled hemorrhagic groin injury.

**MATERIALS AND METHODS**

**Animal Model**

The experiments reported herein were conducted according to the principles set forth in the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 1996). The Naval Medical Research Center/Walter Reed Army Institute of Research Institutional Animal Care and Use Committee approved the study; all procedures were performed in an animal facility approved by the Association for Assessment and Accreditation for Laboratory Animal Care (AAALAC).

Yorkshire swine (30–40 kg, Animal Biotech Industries, Danboro, PA) were fed until the night before experiment and had free access to water. Anesthesia was induced with intravenous injection of ketamine hydrochloride (HCL) (30 mg/kg) and inhalation of 3% isofluorone. After placement of endotracheal tube, the isofluorone concentration was reduced to 2.2% until initiation of injury. After the onset of bleeding, the level was reduced to 1% to 1.5% and then regulated to maintain sedation thereafter. The animals were allowed to breathe spontaneously using a mixture of oxygen and air administered through a Narkomed M ventilator (North American Dräger, Telford, PA). End tidal CO\textsubscript{2} and respiration rate were continuously monitored and regulated between 34 and 45 mm Hg, and were intermittently recorded. Rectal temperature was monitored and maintained between 36.0 and 37.8°C using a Bair Hugger device (Model 505, Bair Hugger, MN). An 18G angiocatheter was placed in the right carotid artery and connected to the arterial line to acquire blood pressure and withdraw blood samples. The external jugular vein was then cannulated with a 22G angiocatheter and 9Fr introducer to place a 7.5Fr oximetric thermodilution pulmonary artery catheter (Schein Care Corp., Irvine, CA). The catheter was attached to a hemodynamic monitoring system (Hewlett Packard, Palo Alto, CA) to allow for continuous monitoring of the mean pulmonary artery pressure (MPAP). Resuscitation fluid was infused through this venous access. All catheters were flushed with a citrated flush solution (50 mL of acid-citrate-dextrose in 500 mL of 0.9% saline solution) to maintain patency. Pulse oximetry data (Data–Omedex) was obtained from either foot or tail extremity.

**Products**

The standard gauze dressing consisted of a thick $8 \times 10$ inch absorbent gauze pad with elastic bandage (Cinch Tight, H&H Associate, Bena, VA). QuikClot formulations either granular (lot 0308C) or bagged (lot 0708N) were obtained from Z-Medica Corp.; both products had the same (1%) moisture content and known exothermic reactivity. The bagged (ACS) formulation exhibited an increased bead size ($1.7–2.4$-mm versus $0.4–0.8$-mm diameter granules in original QuikClot), and was contained in a mesh bag. Both products required standard dressing with application of manual pressure on the dressing.

**Injury**

After a brief period of stabilization, the groin area was exposed and abductor and quadriceps muscles exposed in the proximal medial right thigh through a surgical incision. Injury was induced by transecting the femoral blood vessels to produce uncontrolled hemorrhage as described by Alam et al.\textsuperscript{7} This injury involves cutting the superficial and deep muscular injection of ketamine hydrochloride (HCL) (30 mg/kg) and inhalation of 3% isofluorone. After placement of endotracheal tube, the isofluorone concentration was reduced to 2.2% until initiation of injury. After the onset of bleeding, the level was reduced to 1% to 1.5% and then regulated to maintain sedation thereafter. The animals were allowed to breathe spontaneously using a mixture of oxygen and air administered through a Narkomed M ventilator (North American Dräger, Telford, PA). End tidal CO\textsubscript{2} and respiration rate were continuously monitored and regulated between 34 and 45 mm Hg, and were intermittently recorded. Rectal temperature was monitored and maintained between 36.0 and 37.8°C using a Bair Hugger device (Model 505, Bair Hugger, MN). An 18G angiocatheter was placed in the right carotid artery and connected to the arterial line to acquire blood pressure and withdraw blood samples. The external jugular vein was then cannulated with a 22G angiocatheter and 9Fr introducer to place a 7.5Fr oximetric thermodilution pulmonary artery catheter (Schein Care Corp., Irvine, CA). The catheter was attached to a hemodynamic monitoring system (Hewlett Packard, Palo Alto, CA) to allow for continuous monitoring of the mean pulmonary artery pressure (MPAP). Resuscitation fluid was infused through this venous access. All catheters were flushed with a citrated flush solution (50 mL of acid-citrate-dextrose in 500 mL of 0.9% saline solution) to maintain patency. Pulse oximetry data (Data–Omedex) was obtained from either foot or tail extremity.
bowl; aspiration was directed toward the blood accumulating in the groin cavity and not directly at the site of injury.

**Treatment**

After 3 minutes of free bleeding (simulating the response time for arrival of the first responder), the animals (n = 32) were randomly assigned to treatment regimen in a blinded fashion and evenly distributed among four treatment groups (n = 8 per group): (1) no treatment (NONE); (2) standard dressing (SD); (3) granular QuikClot (QC); and (4) bagged QuikClot (ACS). Before application of hemostatic agents, excess blood was evacuated from the wound without disturbing the vascular injury site. During application of hemostatic agents, the granular formulation was poured into the wound whereas the ACS bags were placed to best follow the contours of the wound. Immediately afterward, the wound was packed with standard dressing and manual compression pressure (approximately 150 mm Hg) was applied for 5 minutes, monitored by a pediatric lightly inflated cuff (SoftCuff, GE) placed in the standard dressing and recorded with a handheld digital manometer (HM28, Dwyer, MI City, IN). At 8 minutes, manual pressure was released and the wound was closed for the entire length of the experiment (4 hours) by clamping the skin flaps together. At 15 minutes after onset of hemorrhage, a bolus volume of intravenous resuscitation isotonic colloidal fluid (500 mL of Hextend; Biotime, Emeryville, CA) was given through the jugular catheter during a span of 30 minutes using a Masterflex pump (Cole Parmer, Vernon Hills, IL) corresponding to a delivery rate of approximately 15 mL/min. Animals were monitored for a total of 4 hours then euthanized by injection (100 mg/kg) of Euthasol solution. The animal was then de-instrumented and the dressings were removed and weighted.

**Histologic Scoring**

After euthanasia or spontaneous death, gross necropsy evaluation of each animal was performed with particular emphasis on muscle and surrounding wound tissues. Tissues were sectioned from the wound site where the dressing was applied and up to 5 cm away from the wound site. Tissues were fixed in 10% formalin, embedded in paraffin, cut by microtome (6 μm), and stained with hematoxylin and eosin (H&E). A board certified veterinary pathologist who was blinded to the experiment examined all tissues with use of light microscopy. Degenerative necrosis and edema were qualitatively assessed in muscle, nerve, and vessels according to relative abundance (score 0–5) and severity (score 0–4). A score index was computed as abundance x severity for all surviving animals and then averaged and expressed as a percent over a maximum score of 20 (4 × 5).

**Data Acquisition**

Shed blood volume was collected in a sealed container (MediVac-2L, CardinalHealth) and continuously weighed on a top-loading scale (Mettler, PS 5100). Rectal temperature and wound temperature at the interface of blood and dressing were continuously recorded using an analog temperature monitor (BAT 12, PhysiTemp, PA). Blood pressure (mean arterial pressure [MAP], diastolic, and systolic) and heart rate (HR) were continuously measured on a blood pressure analyzer (BPA) (Micro-Med Inc, Louisville, KY). Software (Labview interface version 4, National Instrument, Austin, TX) was used to acquire data every 5 seconds from the BPA, top-loading scale, temperature monitor, and manometer; data were directly downloaded into an Excel spreadsheet (Microsoft Inc., Redmond, WA) for further analysis. End-tidal CO₂, isofluorane level, respiration rate, and MPAP, were manually recorded every 5 minutes for the first hour and every 15 minutes thereafter.

**Blood Analysis**

The volume of blood loss (mL) was determined from the weight of blood lost by the ratio of 1.056 g/mL. The estimated blood volume (EBV) was calculated relative to the animal’s weight with an approximation of 65 mL blood per kg. The experimental blood loss was divided into pretreatment hemorrhage (time 0–3 minutes) and posttreatment hemorrhage (time 3 minutes to end point); posttreatment shed blood consisted of aspirated blood (collected by vacuum suction) and blood absorbed in the standard and hemostatic dressings, which were weighed before application and at the end of the experiment. Blood retained in the QC granules was more difficult to assess as many granules adhered to the wound preventing complete recovery and obtaining total weight of the absorbed blood. In QuikClot-treated animals, absorbed blood loss represents the blood contained in both the Cinch Tight gauze and in the QC or ACS dressings.

**Statistics**

All data are presented as group means ± SD. One-way analysis of variance (ANOVA) with χ² for linear distribution was performed to determine significance at p ≤ 0.05 for comparison of data regarding blood loss and survival. The primary outcome (dependent variable) was 4-hour survival. One analysis compared the proportion of animals that survived to 4 hours across all four treatment groups using Fisher’s exact test. The second analysis utilized time-to-event based analyses (e.g. Kaplan-Meier, Cox Proportional hazards regression) to compare survival rates across the treatment groups. The secondary outcomes of interest for this study (e.g. blood loss, MAP, MPAP) were continuous in nature and compared with ANOVA among the treatment groups.

**RESULTS**

**Hemorrhage Severity**

Thirty-two animals used in the present study had an average weight of 34.1 ± 3.2 kg and an average initial MAP of 76.0 ± 9.5 mm Hg. The average blood loss at 3 minutes (before randomization and initiation of treatment) was 44.7% ± 11.9% EBV with an initial bleeding rate of 639 ± 197 mL/min.
The MAP sharply decreased in the first 3 minutes of uncontrolled bleeding to an average of 14.1 ± 11.2 mm Hg. All animals were randomized into four separate treatment groups; there were no differences in the drop in blood pressure or in the level of blood loss among the four groups (Table 1). The compression pressure that was applied manually on the dressing from 3 to 8 minutes averaged 159 ± 10 mm Hg; the average compression pressure when the wound flaps were closed after 8 minutes was 36 ± 6 mm Hg, which was also consistent and not significantly different among groups. The MAP of QC- and ACS-treated animals was transiently increased upon application of dressing and manual pressure, and remained permanently elevated in surviving animals, above 50 mm Hg, after initiation of fluid resuscitation at 15 minutes posthemorrhage (Fig. 1). The MAP of animals treated with SD was also transiently elevated but failed to increase thereafter. MPAP dropped immediately after injury and, although quite variable, increased in all groups after initiation of fluid resuscitation (Fig. 2). In all surviving animals, MPAP increased to and stabilized at approximately 10 mm Hg. In nonsurvivors, MPAP either did not reach this threshold or was only transiently increased to this level. Each individual NONE pig exhibited MPAP values <10 mm Hg throughout the postinjury sequence.

**Survival**

None (0%) of the nontreated animals survived to the 4-hour end point as they continuously bled to death (Fig. 3, Table 1) and died at an average time of 60 minutes (range 15–125 minutes). The application of SD supported survival in only one animal (1 of 8, 12.5% survival) compared with 75% survival in animals treated with either QuikClot formulations (each group 6 of 8 versus SD \( p < 0.05 \) and versus NONE \( p < 0.01 \)). There was no difference between the QuikClot (QC and ACS), or between the SD and NONE groups. The time to death from the injury in the SD-treatment group (96.8 ± 69.3 minutes) was not significantly different from that of the NONE controls (60 ± 42 minutes). However, the time to death in the QC and ACS-treatment groups (188 ± 91 minutes and 194 ± 86 minutes, respectively) were both significantly higher than that of the SD (\( p < 0.02 \)) and NONE (\( p < 0.001 \)) treatment groups.

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**Table 1 Experimental Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (kg)</th>
<th>Initial MAP (mm Hg)</th>
<th>Blood Loss (3 min; %EBV)</th>
<th>MAP (3 min; mm Hg)</th>
<th>Survival Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>33.8 ± 3.4</td>
<td>78.9 ± 11.5</td>
<td>43.2 ± 14.9</td>
<td>15.7 ± 14.7</td>
<td>60.0 ± 42.3</td>
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<tr>
<td>SD</td>
<td>34.4 ± 2.0</td>
<td>79.6 ± 10.5</td>
<td>39.8 ± 13.3</td>
<td>19.8 ± 12.9</td>
<td>96.8 ± 69.3</td>
</tr>
<tr>
<td>QC</td>
<td>35.0 ± 4.0</td>
<td>73.2 ± 7.9</td>
<td>48.9 ± 10.4</td>
<td>9.2 ± 4.4</td>
<td>187.6 ± 91.1</td>
</tr>
<tr>
<td>ACS</td>
<td>33.1 ± 3.5</td>
<td>72.2 ± 6.8</td>
<td>47.1 ± 8.0</td>
<td>11.6 ± 7.8</td>
<td>193.5 ± 86.2</td>
</tr>
</tbody>
</table>

Data indicate the mean ± standard deviation of all animals (n = 8/group) in each of the experimental groups including nontreated (NONE) or treated with standard dressing (SD), granular QuikClot (QC), or bagged QuikClot (ACS).

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**Fig. 1.** Blood pressure during first hour of experimental treatments. Data indicate mean arterial blood pressure (MAP) ± SD for animals (n = 8) treated with either standard dressing (△), granular QC (●), or bagged ACS (○) at indicated times after initiation of hemorrage. Arrows indicate 1: application of dressing after femoral vessel transection (initiation of treatment \( t = 3 \) min), 2: end of manual pressure application \( t = 8 \) min, and 3: initiation of Hextend infusion \( t = 15 \) min. Standard deviation bars were omitted on the data for standard dressing treatment to provide clarity for comparison of data on QuikClot formulations.

**Fig. 2.** Mean pulmonary artery pressure presented for all experimental groups. Data indicate mean pulmonary artery pressure (MPAP) ± SD for animals (n = 8) that were untreated (▲) or treated with standard dressing (△), granular QC (●), and bagged ACS (○). Error bars represent SD for QC and ACS formulations of QuikClot; standard deviation bars were omitted on the data for none and standard dressing treatments to provide clarity for comparison of data on QuikClot formulations. Arrow indicates time of initiation of fluid resuscitation (15 min).
Wound Temperature and Histologic Results

Significantly elevated wound site temperatures were observed in animals treated with QC or ACS. The elevation of temperature at the wound and QuikClot interface peaked at approximately 1 to 2 minutes after application of the dressing and reached a comparable maximum of 58.1 ± 4.5°C and 58.2 ± 5.3°C with QC and ACS, respectively. These temperatures were significantly higher (p < 0.01) compared with that of SD (37.8 ± 0.4°C) and NONE (37.5 ± 0.7°C) control groups, which were similar to the animal’s preintervention body temperature. In both QC- and ACS-treated animals, the temperature declined to 40°C by 60 minutes (see Fig. 4 for representative experiment). Coincident with the high temperatures, a visual discoloration (paler, hypoperfused aspect) of the muscular tissue adjacent to the wound was evident in animals from the QC and ACS groups (Fig. 5). Tissues from SD and NONE controls were unremarkable. Histologic examinations of the tissues of animals that survived 4 hours in the QC and ACS groups showed edema but edema was not seen in the SD and NONE groups or in pigs in the ACS and QC groups that died before 4 hours. Lesions occurred inconsistently but were seen more often in tissue exposed to ACS as compared with QC. The degeneration necrosis index at the wound site for the animals treated with QC or ACS was <4% and was absent in distal sections. Scores of >5% representing edema were detected at the wound site of surviving animals; scores <2% were noted as far as 2 cm from the wound site in ACS-treated animals compared with less than 1 cm away from the wound site in QC-treated animals. The animals that survived the entire 4-hour experimental period, showed few or no myofibrils and no deep necrosis or fibrosis upon examination with use of light microscopy. Early scattered coagulative necrosis was observed in less than 5% of the muscle and connective tissue.

Bleeding Control

There were no differences in the average blood loss at 3 minutes in all four treatment groups (44.7% ± 11.9% EBV). The blood loss after the first 3 minutes consisted of blood that was freely oozing from the wound (i.e. aspirated blood) and blood that was absorbed into the SD, QC, or ACS dressings.
(i.e. absorbed blood). The levels of blood loss in each category for all experimental animals are shown in Table 2. The posttreatment blood losses in both the ACS-treated animals (10.3% EBV) and SD-treated animals (22.3% EBV) were significantly lower (p < 0.01 and p < 0.04, respectively) than the blood loss in NONE-treated animals (31.5% EBV). The blood loss in the ACS-treated animals was also significantly lower than that of the SD-treated animals (p < 0.05). The blood loss measured in the QC-treated animals (7.5% EBV) could not be accurately measured as QC granules adhered to the wound and could not be completely removed for quantification. Interestingly, both ACS and SD dressings absorbed similar quantities of blood indicating that the significant difference in posttreatment blood loss was principally a result of aspirated blood levels (1.7% and 12.7% EBV), respectively. In these cases, the absorption capacity of the dressing was exceeded, and unabsorbed blood that oozed out of the wound was collected by aspiration. In three of the eight animals that survived for more than 30 minutes in the NONE group, episodes of rebleeding were observed that were associated with increases in MAP. In the SD group, four of the five animals that survived for more than 30 minutes died from rebleeding after MAP improved to >45 mm Hg during resuscitation. These bleeding episodes required aspiration of shed blood that was also coincident with sharp decreases in MAP. These drops in MAP that may be associated with rebleeding (and absorption of blood into hemostatic dressing) were typically seen during the experimental period. In animals treated with either of the QuikClot formulations, such drops in MAP were usually brief and immediately followed by rapid compensation of MAP (see Fig. 6). In the majority of these animals, strong, firm clots located at the edge of the transected blood vessels at the site of contact with the hemostatic dressing were observed at the end of the experimental period after removal of the dressing.

**DISCUSSION**

The experiments described here utilize a modified delivery system (bagged) for the application of QuikClot granules. This modification (bagged QuikClot or ACS) facilitated the local administration of product while eliminating its possible dispersion under adverse conditions. It also permitted more rapid and complete removal of granules from the wound site as compared with the original granular formulation of QuikClot. Most importantly, this modification did not affect the efficacy of the product. The modified bagged formulation of QuikClot was also significantly able to reduce mortality in a groin injury model of uncontrolled hemorrhage (25% versus 87.5% with standard treatment, p < 0.01). This capacity to increase survival relative to standard treatment was comparable to that observed using the original QuikClot granules (both were 87.5% effective). The objective of the current study also included evaluating the hemostatic capacity, temperature effects, and histopathologic results associated with ACS and comparing these parameters with the original granular QC formulation. The findings confirmed those reported by Alam et al., who used QC in a similar animal model.5 The elevated temperatures with both QC and ACS were similar in magnitude and in a range comparable to that reported in the literature (53–64°C).5 Also, both QuikClot formulations (QC and ACS) were similarly efficacious in arresting bleeding. The critical 3-minute uncontrolled bleed after vascular injury (with an initial rapid blood loss of approximately 45% EBV, equivalent to 30 mL/kg) was uniformly fatal without treat-

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**Table 2 Effect of Hemostatic Treatment on Blood Loss**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pretreatment Blood Loss</th>
<th>Posttreatment Blood Loss</th>
<th>Aspirated</th>
<th>Absorbed</th>
<th>Total Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>43.2 ± 14.9</td>
<td>31.5 ± 21.8</td>
<td>30.9 ± 22.3</td>
<td>0.6 ± 1.3</td>
<td>74.7 ± 3.9</td>
</tr>
<tr>
<td>SD</td>
<td>39.9 ± 13.3</td>
<td>22.3 ± 12.6</td>
<td>12.7 ± 12.6</td>
<td>9.6 ± 3.5</td>
<td>62.2 ± 17.0</td>
</tr>
<tr>
<td>QC</td>
<td>48.9 ± 10.4</td>
<td>7.4 ± 7.1</td>
<td>4.4 ± 6.7</td>
<td>3.0 ± 1.7*</td>
<td>56.3 ± 15.6</td>
</tr>
<tr>
<td>ACS</td>
<td>47.1 ± 8.0</td>
<td>10.3 ± 6.9</td>
<td>1.7 ± 2.6</td>
<td>8.5 ± 5.9</td>
<td>57.3 ± 9.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation percent estimated blood volume (8 animals per group) and indicate blood loss at 3 min (pretreatment blood loss) and total blood loss at end of experiment. Posttreatment blood loss consists of blood that was removed by aspiration and blood that was absorbed in applied dressings. *Assessment of total blood loss was inaccurate because of inability to completely collect all QC granules.

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**Fig. 6.** Measurement of blood pressure after ACS treatment of animals exposed to uncontrolled hemorrhage. MAP recordings observed in a representative animal treated with ACS Drops in MAP were usually brief and immediately followed by rapid compensation of MAP, and may be associated with rebleeding.
ment and confirmed the severity of this uncontrolled hemorrhage model. The maximum bleeding took place during the first minute of injury and the subsequent rate of blood loss was diminished during the ensuing minutes; this reduction in rate of active bleeding was related to the decreased blood pressure (MAP at 3 minutes: 14.1 ± 11.2 mm Hg). Although the 3-minute time interval was chosen to reflect anticipated response time of first responders in a military scenario, the resultant hypotensive condition unquestionably reduced the actual hemostatic “challenge” presented to the experimental dressings. Future treatment applications may be assessed at an earlier time point where high (~500 mL/min) rate of blood loss within the first minute may saturate the dressing more rapidly and influence its ability to promote clotting.

In this very severe hemorrhage model (blood loss ~ 45% EBV), chances of survival are negligible as denoted by others as well as by the demise of all nontreated animals described here. Although not delineated here, four of the animals that had exhibited blood losses greater than 45% EBV survived after treatment with QuikClot. The capacity for this treatment to allow animals to survive for up to 4 hours is also interesting because animals are still hypovolemic at the end of the experimental period despite fluid resuscitation (infusion of 500 mL Hextend is equivalent to only 25% EBV). The observation that this hypovolemic resuscitation was sufficient to maintain MAP above 40 mm Hg, supports the hypothesis that survival is fundamentally dependent upon the ability of the animals to compensate and restore blood pressure as well as other vital indices. It was observed that the majority of animals that did not survive the entire 4-hour experiment died within the first hour after injury. It was also noted that treatment with SD alone was not sufficient to increase and stabilize MAP, except in the one case in which the animal survived. These results clearly demonstrate that physiologic compensation mechanisms including pulmonary pressure were better sustained in animals treated with the QC or ACS hemostatic dressings. This suggests that bleeding arrest contributed early to a better hemostatic recovery and reduction of the shock phase. It should be noted that the application of constant manual compression on the dressings, which were all treated similarly in this regard, might have contributed to efficacy of the dressings. However, in battlefield conditions, first responders may be required to devote their time and attention to other asymmetric, evolving priorities and will not be able to attend to the wound so methodically. Securing the hemostatic dressings with an elastic bandage capable of providing constant pressure may therefore prove to be an additional benefit.

It was observed that all surviving animals (regardless of treatment) exhibited MAP values >18 mm Hg at 15 minutes. This capacity to elevate MAP may be a key criterion for determining survival. In fact, the survival of animals in the experiments described here was directly related to their capacity to restore MAP during this early time period between the removal of manual pressure on the dressing and the initiation of fluid resuscitation; if MAP was not restored above 18 mm Hg in this time frame, the animals did not survive. Perhaps not coincidentally, all animals that died in the QC (2 of 8) and ACS (2 of 8) groups did not exhibit MAP values above 18 mm Hg at any point during this critical time period. This invites speculation that perhaps there are situations, dependent upon the patient’s condition in the immediate postinjury period, that are not amenable to treatment with hemostatic dressings as described here.

As stated by Pusateri et al., field injuries are diverse and one single animal experimental model cannot represent all potential situations. Thus, distinct hemostatic products may be more effective depending on the origin (arterial or venous) of bleeding as well as hemorrhage models used to evaluate such products. Initially, both model injuries reveal a rapid arterial bleed but it is possible that clot stability is different in a punctured artery as opposed to transected vessel (e.g. arterial vs venous blood). In the groin injury model described here, the animals in the NONE group illustrated the phases of the bleeding events. Initial bleeding was primarily of arterial origin and was characterized by a relatively high pressure and shear rate. Subsequent bleeding, discerned by the color of the blood in the NONE animals, was predominantly from venous origin. The precise mechanism(s) by which Zeolite is able to arrest bleeding in these injuries is unclear. It is surmised that the absorption of water by the Zeolite beads concentrates platelets and clotting factors thereby promoting rapid clot formation. The negatively charged surface of the zeolite beads may initiate the intrinsic coagulation cascade and blood coagulation factors could be transiently concentrated near the bead surface because of the strong water adsorption. As this may occur upon initial contact of QC or ACS with blood, coagulation reactions might be subsequently and rapidly nullified by the exothermic reaction as relatively small increases in temperature were seen to have beneficial effects on clot formation. Alternatively, the exothermic reaction of QC could promote cauterization within minutes after application. However, the increase of temperature above physiologic range for a period of 60 minutes seemed to have produced some local thermal tissue injury. Although overt tissue damage was not seen at the 4-hour end point, there was evidence that ACS, and to a lesser extent QC, induced some localized edema. More substantiated tissue damage including thermal necrosis and skin necrosis was demonstrated at later times by others, and substantiates efforts to evaluate products with lesser exothermic reaction.

Fabric material from the ACS did not appear to act as a disruption barrier or decrease exothermic heat. As mentioned, histologic sections showed some coagulative necrosis at the QuikClot and wound interface, but such changes were not seen at sites distal to the wound. This occurrence of coagulation in tissue did not extrapolate to systemic hemostasis (data not shown). Although similar in many aspects, the removal of ACS bags left a clean wound that could be rapidly and readily accessible for surgical repair; in contrast, removal of loose granular QC was less complete and more time

Comparison of Bagged Versus Granular QuikClot
consuming. In both cases, clotted blood could be seen at the
top of the inguinal cavity upon removal of the dressings;
also, blood clots appeared firmer with both QuikClot hemo-
static dressings as compare with standard dressing. How-
ever, this did not prevent oozing after removal of the
dressing. In conclusion, both granular and bagged Quik-
Clot were superior to standard dressing in severe groin
injury of uncontrolled hemorrhage. Both QC and ACS
showed comparable efficacy in controlling bleeding and sur-
vival, and exhibited comparable temperature elevation and ther-
mal effects at the wound site.

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Alterations in hemostasis associated with hyperthermia in a canine
Hemostatic Efficacy of a Recombinant Thrombin-Coated Polyglycolic Acid Sheet Coupled With Liquid Fibrinogen, Evaluated in a Canine Model of Pulmonary Arterial Hemorrhage

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Background: In thoracic surgery, although infrequent, we encounter unexpected damage to the pulmonary artery (PA). In the present study, we evaluated the hemostatic efficacy of a newly developed fibrin-based sheet material, thrombin sheet, coupled with liquid fibrinogen (TSF), in an experimental model of PA hemorrhage.

Methods: Female beagles (n = 8) were used for the study. Left thoracotomy was performed under general anesthesia. PA injury (approximately 4 × 2 mm) was created, and repaired by TSF (TSF group) or TachoComb (TC group). The animals were allowed to survive, and the repaired site was evaluated 4 weeks after the experiment.

Results: The number of sheet application and compression procedures required for hemostasis was increased in the TC group compared with in the TSF group (TC vs. TSF, 4 ± 1 vs. 1 ± 0.5, p = 0.01, unpaired t test). The time required to achieve hemostasis was increased in the TC group compared with in the TSF group (TC vs. TSF, 7 ± 3 vs. 1 ± 0.5 minutes, p = 0.01, unpaired t test). The amount of bleeding during the hemostasis procedure was increased in the TC group compared with in the TSF group (TC vs. TSF, 48 ± 22 vs. 3 ± 3 g, p = 0.01, unpaired t test). At 4 weeks, rethoracotomy revealed no apparent indication of delayed bleeding, such as intrathoracic hematoma formation or excessive adhesion formation in the vicinity of PA, in either group. Histologically, the vessel lumen was well sustained in both groups, with no apparent stenosis or thrombus formation.

Conclusion: The hemostatic efficacy of TSF was superior to TC in this particular experiment. Single application of TSF was sufficient to achieve hemostasis in all but one animal. Compression time of approximately 1 minute was also very short albeit that the bleeding was from the PA and not an artery. These results were presumably because the adhesion was stronger, faster, and the sheet was more pliable in TSF compared with TC.

Key Words: Recombinant thrombin sheet, Hemostasis, Pulmonary artery.


In thoracic surgery, although infrequent, we encounter unexpected damage to the pulmonary artery (PA) resulting in moderate to massive hemorrhage. In most cases, bleeding can be controlled on the spot by manual compression, but compression needs to be released at some point to repair the damage, either to directly suture the vessel, or to sufficiently isolate the vessel, clamp it, and control the bleeding. Significant blood loss can ensue during this period. It will be possible to reduce this blood loss if a ready-to-use hemostatic material, capable of swift hemostasis becomes available.

Hemostatic materials exploit various mechanisms such as absorbing and concentrating components of blood, increasing the enzymatic activity of clotting factors, or activating platelets.1–3 Topical hemostatic agents utilizing materials such as cellulose or collagen provide mechanical scaffolds on which thrombus forms, but lack any inherent coagulation potential.4,5 In this regard, fibrin-based materials can mimic thrombus formation and currently seem to be most effective.6–11

We have developed recombinant thrombin,12,13 which was lyophilized onto a bioabsorbable synthetic nonwoven polyglycolic acid fabric (Neoveil, Gunze K. K., Kyoto, Japan) to yield a new fibrin-based sheet material, thrombin sheet (TS).14 TS combined with liquid fibrinogen (TSF), is capable of swift hemostasis even when applied inside a blood pool. Fibrinogen solution is dripped onto the sheet immediately before application. Neoveil is loosely fabricated, and the sheet thickness is adjusted to 0.15 mm. This makes TSF quite supple so that it is able to securely conform to the contour of the applied site.

The hemostatic effect of fibrin-based materials in vascular injuries have been evaluated extensively using arterial injury models.1–3,6,8–11 To our knowledge, control of hemorrhage from the PA has not been adequately assessed.
Although blood pressure in the artery is much higher in comparison with that of the PA, adequate attachment of the sheet material may be more difficult to achieve in the PA because the vessel wall is more easily deformed by compression. Therefore, materials that control arterial hemorrhage may not necessarily be effective in PA hemorrhage.

In the present study, we evaluated the hemostatic effect of TSF in an experimentally created PA hemorrhage model. The efficacy of TSF was compared in the same model with that of TachoComb (TC) (ZLB Behring Co., Ltd., Bern, Switzerland), a widely used commercially available fibrin-based sheet product. We also measured in vitro fibrin formation in each material as a parameter of hemostatic potential.

**MATERIALS AND METHODS**

**Preparation of Thrombin Sheet**

Preparation of TS has been described previously. Briefly, mannitol (Nakarai Kagaku, 213-03, Kyoto, Japan), with a final concentration of 0.5% to 1.5%, and 40 mmol/L of calcium chloride were added to a solution containing 0.5% to 2% of glycerol. Recombinant thrombin was added to make the final concentration 1,500 U/mL. This solution was dripped at a rate of 0.05 mL/cm² and spread evenly using rubber-tipped rods onto a bioabsorptive synthetic nonwoven fabric (3 cm × 3 cm) made of polyglycolic acid, Neovel (thickness, 0.15 mm). The sheet was frozen at −80°C for 2 hours and dried to fix the recombinant thrombin. The sheet was trimmed to 1.5 cm × 1.5 cm for use in this experiment. The sheet was dipped in 0.2 mL of liquid human fibrinogen (Bolheal, Chemo-sero-therapeutic Research Institute, Kumamoto, Japan). The liquid fibrinogen seeped evenly into the sheet within seconds. The sheet was then immediately applied.

**Animal Experiment**

Female beagles (Kitayama Labes Co. Ltd., Nagano, Japan) (n = 8) were used for the study. Body weight was measured before induction of anesthesia. Anesthesia was induced by subcutaneous injection of atropine sulfate (0.25 mg per animal), followed 10 minutes after by intramuscular injection of xylazine (1 mg/kg) and ketamine (10 mg/kg). The radial vein was canulated. Anesthesia was maintained by continuous infusion of 0.1% ketamine in 5% glucose at a rate of approximately 1 mL/min. After injection of suxamethonium (10 mg per animal), the animal was intubated and mechanically ventilated with 40% oxygen. Tidal volume was approximately 200 mL, and respiratory rate was 14 breaths per minute. Empirically, mean systemic arterial blood pressure was maintained at approximately 100 mm Hg during this anesthesia protocol.

The animal was placed in a right lateral position, and left fourth intercostal thoracotomy was performed. The interlobar portion of the left PA was used for the experiment. A 2-mm plastic catheter with an 18-gauge needle tip was gently inserted into the PA, and PA pressure was measured until the values stabilized (for approximately 1 minute). Bleeding during this procedure was negligible. Next, the vessel wall adjacent to the needle insertion site was held with fine-toothed forceps, and the vessel wall was resected with fine scissors so as to expand the needle hole proximally. Accounting for the thin and soft PA wall, we preferred this procedure to the use of a punch device. In our preliminary experiment, the laceration thus created was approximately 4 mm × 2 mm. The needle catheter was removed, and free bleeding was visually confirmed for approximately 3 seconds, after which it was controlled by manual compression. Blood in the thoracic cavity was thoroughly suctioned. TSF (TSF group, n = 4) or TC (TC group, n = 4), both 1.5 cm × 1.5 cm in size, was prepared for application. Manual compression was released, and immediately the sheet was applied to cover the laceration. Manual compression was applied over the sheet for 1 minute. If bleeding was not controlled, an additional sheet was applied followed by another minute of manual compression. This was repeated until bleeding was visually controlled. Bleeding during this period was absorbed using gauze, and measured in grams. Hemostasis was confirmed by observation for an additional 10 minutes, and then the chest was closed. Ketoprofen (1 mg/kg) and ampicillin sodium (15 mg/kg) was injected intramuscularly. The animals were allowed to recover and then were returned to their cages. After 4 weeks, the animals underwent rethoracotomy under general anesthesia and the left chest cavity was observed. The interlobar portion of the left PA was carefully inspected for traces of secondary bleeding, for the magnitude of tissue adhesion, and for the presence of residual materials. PA pressure measurement was performed as previously, distal to the site of vessel injury. The animals were killed by pentobarbital overdose, and the left PA was resected together with the left lung. The specimens were fixed in 10% buffered formalin, and embedded in paraffin. Three micrometer paraffin sections were stained with hematoxylin and eosin for histologic examinations.

The School of Medicine Keio University Institutional Animal Care and Use Committee approved all animal studies, which were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Academies Press.

Data are shown as mean ± standard deviation. Comparisons were made between groups using unpaired t test and within groups using paired t test (StatView, SAS Institute Inc., Cary, NC). Significance was assumed at p < 0.05.

**In Vitro Measurement of Fibrin Formation**

The fibrin clots were prepared for in vitro analysis as follows. In the TC group, a piece of the sheet (0.5 cm × 0.5 cm) was soaked with 50 µL of saline containing 10 U/mL of factor XIII, 50 U/mL of recombinant thrombin, and 25 mmol/L of CaCl₂, and then incubated for 5, 10, and 30 minutes at 37°C. The reaction was stopped by adding 50 µL of stop solution (4 mol/L urea, 5% sodium dodecyl sulfate (SDS), and 10% 2-mercapto ethanol). Fibrin was dissolved overnight.
In the TSF group, 12.5 μL of 20 mg/mL fibrinogen containing 25 mmol/L of CaCl₂ was added to TS (size, 0.5 cm × 0.5 cm; thrombin, 75 U/cm²), and incubated for 5, 10, and 30 minutes at 37°C. The reaction was stopped by adding of 12.5 μL stop solution as in the treatment for TC. SDS-polyacrylamide gel electrophoresis was performed according to the method of Laemmli. About 1 g of fibrinogen was subjected to SDS-polyacrylamide gel electrophoresis on a 7.5% polyacrylamide gel under reducing conditions. The gel was stained with Coomassie brilliant blue R-250.

RESULTS

All the animals survived. Body weight was comparable between groups before the experiment (TC vs. TSF, 10.0 ± 1.0 vs. 10.4 ± 0.2 kg, p = 0.50) and at 4 weeks after the experiment (TC vs. TSF, 11.6 ± 0.9 vs. 11.7 ± 0.6 kg, p = 0.1). Within groups, body weight was increased in both groups at 4 weeks after the experiment (TC group p = 0.03, TSF group p = 0.01).

Mean PA pressure was comparable between groups before vessel laceration (TC vs. TSF, 28 ± 5 vs. 27 ± 9 mm Hg, p = 0.96) and at 4 weeks after the experiment (TC vs. TSF, 32 ± 3 vs. 30 ± 1 mm Hg, p = 0.2). Also, within groups, mean PA pressure was comparable in both groups at 4 weeks after the experiment, compared with values before vessel laceration (TC group p = 0.59, TSF group p = 0.21).

Hemostasis was effectively achieved in both groups after sheet application. In the TSF group, the laceration could be clearly seen through the sheet (Fig. 1, arrow). The number of sheet application and compression procedures required for hemostasis was increased in the TC group compared with in the TSF group (TC vs. TSF, 4 ± 1 vs. 1 ± 0.5, p = 0.01). The time required to achieve hemostasis was increased in the TC group compared with in the TSF group (TC vs. TSF, 7 ± 3 vs. 1 ± 0.5 minutes, p = 0.01). The amount of bleeding during the hemostasis procedure was increased in the TC group compared with in the TSF group (TC vs. TSF, 48 ± 22 vs. 3 ± 3 g, p = 0.01).

At 4 weeks, rethoracotomy revealed no apparent indication in either group of delayed bleeding, such as intrathoracic hematoma formation or excessive adhesion formation in the vicinity of the PA. Macroscopically, adhesion of the lung to the site of sheet application was more apparent in the TC group compared with the TSF group. Residual material was present in both groups, and more prominent in the TC group. Histologically, the vessel lumen was well sustained in both groups, with no apparent stenosis or thrombus formation. However, thickening of the adventitia and the perivascular sheath seemed to be more prominent in the TC group (Fig. 2).

In vitro fibrin formation was more prominent in the TSF group compared with in the TC group. In the TSF group, γ-γ cross-linking was formed within 10 minutes, and α-α polymer was observed. On the other hand, we identified only a trace amount of γ-γ cross-linking in TC group (Fig. 3).
Material commercially available in Europe and Japan. Sim-

store, particularly for use in combat settings. TC is one such

ready for immediate use. Dry materials are also easier to

thrombin and fibrinogen, lyophilized onto a sheet material

These materials should optimally contain both components,

end, dry fibrin-based hemostatic materials are being devel-

oped extensively for potential use, particularly in trauma.8,9,11

in Europe and Japan for many years. Most formulations come

as solutions of dissolved thrombin and fibrinogen, which are

mixed on application. This form of liquid application is

more suitable because it can withstand the initial outflow of

blood, and can be held with pressure after application. To this

end, the TSF is quite supple and conforms considerably

for a more definitive hemostasis (data not shown). This prop-

erty can be considered comparable with what is reported for

the American Red Cross fibrin dressing.8,9 Although we do

results are promising.

Fibrin-based sealants have been commercially available

in Europe and Japan for many years. Most formulations come

as solutions of dissolved thrombin and fibrinogen, which are

mixed on application. This form of liquid application is

obviously not well suited for hemostasis in vessel injuries

where there is significant outflow of blood. Solid material is

more suitable because it can withstand the initial outflow of

blood, and can be held with pressure after application. To this

end, dry fibrin-based hemostatic materials are being develop-

ed extensively for potential use, particularly in trauma.8,9,11

These materials should optimally contain both components,

thrombin and fibrinogen, lyophilized onto a sheet material

ready for immediate use. Dry materials are also easier to

store, particularly for use in combat settings. TC is one such

material commercially available in Europe and Japan.16 Sim-

ilar dry-sheet type fibrin-based sealants have been exten-

sively evaluated in a variety of hemorrhage models. The

results are promising.

Compared with dry materials, TSF is semidry, and may

not be ideal for use in trauma settings because liquid fibrin-

ogen needs to be separately prepared. But our attempt to

include dry fibrinogen into a sheet material considerably

increased the rigidity of the sheet, as is the case with TC. To

this end, the TSF is quite supple and conforms considerably

to the contour of the applied site in comparison with how well TC conforms. We considered that this may be

advantageous for bleeding during surgery, particularly from

the PA, which is distributed three dimensionally in the tho-

racic cavity with branching from short segments and is sur-

rounded by lung tissue, which inflates and deflates during

ventilation.

In the present study, we investigated the efficacy of fibrin-based sheet type materials in a PA injury model. He-

mostasis in vessel injury has been evaluated quite extensively

in swine aortic models.2,8–11 Considering the size of the

animals used, approximately 10 kg dogs versus approxi-

mately 40 kg pigs, we consider the laceration size in the

present study (4 mm × 2 mm) to be sufficiently large,

relative to the laceration size in the widely reported swine

model of aortic bleeding (4 mm × 4 mm). In our preliminary

experiment, PA injury could not be controlled by manual compression alone.

Both TSF and TC were capable of adequately controlling

PA hemorrhage in this study. Because PA pressure is signif-

icantly lower compared with systemic arterial pressure, re-

duction in blood flow caused by stenosis may more readily

ensue compared with the response of arteries of similar cal-

iber. Based on the PA pressure measurements and histologic

observations, vessel stenosis or intraluminal thrombosis was

not apparent with the use of either material in this study 4

weeks after application, despite the relatively large laceration

size. Histologically, thickening of the adventitia and the

perivascular sheath was suspected in the TC group, which

may in part be because of the increased number of sheet

applications.

Overall, the efficacy of TSF was superior to that of TC in

this particular experiment. A single application of TSF was

sufficient to achieve hemostasis in all but one animal in

which the sheet was misplaced, and the vessel laceration was

only partially covered on the first application. Compression

time of approximately 1 minute was also very short albeit that

the bleeding was from the PA and not an artery. These results

were observed presumably because the adhesion was stron-

ger, faster, and the sheet was more pliable in TSF compared

with in TC.

Fibrinogen is a multidomain protein composed of three

polypeptide chains termed \( \alpha \), \( \beta \), and \( \gamma \). Thrombin binds to

fibrinogen and cleaves fibrinopeptide A and fibrinopeptide B,

and assembles to form fibrin. In the presence of factor XIII

and \( Ca^{2+} \), fibrin undergoes intermolecular covalent cross-

linking, which was not as prominent in the TC group com-

pared with in the TSF group. The stronger and faster adhesion

may have been at least in part a result of the facilitated

formation of fibrin in TSF as shown in vitro, although in vivo

relevance may be less because tissue-derived coagulation

factors exist. TSF also allowed for visualization of the lacer-

ation through the applied sheet, which was not possible with

TC. This enables suturing of the laceration through the TSF

for a more definitive hemostasis (data not shown). This prop-

erty can be considered comparable with what is reported for

the American Red Cross fibrin dressing.8,9 Although we do

DISCUSSION

Fig. 3. SDS-PAGE of in vitro formed fibrin in thrombin sheet plus

liquid fibrinogen (TSF group), and TacoComb (TC group). Lane 1,

molecular weight marker; lane 2, fibrinogen; lane 3, TSF group

reaction for 5 minutes; lane 4, TSF group reaction for 10 minutes;

lane 5, TSF group reaction for 30 minutes; lane 6, TC group

reaction for 5 minutes; lane 7, TC group reaction for 10 minutes;

lane 8, TC group reaction for 30 minutes. In vitro fibrin formation

was more prominent in the TSF group compared with in the TC

group. In the TSF group, \( \gamma-\gamma \) cross-linking was formed within 10

minutes, and \( \alpha-\alpha \) polymer was observed. On the other hand, we

identified only a trace amount of \( \gamma-\gamma \) cross linking in TC group.
not have any experience with this material because of lack of access, the reports indicate that the American Red Cross dressing also achieves superior hemostasis compared with that of TC. Adhesion of TC to the surgical glove during manual compression was another problem. TC had to be gently scraped off the glove with forceps to leave the sheet in place, which was not the case with TSF. Furthermore, after 4 weeks, TSF induced less adhesion compared with TC, suggesting better biocompatibility, although this difference may just be because of the number of applications required. It is true that both materials sufficiently controlled bleeding in this experiment. However, we think that TSF would be much less stressful to use in a setting of unexpected PA bleeding, considering the multiple applications required for TC, as well as the additional blood loss that occurred during this period.

Despite its efficacy, there are certain constraints associated with fibrin-based materials such as availability and cost. It is also true that fibrin-based materials carry a risk of pathogen transmission, although today this is considered to be minimal as a result of improved screening and purification techniques. To alleviate some of these problems, we used recombinant thrombin for TS and development of recombinant fibrinogen is in progress. Ongoing preliminary studies in rabbit aortic injury models also seem to be promising. Studies are necessary to further clarify the hemostatic efficacy of this material in other organ trauma models and in coagulopathic animals.

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We thank Dr. Yuji Nishiwaki, Department of Preventive Medicine and Public Health, for his helpful comments on statistical analysis.

REFERENCES

EDITORIAL COMMENT
The authors have demonstrated that a new fibrin-based sheet material that is combined with liquid fibrinogen immediately before use (TSF) provides superior hemostasis when compared with a commercially available fibrin-based sheet material, TachoComb (TC), in a canine model of hemorrhage from an acute pulmonary artery injury. They reference a similar study showing hemostatic superiority of an American Red Cross dry fibrin-based sheet dressing for obtaining hemostasis from acute injury. They also, reference studies showing excellent hemostasis for systemic arterial hemorrhage, which, of course, occurs at a much higher pressure than that seen from pulmonary artery hemorrhage. Although the authors point out that there are subtle differences in the physics of the injured low-pressure pulmonary artery compared with the high-pressure aortic perforation, the enhanced efficacy of the TSF in this lower arterial pressure system is predictable. Furthermore, the injury described, herein, might be encountered by a thoracic surgeon doing extirpative surgery for intrathoracic tumors but would be rarely encountered in the injured patient who, typically, would have associated lung injury. Thus, the application of this technique to the injured patient is limited.

This reviewer eagerly awaits subsequent reports defining the benefits of this product in the hands of thoracic surgeons.

Charles E. Lucas, MD
Wayne State University
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Ischemic Preconditioning Prevents Skeletal Muscle Tissue Injury, But Not Nerve Lesion Upon Tourniquet-Induced Ischemia

Matthias Schoen, MD, Robert Rotter, MD, Philipp Gierer, MD, Georg Gradl, MD, Ulf Strauss, MD, Ludwig Jonas, PhD, Thomas Mittlmeier, MD, and Brigitte Vollmar, MD

**Background:** Prolonged ischemia followed by reperfusion (I/R) of skeletal muscle results in significant tissue injury. Ischemic preconditioning (IPC), achieved by brief periods of ischemia before sustained ischemia, has been shown to ameliorate I/R injury in a variety of tissues. We demonstrate that tourniquet hind limb ischemia-induced injury of the muscle benefits from IPC, whereas the peripheral nerve suffers from prolonged ischemia time and mechanical deterioration on IPC.

**Methods:** In anesthetized rats, hind limb ischemia was induced by tourniquet for 3 hours followed by 24 hours of reperfusion. In an additional series of experiments, IPC (three cycles of 10 minutes I/10 minutes R) preceded hind limb ischemia. Sham-operated animals without ischemia served as controls. Skeletal muscle tissue injury was assessed with respect to microcirculation, inflammatory cell response, and cell integrity using intravital fluorescence microscopy, Western blot protein analysis, and tissue histochemistry. Analysis of tactile and thermal allodynia served as indicators for posts ischemic pain. In addition, motor nerve conduction velocity and transmission electron microscopy allowed assessing posts ischemic nerve lesion.

**Results:** Tourniquet of the hind limb caused marked perfusion failure, enhanced leukocyte-endothelial cell interaction, and apoptotic cell death. IPC was able to improve microvascular perfusion and to reduce inflammatory cell response. Of interest, apoptotic cell death, assessed by cell nuclear morphology in vivo as well as Western blot and immunohistochemical analysis of caspase-3 cleavage, can be substantially reduced by IPC in tourniquet ischemia of the hind limb. Application of the tourniquet abolished nerve conduction in all animals. Non-IPC-treated animals still showed tactile allodynia, whereas IPC further caused loss of pain sensation and motor function of the postischemic hind limb.

**Conclusions:** High susceptibility of the peripheral nerve to compression-induced ischemic injury disproves IPC in its clinical application for surgical procedures requiring prolonged tourniquet ischemia.

**Key Words:** Microcirculation, Fluorescence microscopy, Apoptosis, Leukocyte, Peripheral nerve.


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both skeletal muscle tissue injury and nerve lesion on prolonged tourniquet ischemia.

**METHODS**

**Animals and Experimental Groups**

The experiments were performed in a total of 26 male Sprague Dawley rats (body weight [bw] 300–350 g; Charles River Laboratories, Sulzfeld, Germany), kept on water and standard laboratory chow ad libitum. The local animal rights protection authorities approved the experimental protocol (LVL-MV/TSD/7221.3-1.1-049/04), which followed the National Institutes of Health guidelines for the care and use of laboratory animals.

One group of animals (n = 6) was subjected to 3 hours of ischemia followed by 24 hours of reperfusion, by using a tourniquet maneuver of the hind limb. For this purpose, a tourniquet was tightened around the left hind limb proximal to the extensor digitorum longus (EDL) muscle just above the trochanter major. Usage of a rubber ring (internal diameter, 14.5 mm) guaranteed a tight fit that produced ischemia similar to that of an inflated blood pressure cuff-induced ischemia (approximately 300 mm Hg). Additionally, six animals underwent IPC before the sustained ischemic period, induced by three cycles of 10 minutes ischemia followed by 10 minutes reperfusion each. Sham-treated animals without hind limb ischemia served as controls (n = 6). During hind limb ischemia, animals were anesthetized with 6% pentobarbital sodium (55 mg/kg bw intraperitoneal; Narcoren, Merial GmbH, Hallbergmoos, Germany) and placed in lateral position on a heating pad for maintenance of body temperature at 37°C. After removal of the tourniquet, animals were allowed to awaken and recover from anesthesia in single cages until the final experiment.

**Laser Doppler Flowmetry**

Erythrocyte flux within the skin of the hind limb was assessed by means of laser Doppler flowmetry (Periflux PF3; Perimed KB, Stockholm, Sweden), which has been shown to be suitable for estimation of skin microvascular perfusion. Measurements were performed directly before the 3-hour period of ischemia, at the end of ischemia, as well as during the first 30 minutes of reperfusion during awakening of the animals from anesthesia.

**Intravital Fluorescence Microscopy of the EDL Muscle**

Intravital fluorescence microscopy of skeletal muscle microcirculation was performed 24 hours after hind limb ischemia. For this purpose, animals were reanesthetized with pentobarbital (55 mg/kg bw intraperitoneal), placed on a heating pad for maintenance of body temperature at 37°C, tracheotomized, and mechanically ventilated (tidal volume 1 mL/100 g bw; 50 breaths/min). A polyethylene catheter (PE-50; Portex, Hytehe, Kent, United Kingdom) was placed in the right carotid artery for injection of fluorescent dyes, continuous monitoring of systemic hemodynamics (Sirecust; Siemens, Munich, Germany), and blood sampling.

Subsequently, the EDL muscle was microsurgically prepared to allow direct access for high-resolution multi-fluorescence microscopy. The preparation technique was first described by Tyml and Budreau and modified for in vivo microscopy by Schaser et al. During preparation, the tissue was superfused with 37°C warm physiologic saline solution to prevent drying and was finally covered with a cover glass.

During the 20-minute stabilization period after completion of surgery, in vivo microscopy of the EDL muscle was performed, as previously described. For contrast enhancement of the microvascular network and for in vivo staining of leukocytes, a single bolus of fluorescein-isothiocyanate-labeled dextran (15 mg/kg bw, Sigma, Deisenhofen, Germany) and rhodamine 6G (0.15 mg/kg bw, Sigma) was injected. For analysis of apoptotic cell death, in vivo staining of myocyte nuclei was achieved by injection of bisbenzimide (Hoechst 33342; 10 µmol/kg; Sigma). In vivo microscopy was performed using a Nikon microscope (E600-FN, Nikon, Tokyo, Japan) equipped with a 100 W mercury lamp and filter sets for blue (excitation/emission, 465–495 nm/505 nm), green (510–560 nm/575 nm), and ultraviolet (340–380 nm/400 nm) epi-illumination. By use of water-immersion, objectives (Plan Fluor ×20/0.7 W and ×40/0.80 W, Nikon), final magnifications of ×306 and ×630, were achieved. Images were recorded by means of a charge-coupled device video camera (FK 6990-IQ-S; Pieper, Schwerte, Germany) and transferred to an S-VHS video system for subsequent off-line analysis. Duration of continuous light exposure per observation area was limited to 60 seconds at maximum to avoid phototoxic effects. At the end of the experiments, arterial blood was withdrawn and muscle tissue was preserved for subsequent analysis.

**Laboratory Analysis**

Arterial blood samples were withdrawn for analysis of blood gases (Rapidlab 348; Bayer Vital, Fernwald, Germany) and blood cell count using a Coulter Counter (AcTdiff; Coulter, Hamburg, Germany).

**Microcirculatory Analysis**

The videotaped images were analyzed off-line using a computer-assisted microcirculation image-analysis system (CapImage; Zeintl, Heidelberg, Germany). As previously described, functional capillary density was defined as the total length of red blood cell-perfused capillaries per observation area and given in centimeter per square centimeter. For assessment of leukocyte-endothelial cell interaction in post-capillary venules, flow behavior of leukocytes was analyzed with respect to free floating, rolling, and adherent leukocytes. Rolling leukocytes were defined as those cells moving along the vessel wall at a velocity less than 40% of that of leukocytes at the centerline and were expressed as a percentage.
of the total leukocyte flux. Venular leukocyte adherence was defined as the number of leukocytes not moving or detaching from the endothelial lining of the vessel wall during an observation period of 30 seconds. Leukocyte adherence was expressed as nonmoving cells per endothelial surface (n/mm²), calculated from the diameter and length of the vessel segment analyzed, assuming cylindrical microvessel geometry. In postcapillary venules, centerline red blood cell velocity was determined using the line-shift method (CapImage). Microvascular permeability was assessed by venular macromolecular leakage of fluorescein-isothiocyanate-dextran and analyzed densitometrically by the ratio of extra-to-intravascular fluorescence intensity in muscle tissue. Within 10 observation fields of skeletal muscle, apoptotic cell death was assessed by counting the number of bisbenzimide-stained cells that showed apoptosis-associated condensation, fragmentation, and crescent-shaped formation of their nuclear chromatin (n/observation field).17,18

Analysis of Tissue Edema

The extent of skeletal muscle tissue edema was determined in biopsies obtained from the tibialis anterior muscle at the end of the 24-hour observation period. After assessment of wet weight the muscle was dried for 72 hours in a laboratory oven (60°C) and weighed again (dry weight) for calculation of the wet-to-dry weight ratio.

Western Blot Analysis

For whole protein extracts and Western blot analysis of cleaved caspase-3, muscle tissue was homogenized in lysis buffer (1 mmol/L Tris, pH 7.5, 5 mmol/L NaCl, 250 mmol/L ethylenediamine tetra-acetic acid, 10% Triton-X 100, 4% NaN₃, 100 mmol/L phenylmethylsulphonyl fluoride [PMSF]), incubated for 30 minutes on ice and centrifuged for 30 minutes at 10,000g. The supernatant was saved as whole protein fraction. Before use, the buffer received a protease inhibitor cocktail (100 μL; 1:10 vol/vol; Sigma). Protein concentrations were determined using the bicinchoninic acid protein assay (Pierce, Rockford, IL) with bovine serum albumin as standard. Equal amounts of protein per lane (40 μg of whole muscle tissue lysate) were separated discontinuously on 14% sodium dodecyl sulfate polyacrylamide gels and transferred to a polyvinylidifluoride membrane (Immobilon-P transfer membrane; Millipore, Billerica, MA). After blockade of nonspecific binding sites, membranes were incubated for 2 hours at 37°C with a rabbit polyclonal cleaved caspase-3 antibody (1:1000; Cell Signaling Technology, Frankfurt, Germany) followed by a secondary peroxidase-conjugated donkey antirabbit immunoglobulin (Ig)-antibody (1:2000; Cell Signaling Technology). Equal protein loading was proven by β-tubulin bands. Protein expression was visualized by luminol-enhanced chemiluminescence and exposure of membrane to blue light-sensitive autoradiography film (Hyperfilm ECL; Amersham, Freiburg, Germany). Signals were assessed densitometrically and normalized to β-tubulin.

**Immunohistochemistry**

To study activation of caspase-3 by immunohistochemistry, 4 μm sections of paraffin-embedded EDL muscle tissue specimens were incubated overnight at 4°C with a rabbit polyclonal cleaved caspase-3 antibody (1:500; Cell Signaling Technology). This antibody detects endogenous levels of the large fragment (17/19 kDa) of activated caspase-3, but not full-length caspase-3. A horse radish peroxidase-labeled

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**Table 1 Systemic Hemodynamics and Arterial Blood Analysis in Rats That Underwent Either Tourniquet Ischemia of the Hind Limb (ischemia) or Ischemic Preconditioning (IPC) Followed by Tourniquet Ischemia of the Hind Limb (IPC/ischemia). Sham-Treated Animals Served as Controls (sham)**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Ischemia</th>
<th>IPC/Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood</td>
<td>116 ± 5</td>
<td>113 ± 1</td>
<td>113 ± 4</td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>312 ± 12</td>
<td>320 ± 11</td>
<td>313 ± 21</td>
</tr>
<tr>
<td>Systemic leukocyte</td>
<td>6.2 ± 0.2</td>
<td>7.2 ± 0.3</td>
<td>5.5 ± 0.6</td>
</tr>
<tr>
<td>count (10⁹/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44 ± 1</td>
<td>43 ± 1</td>
<td>43 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.01</td>
<td>7.44 ± 0.02</td>
<td>7.49 ± 0.01</td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>3.4 ± 0.5</td>
<td>3.4 ± 1.0</td>
<td>5.5 ± 0.8</td>
</tr>
</tbody>
</table>

Data are given as means ± SEM.

**Fig. 1.** Erythrocyte flux within the hind limb skin of rats that underwent either tourniquet ischemia of the hind limb (open circles) or ischemic preconditioning (IPC) followed by tourniquet ischemia of the hind limb (closed triangles). Sham-treated animals served as controls (closed circles). Measurements were obtained at baseline (B), i.e., before ischemia, at the end of ischemia (I), and during the first 30 minutes after reperfusion, using Laser Doppler flowmetry. Values are given in percentage of baseline as mean ± SEM; analysis of variance (ANOVA), post hoc comparison; *p < 0.05 versus sham.
goat anti-rabbit Ig-antibody was used as a secondary antibody (1:20; DakoCytomation, Hamburg, Germany). 3,3′-Diaminobenzidine was used as chromogen. The sections were counterstained with hemalaun. Cleaved caspase-3 staining of muscle cells was semiquantitatively scored in 25 consecutive high power fields (400 magnification) from 0 to 3, where no staining = 0, light staining = 1, moderate staining = 2, and intense staining = 3.

Behavioral Observations

All animals were allowed to habituate to the experimental conditions by allowing them to spend several hours in the laboratory on days 3 to 0 preceding any test. Behavioral observation tests were performed at day 1 before as well as at day 1 after hind limb ischemia.

Spontaneous Pain Behavior

By placing animals in a custom-made acrylic plastic (Plexiglas) cage of $16 \times 15 \times 22 \, \text{cm}^3$, the spontaneous behavior was observed without intervention of the observer as initially described by Attal et al. and recently published by our group. After 10 minutes habituation, different positions of the lesioned hind paw were rated three times for 300 seconds during a 15-minutes period according to a numerical scale: 0 = the operated paw is pressed normally on the floor; 1 = the paw rests lightly on the floor and the toes are in a

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**Fig. 2.** Intravital fluorescence microscopy with analysis of functional capillary density (A), leukocyte rolling (B), leukocyte adherence in postcapillary venules (C), and apoptotic cell death (D) in the EDL muscle of rats that underwent either tourniquet ischemia of the hind limb (ischemia) or ischemic preconditioning (IPC) followed by tourniquet ischemia of the hind limb (IPC/ischemia). Sham-treated animals served as controls (sham). Measurements were obtained on day 1 after ischemia. Values are given as mean ± SEM; ANOVA, post hoc comparison; *p < 0.05 versus sham; #p < 0.05 versus ischemia.
ventroflexed position; 2 = only the internal edge of the paw is pressed on the floor; 3 = only the heel is pressed on the floor and the hind paw is in an inverted position; 4 = the whole paw is elevated; 5 = the animal licks the operated paw. The score during a 5-minute period provides an index of spontaneous pain intensity for each rat and was calculated by the formula \( t_1 + 2t_2 + 3t_3 + 4t_4 + 5t_5/300 \) seconds, where \( t_1, t_2, t_3, t_4, \) and \( t_5 \) are the durations in seconds spent in the categories 1, 2, 3, 4, or 5, respectively.\(^{17}\)

**Thermal Stimulation**

The acrylic plastic cage described above allowed us to change the bottom layer to a heating plate and a cold plate, set to either 40°C or 4°C, respectively. After a habituation period of 10 minutes, hind paw responses to thermal stimuli, i.e., different positions of the lesioned hind paw were rated three times for 300 seconds during a 15-minute period according to the formula given above.\(^{17}\)

**Mechanical Stimulation**

For assessment of tactile allodynia, the hind limb withdrawal threshold evoked by stimulation of the hind paw by von Frey filaments was determined while the rat was placed on a metal mesh floor with 0.6 × 0.6 cm\(^2\) cells. After a 10-minute accommodation period mechanical stimuli were applied to the affected foot pad with six calibrated filaments (Semmes-Weinstein Monofilaments; North Coast Medical, Morgan Hill, CA) ranging from 0.6 g to 15.0 g (5.83–147 mN) until the filament just bent. A single trial of stimuli consisted of six applications of filaments at a frequency of 1/s. Five trials were performed at 3-minute intervals. The paw withdrawal response frequency in each of these five trials was expressed as a percent response frequency: foot withdrawals/6/5 × 100 = % response frequency.\(^{20}\) The same procedure was repeated for each filament in ascending order starting from the weakest, similarly to the results recently published by our group.\(^{17}\)

**Motor Nerve Conduction Study**

In an additional set of animals (each \( n = 4 \) per group), the sciatic nerves of both hind limbs were exposed at 24 hours after tourniquet application and stimulated supramaximally as defined as 110% to 130% of the stimulation current, which gave the maximal response. Anodal square wave pulses of 0.1 m/s duration at a frequency of 0.2 Hz were applied directly to the proximal and distal part of the dissected sciatic nerve, using a stimulator (A320; World Precision Instruments, Berlin, Germany) triggered by LabView-based software (National Instruments, Austin, TX). A ground electrode was placed subcutaneously between stimulating and recording electrodes.\(^{21}\) Compound muscle action potentials were recorded electromyographically by needle electrodes (Medtronic Functional Diagnostics, Skovlunde, Denmark) positioned in the extensor muscles of the hind limb. The reference needle electrode was located periostally at the dorsum of the hind paw. Rectal temperatures were kept in the range of 37°C to 38°C using a heated blanket. Data were filtered with a band pass between 30 Hz and 1.3 kHz and amplified with a gain of 1 V/mV by an EXT-10 C amplifier (Npi electronics, Tamm, Germany). Further digitalizing and analysis were performed using the LabView-based software on a personal computer.

**Transmission Electron Microscopy**

Sciatic nerves were fixed with 4% glutaraldehyde in 0.1 mol/L phosphate buffer at pH 7.4. After washing in buffer, the tissue samples were postfixed with 1% OsO\(_4\) for 1 hour. After dehydration in a graded series of alcohol, the sample was embedded in araldite (Fluka, Buchs, Switzerland). With use of an ultramicrotome (Ultracut SWS; Leica, Bensheim, Germany), semithin sections were pre-
pared and stained with 1% toluidin blue for conventional light microscopy. Ultrathin sections were stained with uranyl acetate and lead citrate for transmission electron microscope (TEM) analysis (EM 902 A; Zeiss, Oberkochen, Germany).

Statistical Analysis

After approving the assumption of normality and equal variance across the groups, statistical evaluation was performed using analysis of variance and the post hoc comparison test, including correction of the alpha error according to Bonferroni probabilities to compensate for multiple comparisons (SigmaStat; Jandel, San Rafael, CA). Data are given as mean ± SEM. Statistical significance was set at p < 0.05.

RESULTS

Systemic Parameters and Macrohemodynamics

Animals of all groups did not differ with respect to mean arterial blood pressure, heart rate, systemic blood cell counts, pH, and base excess, and revealed normal hemodynamics and physiologic acid-base balance (Table 1).

Laser Doppler Flowmetry

Erythrocyte flux values remained almost constant throughout the observation period in the untreated sham controls (Fig. 1). During tourniquet application, complete ischemia could be verified in all animals by means of laser Doppler flowmetry with assessment of only background signals (Fig. 1). On tourniquet release for reperfusion of the hind limb, animals revealed a hyperemic response with a 1.5- to 2-fold increase in erythrocyte flux values during the first 30 minutes. In rats exposed to IPC before hind limb I/R, this hyperemic response tended to be more pronounced and reached more than 200% of baseline values during early reperfusion (Fig. 1). Postischemic flux values constantly exceeded those found in non-IPC–treated animals, underlining the initial effect of IPC on microvascular blood flow (Fig. 1).

Fluorescence Microscopic Analysis of EDL Microcirculation and Tissue Integrity

Tourniquet-induced ischemia of the hind limb for 3 hours followed by reperfusion markedly impaired skeletal muscle microcirculation and cell integrity (Fig. 2). Nutritive perfusion, as given by the functional capillary density, was found reduced to almost 55% of values observed in nonischemic controls (Fig. 2A). In addition, hind limb ischemia evoked leukocyte activation with a significant threefold increase in the fraction rolling along the endothelial lining of postcapillary venules (Fig. 2B). Furthermore, the number of firmly adherent leukocytes was found increased with five times the values found in controls (170 ± 7 cells/mm² vs. controls: 35 ± 4 cells/mm²; Fig. 2C). Notably, postischemic muscle tissue presented with approximately 4% of cells with nuclear chromatin condensation and fragmentation as characteristic signs for cell apoptosis, whereas nonischemic muscle tissue lacks apoptotic cell death (Fig. 2D).

Repetitive cycles of brief periods of ischemia before sustained ischemia of the hind limb, i.e., IPC, proved to diminish ischemia-induced deterioration of muscle microcirculation and tissue injury. Functional capillary density was found above 300 cm/cm² in IPC-treated animals, how-
ever, remained markedly below physiologic values of approximately 450 cm/cm² seen in sham-treated controls (Fig. 2A). IPC was also able to limit postischemic increase of leukocyte adherence (Fig. 2C), although IPC did not affect rolling behavior of leukocytes (Fig. 2B). Of interest, IPC fully protected tissue from I/R-induced apoptotic cell death (Fig. 2D).

**Macromolecular Leakage and Paw Edema**

As assessed by the ratio of outer-to-inner vessel fluorescence intensity, macromolecular leakage did not significantly differ between groups (sham: 0.81 ± 0.05; ischemia: 0.91 ± 0.07; IPC/ischemia: 0.83 ± 0.03). Wet-to-dry weight ratio of the tibialis anterior muscle indicated edema formation in the hind limb ischemia groups, as given by a rise to 4.6 ± 0.4 (ischemia) and 4.5 ± 0.3 (IPC/ischemia) when compared with the corresponding value in controls (4.1 ± 0.2).

**Western Blot Analysis and Immunohistochemistry of Cleaved Caspase-3 in Postischemic Muscle Tissue**

To confirm apoptotic cell death after muscle I/R, caspase-3 activation was studied using Western blot analysis of cleaved caspase-3. Marked activation of caspase-3 was shown in muscle tissue lysates on I/R, whereas caspase activation was significantly lower in controls and IPC-treated animals (Fig. 3). Using a semiquantitative scoring system, analysis of intensity of muscle cell cleaved caspase-3 staining revealed an index of almost three in postischemic muscle tissue, denoting apoptotic cell death (Fig. 4). Noteworthy, IPC profoundly reduced the I/R-associated rise in apoptotic cell death of muscle tissue with a scoring index of approximately 1.9 (Fig. 4).

**Behavioral Observations**

The measure of mechanical nociceptive withdrawal response, involving the application of von Frey fibers over the plantar aspect of the hind paw, showed a rise in response frequency with increased fiber strength (6.0–15 g) 24 hours after hind limb ischemia (Fig. 5). In contrast to this, there was a loss of motor response to pain sensation in IPC-treated animals, showing a similar increase of response frequency, as observed in nons ischemic sham-treated controls (Fig. 5). Placement of rats on either the 40°C hot or the 4°C cold plate caused normal hind paw withdrawal with an index of <0.1 without differences among animals of the three experimental groups. Hind paw responses on cold and hot stimulation did not even differ when compared with those under thermally neutral conditions (data not shown).

**Motor Nerve Conduction**

Further conductional assessment was performed by eliciting compound muscle action potentials in the extensor muscles of the hind limb by sciatic nerve stimulation proximal and distal of the tourniquet. Latencies were measured from the stimulus artifact to the onset of the negative M-wave deflection. Motor nerve conduction velocity was calculated by the ratio of the latency differences and the distance between both stimulating electrodes. Motor conduction velocities in the nonischemic contralateral hind limbs, which served as controls, showed no difference between the ischemia (62 ± 3 m/s) and IPC/ischemia (61 ± 3 m/s) groups (p = 0.81). No compound muscle action potentials could be elicited in the tourniquet ischemia-exposed limbs. This was not substantially changed by IPC (p = 0.36, n = 4 per group), although in one of four limbs the edema was much less pronounced and a decelerated (36.5 m/s) and reduced compound muscle action potential could be elicited.

**TEM of Sciatic Nerves**

Using TEM, there was evidence for compression-like nerve lesion in both of the experimental groups undergoing tourniquet ischemia of the hind limb (Fig. 6). In contrast to
intact neural morphologic findings in control animals (Fig. 6A and B), sciatic nerves of the postischemic hind limbs presented with axonal degeneration, formation of myelin figures within Schwann’s cells and axons, swelling of mitochondrial matrix (D), as well as peri- and endoneurial edema of the posts ischemic nerve (C and D). There is intact neural morphology in the control animal (A and B). (A and C), magnification ×200; (B and D), magnification ×11,100.

DISCUSSION

Rats exposed to prolonged hind limb I/R exhibited hyperemia on initial reperfusion of the ischemic extremity, followed by manifestation of skeletal muscle tissue injury after 24 hours. In addition to no reflow of individual capillaries, posts ischemic reperfusion revealed a high number of leukocytes, interacting with the venular endothelium. Leukocytes, both loosely rolling along and firmly adhering to the endothelial wall, serve as indicators of ongoing inflammation on 24 hours of posts ischemic reperfusion. Of interest, in vivo microscopy revealed a considerable number of apoptotic cells on hind limb I/R. In addition to the morphologic sign of muscle cell injury, animals exhibited increased pain on mechanical stimulation, but not heat- or cold-induced allodynia. Thus, I/R injury of the hind limb presents with perfusion failure, leukocytic inflammation, and edema formation as well as myocyte apoptosis and mechanical allodynia. Notably, IPC limited the I/R-associated deterioration of skeletal muscle microcirculation and substantially reduced apoptotic cell death. However, IPC was harmful because it sustained posts ischemic nerve lesion.

In the liver, cell apoptosis is a classical feature of posts ischemic reperfusion injury with sinusoidal endothelial cells being the first cell type undergoing apoptosis on reperfusion. Similarly, as shown for IPC in the liver, we could demonstrate that IPC in skeletal muscle tissue down regulates caspase-3 activity. This mechanism might account for the inhibition of cell apoptosis in posts ischemic skeletal muscle tissue on IPC. In line with this, myopathy has been
shown to be associated with substantially increased levels of proapoptotic Bax, Bad, and Bid in skeletal muscle tissue.\textsuperscript{26} The fact that IPC has been shown to confer protection in a variety of different tissues and organs\textsuperscript{25,27–30} without being restricted to specific cells implies the existence of an ubiquitous noncell specific antiapoptotic effect of IPC in preventing apoptosis.\textsuperscript{31}

There is no doubt on the major role of microcirculatory disturbances for I/R-induced tissue injury. In particular, the persistence of nutritive perfusion failure during reperfusion leads to significant tissue hypoxia, which is known to be capable of inducing apoptosis and thus is potentially responsible for this mode of cell death.\textsuperscript{32} In line with this, it is reasonable to state that the initial IPC-induced hyperemic response with better microcirculatory perfusion might mediate the final attenuation of apoptotic tissue injury. In addition, IPC-induced reperfusion tolerance, including less reactive oxygen species and activated neutrophils released,\textsuperscript{33} might contribute to the antiapoptotic potential of IPC. This is evidenced, as the use of both antioxidants\textsuperscript{10} and leukopenic models or antibodies directed against specific adhesion molecules\textsuperscript{34} taught us, they are major, though not the sole, players of reperfusion injury.

Similar to the results shown by others,\textsuperscript{35} 3-hour ischemia of the hind limb did manifest with peripheral nerve injury, i.e., degeneration of myelinated fibers, and presence of neuropathic pain. Tactile allodynia, in which innocuous mechanical stimuli are perceived as painful and are answered by an increased paw withdrawal frequency, is a common symptom on injury to peripheral nerves, resulting from both abnormal excitability of damaged primary afferents and pathologic changes within the central nervous system.\textsuperscript{36} In the present study, animals exhibiting mecano-alldynia, however, lacked temperature-evoked pain. The pain-rating procedure to quantify temperature-evoked pain that we used is identical to that used by other groups,\textsuperscript{19,37} although measurement of foot withdrawal latencies during application of noxious radiant heat stimuli, as described by Hargreaves et al.\textsuperscript{38} might have reflected thermal hyperalgesia more precisely. The temperature of 40°C was chosen in accordance to Kingery et al.\textsuperscript{39} and Meert et al.,\textsuperscript{40} despite the fact that others defined plate temperatures as noxious only when exceeding 40°C.\textsuperscript{19,41} In parallel, the acetone drop method, commonly used to evoke cold-allodynia,\textsuperscript{10,42} might be more irritating than the herein used exposure to a 4°C cold plate.

As expected from previous studies,\textsuperscript{35} no compound muscle action potentials could be elicited on hind limb ischemia of 3 hours. Because needle electrodes sample only a limited number of motor units, we always examined more than five locations within the nerve to obtain representative measurements. The lack of proximally and distally elicited compound muscle action potentials renders an edematous or metabolic degeneration of axons more likely than a simple “neurapraxic” conduction block by compression-induced lesion of the myelin sheath. Most notably in this context is the observation that non-IPC-treated animals exhibited pathologic pain sensation and motor function, whereas IPC-treated animals presented with neuroplegia of their posts ischemic hind limb. Although application of the tourniquet already abolished nerve conduction in all animals, as is similarly described by others,\textsuperscript{35,43} the increase of ischemia time in IPC-treated animals by 3 times 10 minutes might account for the difference in neuropathic pain behavior, implying a certain threshold of ischemia tolerance for peripheral nerves. In support of this view, it has been reported that there was loss of pain sensation and motor function in animals undergoing 4-hour, but not 2-hour, tourniquet of the hind limb.\textsuperscript{44}

The present study confirms the evidence that IPC is a powerful protective mechanism in the posts ischemic muscle tissue, but greatly extends our knowledge in that I/R-associated muscle tissue injury can be markedly reduced by IPC via downregulation of caspase-like activity resulting in attenuation of cell apoptosis. We further provide the novel information that in contrast to these beneficial effects on muscle tissue, IPC aggravates tourniquet-induced peripheral nerve lesion. Thus, IPC disproves itself as a safe tool to limit post-tourniquet neurophysiologic dysfunction if conducted before prolonged (>3 hours) periods of ischemia.

ACKNOWLEDGMENTS

We thank Berit Blendow, Doris Butzlaff, Dorothea Frenz, Maren Nermowski, and Claudia Vergien, Institute for Experimental Surgery, University of Rostock, for excellent technical assistance.

REFERENCES


Experimental Study of Controlled Fluid Resuscitation in the Treatment of Severe and Uncontrolled Hemorrhagic Shock

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**Background:** Hemorrhagic shock is a common clinic emergency case. The fluid resuscitation method in the presurgical care of hypotensive trauma patients is open to debate. This study was conducted to evaluate the general and pathophysiologic effects of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock.

**Methods:** A model of rat with severe hemorrhagic shock and active bleeding was established in 32 Sprague-Dawley rats. The rats were randomly divided into the control group, no fluid resuscitation group (NF group), controlled fluid resuscitation group (NS40 group), and aggressive fluid resuscitation group (NS80 group). Each group contained eight rats. The changes of survival, blood loss, blood platelet, hemoglobin, hematocrit, and serum lactate level were dynamically monitored in the “prehospital phase”. In addition, the apoptosis in the liver, kidney, lung, and small intestinal mucosa of survivors after hemorrhage and resuscitation was detected by light microscopy in hematoxylin-eosin stained tissue sections, flow cytometry, and terminal deoxynucleotidyl transferase dUTP nick end labeling. Via the above-mentioned indexes, the curative effects of three fluid resuscitation methods were compared.

**Results:** Compared with the survival in the NF group (3 of 8), the higher survival rate of the NS40 and NS80 groups (14 of 16) showed significant difference \( (p < 0.05) \). After fluid resuscitation, serum lactate levels in the NS40 and NS80 groups obviously decreased \( (p < 0.01) \) compared with control and NF groups. The shed blood loss from bleeding tail in the NS80 group was obviously increased \( (p < 0.01) \) for the NS80 group compared with the control, NF, and NS40 groups. Compared with that of the control, NF, and NS40 groups, the hemoglobin, hematocrit, and blood platelet of the NS80 group quickly descended in the prehospital phase and showed statistical differences. At the same time, there was some apoptosis in the liver, kidney, lung, and small intestinal mucosa of all survivors. Compared with that of the NF and NS40 groups, the apoptosis of liver, kidney, and small intestinal mucosa of the NS80 group was obviously increased, and showed statistical differences.

**Conclusions:** In severe and uncontrolled hemorrhagic shock, some fluid must be given in proper time to improve tissue perfusion and avoid early death. Among three fluid resuscitation methods, controlled fluid resuscitation can effectively decrease additional blood loss, avoid excessive hemodilution and coagulopathy, improve the early survival rate, and reduce the apoptosis of visceral organs in rats with severe and uncontrolled hemorrhagic shock. This model supports the concept that when surgical care is not readily available, controlled fluid resuscitation should be considered in the treatment of uncontrolled hemorrhagic shock.

**Key Words:** Uncontrolled hemorrhage, Resuscitation, Apoptosis.


Hemorrhagic shock is a common clinic emergency case. Successful treatment includes surgical control of hemorrhage and restoration of tissue perfusion. Current guidelines for presurgical treatment of patients with hemorrhagic shock recommend rapid volume resuscitation to normal blood pressure as quickly as possible. The practice is controversial because aggressive restoration of intravascular volume and rapid increase of blood pressure before securing hemostasis may exacerbate hemorrhage and worsen outcome.

Controlled fluid resuscitation may allow preshock treatment to work with compensatory mechanisms. The concept is to restore some intravascular fluid to the point of deliberate hypotension while taking into consideration hemostatic mechanisms. Such a scheme would balance the seemingly mutually exclusive processes of tissue perfusion and hemostasis. There is a risk, however, that a restriction in fluid resuscitation might increase the likelihood of organ dysfunction caused by impaired perfusion of visceral organs. The current study was undertaken to determine the curative effect of controlled fluid resuscitation in the presurgical treatment of severe and uncontrolled hemorrhagic shock. We also compared the early difference in apoptosis of visceral organs to evaluate end-organ function after different fluid resuscitation methods.

**MATERIALS AND METHODS**

The Ethics Committee of Sir Run Run Shaw Hospital affiliated to Medical College, Zhejiang University approved this study. The rats had unlimited access to food and water before the experiments. After being weighed, the rats were anesthetized with pentobarbital (40 mg/kg intraperitoneally)
and were placed in a supine position on a warming pad (25°C).

After applying povidone-iodine solution, the right carotid artery was isolated and cannulated with a polyethylene catheter through a neck incision. The arterial catheter was used for blood withdrawal and was connected to a pressure transducer and computerized physiograph system for continuous hemodynamic monitoring. In the same way, the left femoral vein was cannulated for fluid infusion. The animals were heparinized (500 U/kg). Blood losses of the procedure were measured by mopping all blood from the incision with preweighed gauze sponges, which were then reweighed. A transformation formula of 1 g = 0.9 mL of blood was used. Only animals whose blood losses were lower than 0.2 mL during the above-mentioned procedure and that were spontaneously breathing 10 minutes after the procedure were included in the study. Among the test rats, 32 fulfilled the inclusion criteria.

Referring to the method created by Capone,1 the model of rat with severe hemorrhagic shock and active bleeding was established. Under light anesthesia, the injury began (time = 0) with blood withdrawal through the carotid arterial cannula four times (at a rate of 1 mL/100 g/5 minutes for the first two times, and 0.5 mL/100 g/5 minutes for the late two times). The shed blood was collected in glass syringes with heparin and reinfused during resuscitation. At 30 minutes, uncontrolled hemorrhagic shock was added to the volume-controlled shock by amputation of the tail at 75% of its length, measured from the tip. The bleeding tail was immediately directed into a container (with heparin) and the amount of shed blood was measured. This phase was called “prehospital phase” and continued for 60 more minutes. During this period, the rats were early resuscitated by infusing normal saline (NS). Fluids were administered via the femoral vein with an infusion pump at the rate of 2 mL/(kg/min). The pump was turned on and off to maintain the mean arterial pressure (MAP) goal.

At 90 minutes, a phase simulating hospital treatment (hospital phase) began. Hemostasis was achieved by tail wound closure. Simultaneously, resuscitation began with infusion of blood and NS solution. The “hospital phase” lasted 60 minutes, and the end points were hematocrit (HCT) of 30% and MAP of 80 mm Hg.

Thirty-two rats were randomly divided into four groups of eight rats each with the sequence of the experiments randomized in blocks of four (1 from each group): group 1 (control group), neither fluid resuscitation nor hemostasis in the prehospital or hospital phases (no treatment); group 2 (no fluid resuscitation group, NF group), no fluid resuscitation in the prehospital phase (no field fluid resuscitation); group 3 (controlled fluid resuscitation group, NS40 group), NS infusion during the prehospital phase to reach and maintain MAP of 40 mm Hg, beginning immediately after the tail cut (field fluid resuscitation to MAP 40 mm Hg); and group 4 (aggressive fluid resuscitation group, NS80 group), NS infusion during the prehospital phase beginning immediately after the tail cut, to reach and sustain MAP of 80 mm Hg (field fluid resuscitation to MAP 80 mm Hg). Groups 2, 3, and 4 had a hospital phase with the same end points: control of bleeding, fluid resuscitation with blood and NS to HCT of 30%, and MAP of 80 mm Hg.

Blood samples (0.3 mL/sample) were taken separately from rats for complete blood count and determining serum lactate level at 0, 30, 60, and 90 minutes, and blood samples (0.2 mL/sample) were collected separately for complete blood count at 120 and 150 minutes. Blood loss in the prehospital phase also included blood withdrawal through the arterial cannula and prehospital blood samples, as well as all losses from the bleeding tail. Except for the first sample, which was included with the initial blood loss, all blood samples of the prehospital phase were replaced with 0.9 mL of NS.

Rats who lived for 150 minutes were regarded as survivors. The surviving rats were immediately killed after resuscitation and hemostasis. The liver, kidneys, lungs, and small intestine were taken out quickly and flushed with 0.01 mol/L cold phosphate buffer solution (pH 7.4).

The left part of the liver, kidneys, lungs, and part of the small intestine were fixed with 10% buffered formaldehyde for routine pathologic examination and terminal deoxynucleotidyl transerase dUTP nick end labeling (TUNEL). A pathologist who was blind to the animals’ resuscitation protocols examined all histologic specimens. The TUNEL detection kit (In situ Cell Detection Kit, AP) was purchased from American Promega Corporation (Madison, WI). The detection procedure was mainly preformed according to the instructions provided by the corporation. Under high power field (400× magnification) of fluorescent microscope, the number of apoptotic cells characterized by the positive staining nucleus in TUNEL staining sections was also counted in 10 randomly selected fields per section. The mean number of apoptotic cells per one field for each rat was calculated for further statistical analysis.

The right part of the organs and part of the small intestine were immediately sent to the central laboratory of Sir Run Run Shaw Hospital for apoptosis assaying by flow cytometer (Beckman Coulter EPICS XL), and the method of Annexin-V/PI staining was used. The Annexin-V/PI staining kit was purchased from Austrian Bender MedSystems Corporation (Vienna, Austria). For each sample, 10,000 cells were measured.

Data were presented as mean ± SD. With SPSS 10.0 software package (SPSS Inc., Chicago, IL), statistical analysis for comparing mean values from the three or four groups was made by one-way analysis of variance and least significant difference t test. Survival rate was compared using Fisher’s exact test. Differences were considered significant at $p < 0.05$. 


RESULTS
Characteristics of the Animal Model
The rats of the uncontrolled severe hemorrhagic shock model suffered approximately 50% blood volume loss based on animal body weight. Without treatment in the control group, eight rats all survived at 30 minutes, four rats survived at 90 minutes, and none survived at 150 minutes. Analysis of variance showed that no statistically significant differences occurred in weight, HCT, PLT (platelet), and HB (hemoglobin) among the rats of the four groups.

Variation of MAP
Prehemorrhage MAP was 114 mm Hg ± 12 mm Hg for the control group, 124 mm Hg ± 9 mm Hg for the NF group, 128 mm Hg ± 10 mm Hg for the NS40 group, and 129 mm Hg ± 7 mm Hg for the NS80 group. At this point, MAP in the NS40 or NS80 group was higher than that in the control group (p < 0.05), but there was no significant difference among the NF, NS40, and NS80 groups.

At the conclusion of blood withdrawal (20 minutes), MAP had decreased to 24 mm Hg ± 3 mm Hg in the control group, 21 mm Hg ± 3 mm Hg in the NF group, 22 mm Hg ± 2 mm Hg in the NS40 group, and 21 mm Hg ± 2 mm Hg in the NS80 group. Thirty minutes before the tail cut, MAP had slightly increased to 33 mm Hg ± 6 mm Hg in the control group, 30 mm Hg ± 4 mm Hg in the NF group, 31 mm Hg ± 4 mm Hg in the NS40 group, and 30 mm Hg ± 2 mm Hg in the NS80 group. There was no statistically significant difference in MAP among the four groups at 20 and 30 minutes.

Blood Loss
The blood withdrawal through the arterial cannula resulted in an initial blood loss of 30 mL/kg, with no difference among groups. The accumulated volume of shed blood from bleeding tail at the conclusion of the prehospital phase (90 minutes) was 1.61 mL/kg ± 0.88 mL/kg in the control group, 1.58 mL/kg ± 0.70 mL/kg in the NF group, 2.13 mL/kg ± 0.78 mL/kg in the NS40 group, and 1.45 mL/kg ± 2.67 mL/kg in the NS80 group (p < 0.01 for the NS80 group compared with the control, NF, and NS40 groups).

Fluid Volumes Administered
The volume of NS given during the prehospital phase was 38.59 mL/kg ± 11.19 mL/kg in the NS40 group and 139.46 mL/kg ± 34.59 mL/kg in the NS80 group (p < 0.01 for the NS80 group compared with the NS40 group). The control and NF groups received no fluid in the prehospital phase.

Survival Rate
All rats survived the first 30 minutes of the experiment. When the hospital phase began (90 minutes), the number of survivors was four in the control group, three in the NF group, eight in the NS40 group, and six in the NS80 group. At the conclusion of the hospital phase (150 minutes), the number of survivors was 0 in the control group, three in the NF group, eight in the NS40 group, and six in the NS80 group.

Compared with the survival rate of the NF group (3 of 8), the higher survival rate of the NS40 and NS80 groups (14 of 16) showed significant difference (p < 0.05). The survival rate of the NS40 group (8 of 8) was significantly higher than that of the NF group (3 of 8), with the comparison showing significant difference (p < 0.05). The survival rate of the NS40 group (8 of 8) was slightly higher than that of the NS80 group (6 of 8), and the survival rate of the NS80 group (6 of 8) was slightly higher than that of the NF group (3 of 8); the comparison showed no statistically significant difference.

HB and HCT
The dynamic changes of HB and HCT are detailed in Tables 1 and 2. The HB and HCT decreased promptly for all groups after the initial blood loss. There was no statistically significant difference in HB and HCT at 0 and 30 minutes of the prehospital phase. All other groups, except for the NS80 group, showed a slight decrease during the next hour of the prehospital phase. For the NS80 group, HB and HCT continued to decrease during the prehospital phase. Compared with that of the control, NF, and NS40 groups, there was statistically significant difference in HB and HCT at 60 and 90 minutes of the prehospital phase (p < 0.01).

Platelet
The dynamic changes of PLT are listed in Table 3. At 0, 30, and 60 minutes of the prehospital phase, there was no statistically significant difference in the PLT of the four groups. However, PLT in the NS80 group was significantly

<table>
<thead>
<tr>
<th>Table 1</th>
<th>HB Changes of Four Groups Rats in the Prehospital Phase (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>0 min</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
</tr>
<tr>
<td>NF</td>
<td>8</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
</tr>
<tr>
<td>NS80</td>
<td>8</td>
</tr>
<tr>
<td>F</td>
<td>0.54</td>
</tr>
<tr>
<td>p</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* p < 0.01 compared with the NS80 group.
lower than that in the control, NF, or NS40 group at 90 minutes of the prehospital phase ($p < 0.05$).

### Serum Lactate Level

There was no statistically significant difference in serum lactate level at 0 and 30 minutes of the prehospital phase. After fluid resuscitation, serum lactate levels in the NS40 and NS80 groups obviously decreased. Compared with the control and NF groups, there was statistically significant difference in serum lactate level at 60 and 90 minutes of the prehospital phase. The dynamic changes of serum lactate level are detailed in Table 4.

### Histologic Results

The liver, kidneys, lungs, and small intestine mucosa of survivors were stained with hematoxylin and eosin for routine microscopic examinations. In hematoxylin and eosin stained sections, none of the visceral organs had necrosis or other visible abnormalities in histologic structure.

### TUNEL Staining Results

In TUNEL-stained sections of the visceral organs of the NF, NS40, and NS80 groups, some positive-staining cells (apoptotic cell) were observed. Fluorescent microscopy revealed that TUNEL-positive cells presented green fluorescence and contracted or fragmented nuclei. Occasionally, apoptotic bodies could be found (Figs. 1–3).

The TUNEL staining results in the visceral organs of the NF, NS40, and NS80 groups are shown in Table 5. The number of TUNEL-positive cells of the kidney and small intestinal mucosa was obviously more in the NS80 group than that in the NF or NS40 group, with the differences showing statistical significance. However, between the NS40 group and the NF group, there was no significant difference in the number of TUNEL-positive cells of the visceral organs.

### Flow Cytometric Analysis

Table 6 shows the flow cytometer results of apoptosis in the visceral organs of the NF, NS40, and NS80 groups.

---

### Table 2 HCT Changes of Four Groups Rats in the Prehospital Phase (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HCT</td>
<td>n</td>
<td>HCT</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>41.9 ± 2.6</td>
<td>8</td>
<td>27.6 ± 1.5</td>
</tr>
<tr>
<td>NF</td>
<td>8</td>
<td>43.0 ± 3.1</td>
<td>8</td>
<td>28.6 ± 2.0</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
<td>43.6 ± 2.9</td>
<td>8</td>
<td>28.3 ± 2.0</td>
</tr>
<tr>
<td>NS80</td>
<td>8</td>
<td>43.4 ± 2.9</td>
<td>8</td>
<td>28.2 ± 2.7</td>
</tr>
<tr>
<td>F</td>
<td>0.54</td>
<td>&gt;0.05</td>
<td>0.32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>p</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* $p < 0.01$ compared with the NS80 group.

### Table 3 PLT Changes of Four Groups Rats in the Prehospital Phase ($10^9/L$)

<table>
<thead>
<tr>
<th>Group</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>PLT</td>
<td>n</td>
<td>PLT</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>1139 ± 136</td>
<td>8</td>
<td>847 ± 165</td>
</tr>
<tr>
<td>NF</td>
<td>8</td>
<td>1196 ± 120</td>
<td>8</td>
<td>768 ± 127</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
<td>1182 ± 102</td>
<td>8</td>
<td>792 ± 90</td>
</tr>
<tr>
<td>NS80</td>
<td>8</td>
<td>1179 ± 144</td>
<td>8</td>
<td>805 ± 131</td>
</tr>
<tr>
<td>F</td>
<td>0.30</td>
<td>&gt;0.05</td>
<td>0.52</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>p</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* $p < 0.05$ compared with the NS80 group.

### Table 4 Serum Lactate Level Changes of Four Groups Rats in the Prehospital Phase (mmol/L)

<table>
<thead>
<tr>
<th>Group</th>
<th>0 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Lactate Level</td>
<td>n</td>
<td>Lactate Level</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>1.51 ± 0.08</td>
<td>8</td>
<td>8.35 ± 1.88</td>
</tr>
<tr>
<td>NF</td>
<td>8</td>
<td>1.66 ± 0.15</td>
<td>8</td>
<td>9.31 ± 1.38</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
<td>1.62 ± 0.22</td>
<td>8</td>
<td>8.71 ± 1.15</td>
</tr>
<tr>
<td>NS80</td>
<td>8</td>
<td>1.58 ± 0.18</td>
<td>8</td>
<td>9.08 ± 0.95</td>
</tr>
<tr>
<td>F</td>
<td>1.19</td>
<td>&gt;0.05</td>
<td>0.74</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>p</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* $p < 0.01$ compared with the control group.
† $p < 0.01$ compared with the NF group.
apoptotic rates of the liver, kidney, and small intestinal mucosa were obviously higher in the NS80 group than those in the NF or NS40 group, and the comparison showed statistically significant difference. In addition, the apoptotic rate of the small intestinal mucosa in the NS40 group was higher than that of the NF group ($p < 0.05$). However, between the NF group and the NS40 group, there were no significant differences in apoptotic rates of the liver, kidney, and lung.

**DISCUSSION**

Conventional guidelines for prehospital treatment of hypotension secondary to hemorrhage after trauma recommend rapid infusion of crystalloid solution to restore normal blood pressure as quickly as possible. This premise is based, in part, on clinical studies and on substantial laboratory data that showed hemorrhagic shock in animals produced with a controlled hemorrhage model was reversible when shed blood was replaced with two to three times that volume of crystalloid solution. Although controlled hemorrhage is a well-defined laboratory model, resuscitation of the patients with multiple injuries and active bleeding may present very different pathophysiology. Sometimes, increased blood pressure from rapid fluid resuscitation can lead to a worsened outcome by disruption of early soft thrombus, coagulopathy, hemodilution, and rebleeding.

The body is good at compensating for hemorrhagic shock. Left undisturbed, it will decrease blood loss and maintain tissue perfusion to some extent through a series of stress reactions. However, compensatory mechanisms are limited in magnitude and duration. Profound initial blood losses or conditions of prolonged transport to the operating room can overwhelm compensation and result in death. On the basis of the above-mentioned theories, some scholars advocate the concept of “controlled fluid resuscitation”, which only administers moderate fluid infusion to prolong the compensatory time of patients with traumatic hemorrhagic shock before surgical hemostasis. Controlled fluid resuscitation means restoring some intravascular volume while taking into consideration hemostatic mechanisms, which allows prehospital treatment to work with compensatory mechanisms, and balances the seemingly mutually exclusive processes of tissue perfusion and hemostasis.

The model of blood withdrawal in the current study combined with active bleeding by tail cut produced a severe and reproducible hemorrhagic shock, in which initial blood loss was about 50% of the circulation blood volume. The mortality rate was 50% to 60% at 90 minutes and 100% at 150 minutes without treatment. Our study showed that early fluid infusion improved short-term survival rate of rats with severe and uncontrolled hemorrhagic shock. In severe shock or under conditions of long transport to surgical care, presurgical tissue perfusion cannot be ignored. Under the circumstances, fluid administration can win some time for further compensation and treatment.

Serum lactate has been shown to be a reliable measure of degree and duration of hypoperfusion, oxygen debt, and changes in oxygen delivery in hemorrhagic shock. Thus, in addition to increased survival rate, fluid resuscitation partly restored tissue perfusion and improved cellular metabolism as indicated by serum lactate level in the experiment. Compared
with aggressive fluid resuscitation, controlled fluid resuscitation also could provide similar or better effects on improving survival rate and metabolic parameters.

The study also indicated that aggressive fluid resuscitation to achieve near normal MAP of 80 mm Hg in the presence of severe uncontrolled hemorrhagic shock induced massive blood loss. The possible pathophysiologic mechanisms to explain the finding are multifactorial. An initial increase in blood pressure and excessive hemodilution may cause vasoconstrictive dysfunction, increase in blood flow through the injured site, disruption of the recent clot at the site of injury, and impairment of coagulation function. This concept was partly supported by dynamic monitoring of blood loss, HB, HCT, and PLT in the experiment. In addition, we also found that controlled fluid resuscitation to maintain MAP of 40 mm Hg could partly reduce these harmful consequences in the presurgical treatment of severe uncontrolled hemorrhagic shock.

At the present time, it is acknowledged that the main causes of death in the late stage of patients with severe trauma or hemorrhagic shock are infection, multiple organ dysfunction syndrome, or multiple organ failure. Recently, several researches found that apoptosis was induced in visceral organs in the early stage of multiple injuries combined with shock, which may play a role in early organ injury and later multiple organ failure. The apoptosis in pathologic conditions can also reflect the severity of disordered internal environment of the body. In particular, significant apoptosis of intestinal mucosa can result in impairment of the mucosa barrier and immune function, which is bound up with endogenous infection and multiple organ dysfunction syndrome.

Our study showed clearly that apoptosis of different extents happened in the visceral organs of the rat survivors in the early period of hemorrhagic shock and resuscitation, especially in the small intestinal mucosa. It showed that intestinal mucosa was the first affected and rapidly changed site when shock occurred. Hotchkiss et al. also demonstrated that the apoptosis of intestinal epithelial and lymphoid tissues occurred extremely rapidly after injury and shock. Apoptotic loss of intestinal epithelial cells may compromise bowel wall integrity and be a mechanism for bacterial or endotoxin translocation into the systemic circulation. Apoptosis of lymphocytes may impair immunologic defenses and predispose to infection. More recently, Diebel et al. revealed the pivotal role of tumor necrosis factor-α in signaling apoptosis in intestinal epithelial cells under shock conditions by CaCO₂ intestinal cell monolayers.

Furthermore, it was obvious that the apoptosis of the liver, kidney, and small intestinal mucosa was statistically higher in the NS80 group than in the NF or NS40 group from the current study. This implies that, in prehospital treatment of severe and uncontrolled hemorrhagic shock, brief and moderate hypotension may be helpful for maintaining organ function and decreasing the later complications of traumatic patients. In recent years, a few clinical observations also supported the same opinions. The inherent mechanism is not completely clear, but may be related to the following factors: (1) aggressive fluid infusion seriously disturbs the internal environment and exacerbates cellular metabolism, which can induce abnormal apoptosis of visceral organs; (2) high amounts of isotonic crystalloid fluid resuscitation may be associated with severe inflammatory reactions triggered by shock, such as activating more polymorphonuclear neutrophil and increasing proinflammatory cytokine levels; and (3) high perfusion pressure of tissue and organ followed by aggressive fluid resuscitation can cause severe ischemia-

### Table 5 TUNEL Staining Results in the Visceral Organs of Three Groups’ Rats (No./High Power Field)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Small Intestinal Mucosa</th>
<th>Liver</th>
<th>Kidney</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF</td>
<td>3</td>
<td>32.4 ± 4.4*</td>
<td>1.4 ± 0.5</td>
<td>1.3 ± 0.7†</td>
<td>6.3 ± 1.3</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
<td>37.8 ± 5.6*</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.6*</td>
<td>5.6 ± 2.0</td>
</tr>
<tr>
<td>NS80</td>
<td>6</td>
<td>48.0 ± 4.0</td>
<td>1.9 ± 0.3</td>
<td>2.6 ± 0.8</td>
<td>5.0 ± 1.6</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>12.23</td>
<td>3.30</td>
<td>8.76</td>
<td>0.61</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* p < 0.01 compared with the NS80 group.
† p < 0.05 compared with the NS80 group.

### Table 6 Flow Cytometric Results of Apoptosis in the Visceral Organs of Three Groups’ Rats (％)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Small Intestinal Mucosa</th>
<th>Liver</th>
<th>Kidney</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF</td>
<td>3</td>
<td>2.55 ± 0.28*†</td>
<td>0.44 ± 0.14‡</td>
<td>1.29 ± 0.18*</td>
<td>2.68 ± 0.43</td>
</tr>
<tr>
<td>NS40</td>
<td>8</td>
<td>5.59 ± 2.43*</td>
<td>0.34 ± 0.12*</td>
<td>1.67 ± 1.18*</td>
<td>2.69 ± 1.00</td>
</tr>
<tr>
<td>NS80</td>
<td>6</td>
<td>9.98 ± 1.01</td>
<td>0.74 ± 0.24</td>
<td>4.62 ± 1.19</td>
<td>2.11 ± 0.42</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>18.88</td>
<td>9.57</td>
<td>15.09</td>
<td>1.12</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* p < 0.01 compared with the NS80 group.
† p < 0.05 compared with the NS40 group.
‡ p < 0.05 compared with the NS80 group.
reperfusion injury by inducing a large amount of oxygen-derived free radicals. Several laboratory studies have shown that ischemia-reperfusion injury can induce apoptosis.\(^{22-24}\) In addition, the apoptosis of the small intestinal mucosa in the NS40 group was higher than that of the NF group because the goal of controlled fluid resuscitation is to restore some perfusion to the organs, which still carries some risk of reperfusion injury.

In sum, our results showed that in severe and uncontrolled hemorrhagic shock, some fluid must be administered in proper time to improve tissue perfusion and avoid early death. The data also confirmed that aggressive fluid resuscitation to restore near normal MAP of 80 mm Hg during uncontrolled hemorrhage obviously induced massive blood loss and excessive hemodilution, and increased the apoptosis of the liver, kidneys, and small intestinal mucosa in rats, which may increase the risk and extent of organ dysfunction. Controlled fluid resuscitation to maintain MAP of 40 mm Hg in the presurgical treatment of severe and uncontrolled hemorrhagic shock can effectively decrease further blood loss, avoid excessive hemodilution and coagulopathy, improve the early survival rate, and reduce the apoptosis of the visceral organs, which may benefit improvement of prognosis. This model supports the concept that when surgical care is not readily available, controlled fluid resuscitation should be considered in the treatment of uncontrolled hemorrhagic shock.

REFERENCES

The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Background: Patients with severe traumatic injuries often present with coagulopathy and require massive transfusion. The risk of death from hemorrhagic shock increases in this population. To treat the coagulopathy of trauma, some have suggested early, aggressive correction using a 1:1 ratio of plasma to red blood cell (RBC) units.

Methods: We performed a retrospective chart review of 246 patients at a US Army combat support hospital, each of who received a massive transfusion (≥10 units of RBCs in 24 hours). Three groups of patients were constructed according to the plasma to RBC ratio transfused during massive transfusion. Mortality rates and the cause of death were compared among groups.

Results: For the low ratio group the plasma to RBC median ratio was 1:8 (interquartile range, 0:12–1:5), for the medium ratio group, 1:2.5 (interquartile range, 1:3.0–1:2.3), and for the high ratio group, 1:1.4 (interquartile range, 1:1.7–1:1.2) (p < 0.001). Median Injury Severity Score (ISS) was 18 for all groups (interquartile range, 14–25). For low, medium, and high plasma to RBC ratios, overall mortality rates were 65%, 34%, and 19%, (p < 0.001); and hemorrhage mortality rates were 92.5%, 78%, and 37%, respectively, (p < 0.001). Upon logistic regression, plasma to RBC ratio was independently associated with survival (odds ratio 8.6, 95% confidence interval 2.1–35.2).

Conclusions: In patients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries.

Key Words: Blood components, Fresh frozen plasma, Trauma, Coagulopathy.

Massive transfusion is defined as the transfusion of 10 or more red blood cell (RBC) units in a 24-hour period.1–3 In civilian trauma centers, the incidence of patients with traumatic injuries receiving massive transfusion ranges between 1% and 3%.3–5 with an incidence reported as high as 15% in patients with the most severe injuries.6 Morbidity rates for massive transfusion patients ranges between 20% and 50%.1,6,7 Currently, 5% of all patients admitted to US combat support hospitals in Iraq require massive transfusions. Mortality rates among these patients is more than 30%.8 The high risk of mortality in massive transfusion patients largely results from the “lethal triad” or “bloody vicious cycle” characterized by hypothermia, metabolic acidosis, and coagulopathy.9–12 In approximately 30% of patients who have received a blood transfusion, coagulopathy results directly from the trauma itself. These patients present in the hypocoagulable state known as the coagulopathy of trauma.13 The coagulopathy of trauma is multifactorial; it is consumptive because of widespread tissue trauma, is augmented by dilution of hemostatic factors from crystalloid, colloid, and component therapy resuscitation, and exacerbated by hemorrhagic shock, metabolic acidosis, hypothermia, hyperfibrinolysis, hypocalemia, and anemia.11,14–19 Alternatively, coagulopathy can develop independent of acidosis and hypothermia secondary to trauma.20 Historically, whole blood was commonly used for patients suffering massive trauma.21,22 By the late 1980s, however, component therapy had almost completely replaced whole blood therapy.23 The primary purpose of component therapy was to improve resource utilization and reduce infectious disease transmission. This was accomplished by replacing blood component deficiencies individually based upon rigorous laboratory analysis. This approach of replacing specific hematologic deficits based upon laboratory analysis extended into the guidelines developed for patients requiring massive transfusion after injury. However, proof of the efficacy of this change in practice was lacking. Current transfusion recommendations were extrapolated from the setting of elective surgery, and may not be applicable to patients with severe trauma who are hypocoagulable, acidicotic, and in hemorrhagic shock. Recently, published reports now recommend a 1:1:1 ratio (i.e. equal parts RBCs, fresh frozen plasma [FFP], and platelets) for component therapy based on a more physiologic regimen and is more similar to the composition of whole blood.1,15,24–28 These recommendations, however,
have been based on anecdotal evidence and not on outcome studies examining the effect of blood product transfusion ratios for trauma patients requiring massive transfusion.

Most deaths (80% to 85%) that occur during combat are not preventable. Sixty-six to 80% of the 15% to 20% of potentially survivable combat-related deaths are a result of hemorrhagic shock. Scoring systems and predictive models that are able to rapidly identify who is at risk for massive transfusion have been recently published. Expeditious recognition and treatment of coagulopathy is important because most patients requiring massive transfusion die within 6 hours of admission. Resuscitation strategies that rapidly identify risk of massive transfusion and quickly address the coagulopathy of trauma should prevent deaths from uncontrolled hemorrhage and improve survival of potentially preventable deaths on the battlefield. Our objective in this retrospective study of patients with severe traumatic injuries requiring massive transfusion at a combat support hospital was to determine whether the ratio of plasma to RBCs transfused would affect survival by decreasing death from hemorrhage.

**METHODS**

The data presented here were obtained under a human use protocol that the Institutional Review Board at Brooke Army Medical Center in San Antonio, TX approved. Using the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute of Surgical Research (USAISR) at Ft. Sam Houston in San Antonio, TX, we performed a retrospective analysis of data for trauma patients admitted to a combat support hospital (CSH) in Iraq between November 2003 and September 2005. The JTTR database was established by the Department of Defense to capture data prospectively from multiple nonintegrated clinical and administrative systems. This database provides comprehensive data collection from the point of injury through discharge from military treatment facilities for non-US military patients and from point of injury through rehabilitation for US patients. Non-US military patients are defined to include coalition soldiers and foreign national patients.

The JTTR was queried for patients who received a massive transfusion, defined as 10 or more RBC units (including both stored RBC and fresh whole blood units) in 24 hours from admission. Data analyzed from the JTTR in this study were Injury Severity Score (ISS), Abbreviated Injury Scale (AIS) scores, primary cause of death, time of death, mortality at hospital discharge, laboratory values, and vital signs at admission to the CSH, (hemoglobin, platelet level, base deficit, International Normalized Ratio [INR], systolic blood pressure, temperature, heart rate), and total crystalloid and blood products (RBC, FFP, cryoprecipitate, recombinant FVIIa [rFVIIa], apheresis platelet [aPLT], and fresh whole blood [FWB] units) administered within 24 hours from admission to the combat support hospital. Because 1 unit of FWB has approximately 1 unit of RBCs, plasma, and platelets, the amount of RBC units transfused was calculated as the number of both stored RBC and FWB units transfused and plasma as FFP plus FWB units. One apheresis platelet unit is equal in number to approximately 6 to 10 units of leukocyte-reduced platelets. The platelet contribution from FWB was not included in the calculation of apheresis platelet units transfused, though FWB has previously been shown to be as effective as 10 units of platelet concentrate. The initial 24-hour amount of crystalloid and blood products transfused was also calculated as liters or units per hour. The rate of crystalloid and blood products per hour was calculated to adjust for the amount of crystalloid and blood products transfused to patients who died less than 24 hours from the initiation of the massive transfusion.

One investigator reviewed each patient’s chart or autopsy results to record all injuries, from which the AIS score and ISS were calculated. Primary outcome for all patients in this study was hospital discharge or overall mortality. For US military patients, this was tracked throughout all levels of care, including discharge from acute care hospitals in the United States. For non-US military patients, mortality was tracked until discharge from the CSH in Baghdad. Non-US military patients were not discharged or transferred until their surgical repair was stable, were not hemodynamically compromised, and did not require vasoactive agents or mechanical ventilation. The length of stay from admission to hospital discharge for both groups was measured. Time to death was defined as the time, in hours, from hospital admission to the time of death. For patients who had two mechanisms of death listed, a 0.5 was used for each in the calculation of the percentage of cause of death in each ratio group.

To analyze the effect of plasma to RBC ratios on mortality, patients were divided into groups based on the ratio of plasma to RBC units transfused. Three separate groups of patients were identified based on a “bootstrapping” technique that combined groups of patients that had similar mortality rates based upon the plasma to RBC ratios transfused to individual patients. With use of this method, the six groups of ratios that were initially constructed were combined to three groups. The plasma to RBC ratio was the number of plasma units divided by the RBC units transfused in the first 24 hours of care at the CSH.

Subpopulations were also analyzed to determine whether injury location affected the relationship between mortality and the ratio of plasma to RBCs transfused. To determine the effect of thoracic and head trauma in relationship to the plasma to RBC ratio and mortality, additional analyses were performed with and without patients who had thoracic or head and neck AIS scores of 4 or 5. The plasma to RBC ratio was also analyzed without the addition of FWB in the ratio, as well as without patients who were treated with rFVIIa.

All variables collected were analyzed to determine which were associated with overall mortality. Logistic regression was then used to determine independent associations between variables measured and overall mortality. The logistic regres-
Vital signs, and laboratory values for the three groups are in Table 1. Severe (AIS scores of 4 and 5) thoracic injuries were more common in the low ratio group compared with in the medium and high groups. All vital signs and laboratory results were comparable, except for hemoglobin, which was significantly lower in the low ratio group compared with in the medium and high groups.

In the first 24 hours of admission, the rate per hour of crystalloid and RBC units administered was less in the high ratio group compared with in the medium and low groups (Table 2). The total amount and rate per hour of plasma as well as the rate per hour of FWB was higher in the medium and high ratio groups \((p < 0.001)\). The low ratio group did not receive aPLTs, which were only used in 27% of patients. Cryoprecipitate was used more in the high ratio group \((p < 0.01)\), though given at a higher rate in the medium and low ratio groups \((p < 0.001)\) and was only used in 51% of the patient population (Table 2).

Nonsurvivors in the low and medium ratio groups died significantly sooner than those in the high ratio group (Fig. 2). Median time of death measured in hours from admission to the hospital was 2 hours (interquartile range, 1–4) in the low group and 4 hours (interquartile range, 2–16) in the medium group, compared with 38 hours (interquartile range, 4–155) in the high ratio group \((p < 0.001)\).

The relationship between plasma to RBC ratios transfused and overall mortality remained in the alternative analyses performed. Differences in mortality remained significant in the high, compared with in the low, ratio group when patients with thoracic and head trauma were individually removed from the analysis (Table 3). The relationship between plasma to RBC ratios transfused and overall mortality also remained when only stored FFP and RBCs (FWB units not included) were used to calculate the ratio, as well as when patients who were treated with rFVIIa were excluded (Table 3).

Table 4 indicates that many of the admission vital signs, laboratory values, and Injury Severity Scores, in addition to the ratio of plasma to RBCs, were associated with overall mortality. Table 5 reveals that the plasma to RBC ratio was independently associated with overall survival (odds ratio 8.6, 95% confidence interval 2.1–35.2) and that both base deficit and AIS for head and neck were independently associated with decreased overall survival upon logistic regression.

Figure 2 displays the primary causes of death in each ratio group. The percentage of deaths from hemorrhage was lower in the high ratio group \((11.5 of 31; 37\%)\), compared with in the low ratio group \((18.5 of 20; 92.5\%)\) \((p < 0.001)\). This represents an absolute reduction of 55% and a relative reduction of 60%. There were fewer hemorrhagic deaths in the high ratio group compared with in the medium ratio group \((p < 0.05)\). Likely reflecting the increased survival time, multiorgan failure deaths were more frequent in the high ratio group compared with in the low ratio group.

Figure 1. Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.

The mortality of low, medium, and high groups were 65%, 34%, and 19%, respectively \((p < 0.001)\). This represents an absolute reduction of 55% and a relative reduction of 60%. There were fewer hemorrhagic deaths in the high ratio group compared with in the medium ratio group \((p < 0.05)\). Likely reflecting the increased survival time, multiorgan failure deaths were more frequent in the high ratio group compared with in the low ratio group.
DISCUSSION

Our results indicate that for patients with significant traumatic injuries requiring massive transfusion, a higher plasma to RBC ratio is independently associated with improved survival, primarily decreasing early (<4 hours from admission) death from hemorrhage. The patients with the lowest mortality rate in our study were transfused a median plasma to RBC ratio of 1:1.4. This study supports recent reports in the literature that have called for the increased transfusion of coagulation factors for patients requiring massive transfusion and that have raised concerns about the increased use of RBCs and crystalloids in critically ill patients.

Earlier massive transfusion protocols developed for patients bleeding a large amount of whole blood, did not replace...
whole blood, but rather called for a much greater percentage of RBC units. Such protocols recommended that FFP only be transfused if prothrombin time (PT) or partial thromboplastin time (PTT) was 1.5 times normal, or after 10 RBC units were transfused. Additionally, these massive transfusion protocols called for 1 unit of FFP to be given for every 4 to 10 RBC units transfused.

Fig. 2. Comparison of the number and percentage of the primary cause of death for all of the deaths in each plasma to RBC ratio group. Number on column represents absolute number that died from each cause listed. When two causes were listed for a patient, they were counted as 0.5. Data presented in hours as median (interquartile range); *Mann-Whitney U test; †Chi Square test. Values with different superscripts (a, b, c) are significantly different (p < 0.05).

Table 3 Comparison of Mortality Rates of Alternative Patient Cohorts and Plasma to RBC Ratios

<table>
<thead>
<tr>
<th>Plasma to RBC Ratio (Range)</th>
<th>Low Ratio (0:22–1:4)</th>
<th>Medium Ratio (1:3.9–1:2.1)</th>
<th>High Ratio (1:2–1:0.59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis*</td>
<td>65% a n = 31</td>
<td>34% b n = 53</td>
<td>19% c n = 162</td>
</tr>
<tr>
<td>Excluding thoracic trauma</td>
<td>57% a n = 23</td>
<td>29% b n = 48</td>
<td>19% b n = 152</td>
</tr>
<tr>
<td>Excluding neurotrauma</td>
<td>62% a n = 26</td>
<td>36% b n = 50</td>
<td>15% c n = 145</td>
</tr>
<tr>
<td>Excluding whole blood†</td>
<td>66% a n = 38</td>
<td>27% b n = 59</td>
<td>19% b n = 149</td>
</tr>
<tr>
<td>Excluding rFVIIa</td>
<td>69% a n = 26</td>
<td>38% b n = 39</td>
<td>15% c n = 100</td>
</tr>
</tbody>
</table>

Values with different superscripts (a, b, c) are significantly different (p < 0.05) (Chi Square Test).

* See Methods Section.
† Ratio calculated as FFP:RBC units.
Multivariate Logistic Regression

Factors in a 1:1:1 ratio (i.e., plasma:RBC:platelets) in patients for a strategy of aggressive early correction of coagulation.

versy in the approach to patients requiring massive transfusion. Given these concerns, there has been recent controversy in the approach to patients requiring massive transfusion based upon clinical or laboratory data. These recommendations are echoed in a clinical practice guideline instituted in September 2004 at US combat hospitals, which support the early use of a 1:1:1 ratio of plasma to RBCs. Cinat et al., in a study of 45 massively transfused patients reported the plasma to RBC ratio for survivors was 1:1.8 compared with 1:2.5 in nonsurvivors (p = 0.06). Cosgriff et al. in a prospective cohort of 56 massive transfusion patients found significant coagulopathy in 47% of patients, predicted by persistent hypothermia and progressive metabolic acidosis. Several other retrospective studies have confirmed the presence of coagulopathy in patients requiring massive transfusion and have called for increased use of coagulation factors. Previous reports of the outcomes of patients requiring massive transfusion have documented similar results in smaller populations. Lucas and Ledgerwood found that coagulopathy was exacerbated in several studies in which trauma patients were transfused less plasma relative to RBCs. Cinat et al., in a study of 45 massively transfused patients the plasma to RBC ratio for survivors was 1:1.8 compared with 1:2.5 in nonsurvivors (p = 0.06). Cosgriff et al. in a prospective cohort of 56 massive transfusion patients found significant coagulopathy in 47% of patients, predicted by persistent hypothermia and progressive metabolic acidosis. Several other retrospective studies have confirmed the presence of coagulopathy in patients requiring massive transfusion and have called for increased use of coagulation factors.

There was an absolute and relative reduction in mortality of 55% and 60%, respectively, in the high (1:1.4) plasma to RBC ratio group compared with in the low (1:8) plasma to RBC ratio group. The correction of the coagulopathy of trauma must begin early, before the patient enters the “bloody vicious cycle”. Our results reinforced this approach, as those in the low plasma to RBC ratio group died from uncontrolled pert opinion or computer modeling. This study is the first to support, with comparative ratio data in three equally injured groups of patients and regression analysis, the concept that early and aggressive replacement of coagulation factors may improve survival by decreasing death from hemorrhage for patients requiring massive transfusions based on data from a large population with traumatic injuries. Interestingly, our results support a report by Hirshberg et al. that used a computer simulation model and found that a plasma to RBC ratio of 2:3 was necessary to effectively minimize coagulopathy in exsanguinating hemorrhage.

Table 4 Analysis of Data Associated With Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS head/neck score, % 4 or 5 (n = 245)</td>
<td>7</td>
<td>19</td>
<td>0.005†</td>
</tr>
<tr>
<td>AIS face score, % 4 or 5 (n = 245)</td>
<td>0</td>
<td>1.4</td>
<td>0.11†</td>
</tr>
<tr>
<td>AIS external score, % 4 or 5 (n = 245)</td>
<td>0.5</td>
<td>0</td>
<td>0.53†</td>
</tr>
<tr>
<td>AIS pelvis/extremity score, % 4 or 5 (n = 246)</td>
<td>28</td>
<td>19</td>
<td>0.13†</td>
</tr>
<tr>
<td>AIS abdomen score, % 4 or 5 (n = 245)</td>
<td>22</td>
<td>36</td>
<td>0.024†</td>
</tr>
<tr>
<td>AIS thorax score, % 4 or 5 (n = 245)</td>
<td>6</td>
<td>20</td>
<td>0.011†</td>
</tr>
<tr>
<td>ISS (n = 246)</td>
<td>17 (13–25)</td>
<td>25 (17–29)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Systolic blood pressure (n = 231)</td>
<td>98 (80–120)</td>
<td>90 (70–109)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Heart rate (n = 233)</td>
<td>112 (91–132)</td>
<td>121 (100–140)</td>
<td>0.052*</td>
</tr>
<tr>
<td>Temperature (n = 195)</td>
<td>96.1 (94.4–97.7)</td>
<td>94.9 (93.2–97.3)</td>
<td>0.049*</td>
</tr>
<tr>
<td>Base deficit (n = 201)</td>
<td>7 (3–12)</td>
<td>13 (8–18)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>INR (n = 212)</td>
<td>1.5 (1.2–1.8)</td>
<td>2.1 (1.6–3.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Platelet level (n = 174)</td>
<td>222 (152–278)</td>
<td>175 (118–234)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Hemoglobin (n = 234)</td>
<td>11.1 (9.0–13)</td>
<td>9.9 (7.2–11.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>% rFVIIa use (n = 246)</td>
<td>34</td>
<td>30</td>
<td>0.44†</td>
</tr>
<tr>
<td>Plasma:RBC ratio (n = 246)</td>
<td>1:1.6 (1:1.3–1:2.2)</td>
<td>1:2.3 (1:1.4–1:5.1)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

n = number of patients with data available.
† Mann-Whitney U test.
†† Chi Square test.
AIS, Abbreviated Injury Scale; ISS, Injury Severity Score; rFVIIa, recombinant Factor VIIa.

Table 5 Odds Ratio Predicting Survival Using Multivariate Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma:RBC ratio</td>
<td>8.6 (2.1–35)</td>
<td>0.003</td>
</tr>
<tr>
<td>AIS head/neck score</td>
<td>0.76 (0.61–0.94)</td>
<td>0.013</td>
</tr>
<tr>
<td>AIS thorax score</td>
<td>0.73 (0.57–0.92)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.0 (0.98–1.01)</td>
<td>0.457</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.1 (0.91–1.2)</td>
<td>0.501</td>
</tr>
<tr>
<td>Base deficit</td>
<td>0.89 (0.84–0.95)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AIS, Abbreviated Injury Scale.
creased mortality rates and they recommend earlier and more intensive care unit with a persistent coagulopathy have elegantly demonstrated that trauma patients who arrive in the intensive care unit with a persistent coagulopathy have increased mortality rates and they recommend earlier and more aggressive use of plasma.36

Our population of patients also received an increased amount of aPLT and cryoprecipitate. One apheresis platelet unit usually also contains 250 to 350 mL of plasma. This increased use of plasma, in addition to platelets and cryoprecipitate, supports the concept of damage control or hemostatic resuscitation.15,26,28 This approach emphasizes the aggressive diagnosis and treatment of coagulopathy in patients at high risk of requiring massive transfusion before it occurs or early in the resuscitation. If successful it will prevent and treat the lethal triad of trauma, which includes the early coagulopathy of trauma, from occurring.15,18,28,62 Similar in philosophical approach to damage control surgery the concept is to “stay out of trouble rather than get out of trouble”.

Our results indicate that the rate per hour of crystalloid and blood products was decreased with higher plasma to RBC ratios. We hypothesize that the early, increased use of plasma in these severely injured patients helped control the coagulopathy of trauma more efficiently, and, as a result required less crystalloid and RBCs per hour during the first 24 hours of resuscitation. Additionally, the use of plasma instead of crystalloids and RBCs helped prevent or limit the development of dilutional coagulopathy.15 Conversely, we believe that patients who received less plasma and more crystalloid and RBCs in the low and medium plasma to RBC ratio groups entered the “bloody vicious cycle”, and died significantly sooner from uncontrolled hemorrhagic shock. The rate of blood products and crystalloid may have also been reduced for the survivors in the high plasma to RBC ratio group as a result of not requiring active resuscitation during the entire 24 hours after initiating a massive transfusion. We suspect that both improved hemostasis and survival, and the lack of need to be actively resuscitated contributed to the decreased rate of products and crystalloid transfused in the high plasma to RBC ratio group.

Patients who received low or medium plasma to RBC ratios died predominantly of hemorrhage at a median of 2 to 4 hours. This supports the concept that patients who require massive transfusion are at risk of early (<6 hours from admission) death from hemorrhage,36 and indicates rapid treatment of coagulopathy with a higher ratio of plasma to RBC prevents early death from hemorrhage. This was evidenced by the median time to death of 38 hours in the high ratio group. Patients who received high plasma to RBC ratios had a higher incidence of death from sepsis and multiorgan failure versus hemorrhage as a result of surviving long enough to develop these complications. This is supported by the median time to death in the low and medium ratio groups compared with in the high ratio group. This relationship was noted in another similar study evaluating the effect of blood products on mortality.63 Because of the retrospective nature of this study, we cannot rule out the possibility that the increased use of plasma, apheresis platelets, and cryoprecipitate may have contributed to these results, as has been previously reported.64

Our results are subject to limitations inherent in retrospective studies, including incomplete data collection, lack of standard timing for measuring variables, and lack of a massive transfusion protocol that was consistently applied to patients. The variable with the highest percentage of missing data was the admission platelet concentration at 30%. It is possible that the exclusion of these missing values may have affected our results, but because ISS and mechanism of injury were equal in all three groups, it is likely that there was a comparable degree of coagulopathy, as has been shown previously.14 Another potential confounder is the possibility that the patients who did not receive plasma did not primarily as a function of dying before they had a chance to receive plasma. These patients may have been more critically ill than the others who were able to wait for plasma to be thawed. Although this is possible, all available indicators of severity of injury including ISS, systolic blood pressure, base deficit, and INR were equal between the three groups of patients which makes this potential confounder less likely.

Despite these limitations, this study is currently one of the largest reviews of patients with massive transfusion in trauma to analyze the effects of blood product transfusion and mortality. Additionally, we were able to adjust for many confounding variables in our regression analysis to include thoracic AIS values, admission hemoglobin concentrations, and rFVIIa use, which were each different in the low, medium, and high ratio groups that were compared. In addition to adjusting for thoracic AIS score in the regression model, we also analyzed the relationship between ratio of plasma to RBCs transfused with the exclusion of patients with severe thoracic injuries. In this analysis, the relationship of increased plasma to RBC ratio and decreased mortality remained between the low and high ratio groups (Table 3).

We believe that our results support the development of randomized controlled trials in animal and human subjects that will evaluate the effect of plasma to RBC ratios transfused to patients at risk of requiring massive transfusions. Ratios tested should also include plasma to RBC ratios of greater than 1:1 to evaluate if more plasma than RBCs would improve survival in coagulopathic patients with severe traumatic injury. Strategies that aggressively treat the coagulopathy of trauma and decrease the use of stored RBCs in patients with severe traumatic injuries including early and increased use of plasma, platelets, cryoprecipitate, or fresh whole blood if available, and the aggressive treatment of hypothermia,
metabolic acidosis, and hypocalcemia need continued study to determine whether they can improve outcomes.

One method that combat support hospitals and some large civilian trauma centers are currently using to facilitate early transfusion of increased plasma to RBC ratios is the use of thawed plasma. Thawed plasma is simply FFP, which after thawing, is kept refrigerated at 4°C for up to 5 days. This product is an American Association of Blood Banks (AABB) approved concept. Thawed AB plasma is stored at amounts equal to that of emergency release type O RBCs in emergency department refrigerators. This allows both blood products to be used immediately and concurrently upon presentation of a patient at risk for massive transfusion. Once thawed plasma is transfused it is immediately replaced by the blood bank to maintain availability for the next patient. Although thawed plasma was not used in the patients analyzed in this study, the results presented here have helped change our practice in the theater of operations and today thawed plasma is widely available at the busiest combat support hospitals, resulting in a decrease in plasma waste. Large civilian trauma centers should consider the use of thawed plasma to permit the transfusion of plasma to RBCs in a 1:1 ratio or at least in a 1:2 ratio at admission for patients with severe traumatic injuries who present with the coagulopathy of trauma. Based upon these data the US Army Surgeon General has recently distributed a policy recommending that a 1:1 plasma to RBC ratio be transfused to all patients with significant trauma and who are at risk for requiring a massive transfusion.

CONCLUSIONS

Recent literature demonstrates that the risk of requiring a massive transfusion can be rapidly identified and death from hemorrhage occurs quickly for patients with severe traumatic injuries requiring massive transfusion. The transfusion of plasma to RBCs in a 1:1 ratio is a rapid treatment that improves survival for patients at risk of hemorrhagic shock. We suggest that the empiric ratio of plasma to RBC should approximate 1:1 for patients with traumatic injuries who are at risk for requiring a massive transfusion.

REFERENCES

Assessment of Adverse Events in the Demise of Pediatric Burn Patients

Dennis C. Gore, MD, Hal K. Hawkins, MD, David L. Chinkes, PhD, Dai H. Chung, MD, Arthur P. Sanford, MD, David N. Herndon, MD, and Steven E. Wolf, MD

Background: Given the contention that survival is to be expected from even the most severely burned child, then, intuitively, at least some pediatric burn victims die because of suboptimal care. The purpose of this study is to assess the impact of any adverse events that may have contributed to the death of burned children.

Methods: Four surgeons with specialty training in pediatric burn care reviewed the clinical course and autopsy findings of 71 burned children who died after admission to a burn center during a 10-year interval. Reviewers were asked to determine the predominant factor or factors contributing to each child’s demise and to assess the significance of any deviations from optimal care.

Results: For the 10 years under review, overall mortality for all pediatric burns was 2.4%. Of these deaths, 25% had burns encompassing less than 50% body surface area. The reviewers identified lung damage as the most frequent cause of death, which was deemed largely unpreventable. Conversely, hypovolemia related to inadequate prehospital fluid resuscitation and failure to obtain and maintain a patent airway were considered the second and third most common factors in a child’s death and deemed preventable under ideal circumstances.

Conclusions: This review implies that deficiencies in health care contribute to the demise of many burned children. The most notable areas for improvement are in fluid resuscitation and airway control. This suggests that quality assurance and educational initiatives to improve these aspects of care may have the greatest impact on further improving survival of burned children.

Key Words: Patient safety, Quality assurance, Medical error.


Historically the main determinants of mortality from burn injury have been age, the extent of burn, and the presence or absence of inhalation injury. Yet with the remarkable advances in burn care and the associated improvements in survival, the “traditional” determinants of skin and lung damage may no longer have a dominant influence on survival of the young. This contention is supported by Sheridan et al., who examined the clinical course of burned children who subsequently died at the Shriners Burns Hospital in Boston. By comparing patients cared for from 1974 to 1980 with those patients seen between 1991 and 1997, and stratified by burn size, these authors concluded that the chance of survival after a burn has greatly improved for children to the extent that even the very young and severely burned child should survive. Dr. Saffle, a recent president of the American Burn Association, echoed this sentiment, commenting that for adolescents and young adults, almost no burn is too extensive to preclude recovery. Demonstrating that such an ambitious goal is possible, we recently reviewed the outcome of pediatric patients with burns of greater than 80% of their body surface. Amazingly, more than 60% of these severely burned victims survived. Yet, regardless of these therapeutic advancements and miraculous survivals, victims of burn injury still die. At our institution alone there were 18 deaths during a past year. Because these publications imply that survival is to be expected, one must conclude that at least some pediatric burn victims die because either the correct intervention was not performed, was not performed in a timely fashion, or was not performed correctly.

The purpose of this study was to appraise the major determinants of death in burned children and assess the impact of any adverse event that may have contributed to the demise of these children. It is hoped that this review and analysis may identify those factors, which are potentially correctable and thereby guide future maneuvers to improve survival.

PATIENTS AND METHODS

Records

Of a total of 3,005 admissions to the Shriners Hospitals for Children in Galveston, TX from January 1992 through December 2001, there were 72 deaths. Except for one child whose family refused autopsy on religious edict, autopsies were performed on all (71) children. All but four of these autopsies were performed by a single pathologist (H.K.H.). Three of these autopsies were performed at the adjacent University Pathology Department of the University of Texas Medical Branch with the findings recorded in the identical format prescribed by the specialty pathologist. The single
remaining autopsy was performed by the county coroner. In addition to the autopsy findings, the pathologist also reviewed each patient’s hospital records and reported a summary of the clinical course for each patient. These clinical case summaries were available for all 72 deaths. For all admissions to the Shriners hospital during this 10-year interval, patient characteristics and demographics were available on computerized hospital records.

Review Process

After approval from the Institutional Review Board, autopsies and clinical course records were reviewed by four surgeons, all of whom have experience in burn care; three having completed postresidency fellowships in burn care at a Shriners Hospitals for Children, the other with fellowship training in pediatric surgery and with more than 10 years experience as a physician consultant at the Shriners Hospitals for Children. Using a standardized form, each reviewer was asked to note the probable cause of death and any associated factors contributing to death. Reviewers were also asked to scale the contribution of any deficiencies in care to the cause of death, from 1 (denoting no error) to 4 (denoting a significant impact of negligence on the child’s death). Also scaled from 1 to 4 by each reviewer were (1) the percent chance that a misadventure caused death and (2) the possibility of surviving to discharge had the error not occurred. For grading items 1 and 2, reviewers agreed on the following scale: 1 = 0% to 15%, 2 = 16% to 50%, 3 = 51% to 84%, and 4 = 85% to 100%. Each reviewer was screened from the decisions of the other reviewers.

Statistics

Patient characteristics between survivors and deaths were compared using a Student’s independent t test. Differences in the incidence of inhalation injury between survivors and deaths were assessed using χ^2. Median values between raters were used to report the incidence of an event. Median and mean values corresponded closely for all variables, so mean values are not reported. Inter-rater agreement was assessed using simultaneous κ-statistics for variables that had an incidence of at least 10%. κ values of greater than 0.7 were considered significant and indicative of strong inter-rater agreement.

RESULTS

The overall mortality for all hospital admissions during the 10 years of review was 2.4%. Comparison of patient characteristics between survivors and deaths is shown in Table 1 with deaths having a significantly greater extent of burn and a higher incidence of inhalation injury. In Table 2, patient’s characteristics are stratified by their severity of burn demonstrating a significant association between a greater surface area burn and increasing mortality. Of note, there were 19 deaths (mortality rate = 0.7%) of patients admitted to the hospital with burns encompassing <50% of their body surface area.

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics</th>
<th>Survivors</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,933</td>
<td>72</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>6.4 ± 2.1</td>
<td>5.7 ± 1.8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>27.6 ± 3.9</td>
<td>26.1 ± 5.1</td>
</tr>
<tr>
<td>TBSA burn (%)</td>
<td>26 ± 5</td>
<td>66 ± 3*</td>
</tr>
<tr>
<td>TBSA third burn (%)</td>
<td>14 ± 4</td>
<td>60 ± 3*</td>
</tr>
<tr>
<td>Inhalation injury (%)</td>
<td>16</td>
<td>60†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 comparison by Student’s t test.
† p < 0.01 comparison by χ^2.

<table>
<thead>
<tr>
<th>Table 2 Deaths Stratified by Severity of Burn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns ≤50% (n = 2,602)</td>
</tr>
<tr>
<td>Number of deaths</td>
</tr>
<tr>
<td>Mortality (%)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>TBSA burn (%)</td>
</tr>
<tr>
<td>Inhalation injury (%)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 comparison by Student’s t test.
† p < 0.06 comparison by χ^2.

<table>
<thead>
<tr>
<th>Table 3 Primary Causes of Death and Factors Contributing to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>Diffuse alveolar lung damage (%)</td>
</tr>
<tr>
<td>Hypovolemia/inadequate resuscitation (%)</td>
</tr>
<tr>
<td>Airway loss/aspiration (%)</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
</tr>
<tr>
<td>Burn wound sepsis (%)</td>
</tr>
<tr>
<td>Anoxia (%)</td>
</tr>
<tr>
<td>Drug reaction (%)</td>
</tr>
</tbody>
</table>

Data are median values.
κ-statistics for inter-rater agreement ≥0.7 considered significant.

The reviewers determined that diffuse alveolar damage of the lungs was the most prevalent primary cause of death (Table 3). Hypovolemia and inadequate emergency resuscitation were considered the second most common cause of death. Loss of airway or aspiration, pneumonia, and burn wound sepsis were designated as the third, fourth, and fifth most common primary causes of death, respectively. Death related to anoxic brain damage occurring at the time of the fire was noted as the cause of death in five children; the sixth most frequent cause of death. One child died from an apparent anaphylactic drug reaction. For the five most frequent causes of death, there was no significant agreement between reviewers with a maximum κ score for airway or aspiration at
0.48. As to whether adverse events contributed to death, reviewers noted diffuse alveolar lung damage as the most common contributing factor to death (Table 3). Burn wound sepsis, pneumonia, hypovolemia or inadequate resuscitation, and airway loss or aspiration completed the five most commonly noted factors contributing to a child’s demise. There was no significant inter-rater agreement in designating an adverse contributing factor with a maximum $\kappa$ score for burn wound sepsis at 0.53.

Reviewer’s assessment as to the significance of any error in each child’s death is shown in Table 4. The cumulative score for all patients on a 1 to 4 scale was 2.4. Thus, in the aggregate opinion of the reviewers, suboptimal care contributed significantly in the demise of approximately 50% of the burn victims. Stratifying the significance of any deficiency in care by cause of death, drug reaction, airway loss or aspiration, and hypovolemia or inadequate resuscitation was considered by the reviewers to be frequently associated with negligence. In contrast, error was not deemed of much importance to either anoxic brain injury or diffuse alveolar lung damage. The impact of a medical misadventure on the demise of each child was also assessed by the reviewer’s determination of a percentage chance that error contributed to a child’s death (Table 5). Also scaled 1 to 4, physician reviewers assessed a cumulative score for this impact of error at 2.3, translating into the reviewer’s perception that medical misadventure contributed to a child’s demise is about 50% of all burn victims. There was, however, a wide range of disagreement as to the impact of error with a $\kappa$ score of only 0.06. Another determination as to the significance of medical error was assessed by the reviewers as the percentage chance that the child would have survived had the error not occurred. Again scaled 1 to 4, reviewers assigned this an overall 2.0 score, meaning approximately one-third of all deaths could have been prevented had a deficiency in care not occurred (Table 6). Again inter-rater variability was high with a $\kappa$ score of 0.06.

Although there was a wide range of disagreement concerning the incidence and severity of medical error, this disparity of opinion did not seem to arise from differences as to the seriousness of an adverse event because the range of values that raters gave for significance of error was usually relatively narrow. In general, there were only systematic differences between raters. For example, rater 3 assessed the significance of error for pneumonia as 1 (i.e. no error) whereas the other reviewers typically gave ratings of 2 or 3. Reviewer 4 often rated the significance of medical error for anoxia as a 3 to 4 suggesting that in his opinion something could have been performed in the initial resuscitation to preserve brain function. In contrast, the other reviewers rated the significance of error for anoxia as a 1 or 2 indicative of their opinion as to the futility of any medical intervention to forego the anoxic brain death. Opinions also varied as to the significance of error with diffuse alveolar lung damage. For example, rater 2 consistently assigned a significance of error of 3 for children dying primarily from lung injury and thereby conveying his opinion that something might have been performed to forego pulmonary failure. Other reviewers consistently gave diffuse alveolar lung damage an error significance score of 1.

### Table 4 Significance of Medical Error to Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Average Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse alveolar lung damage</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypovolemia/inadequate resuscitation</td>
<td>3.0</td>
</tr>
<tr>
<td>Airway loss/aspiration</td>
<td>3.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.3</td>
</tr>
<tr>
<td>Burn wound sepsis</td>
<td>2.5</td>
</tr>
<tr>
<td>Anoxia</td>
<td>1.5</td>
</tr>
<tr>
<td>Drug reaction</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Cumulative score 2.4 ($\kappa = 0.06$).

Scale: 1 = 0%–15%; 2 = 16%–50%; 3 = 51%–84%; 4 = 85%–100%.

$\kappa$-statistics for inter-rater agreement $\geq 0.7$ considered significant.

### Table 5 Inter-Rater Variability for Percent Chance that Error Caused Death

<table>
<thead>
<tr>
<th>Scores</th>
<th>Reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>51 (72)</td>
</tr>
<tr>
<td>2</td>
<td>5 (7)</td>
</tr>
<tr>
<td>3</td>
<td>7 (10)</td>
</tr>
<tr>
<td>4</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

Mean $\pm$ SD 1.61 $\pm$ 1.06 2.89 $\pm$ 1.26 2.37 $\pm$ 1.83 2.35 $\pm$ 1.24

Values presented as no. patients (%) for each score given by a reviewer.

Cumulative score 2.3 ($\kappa = 0.06$).

### Table 6 Inter-Rater Variability for Percent Chance of Surviving had Error not Occurred

<table>
<thead>
<tr>
<th>Scores</th>
<th>Reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>50 (71)</td>
</tr>
<tr>
<td>2</td>
<td>6 (8)</td>
</tr>
<tr>
<td>3</td>
<td>6 (8)</td>
</tr>
<tr>
<td>4</td>
<td>9 (13)</td>
</tr>
</tbody>
</table>

Mean $\pm$ SD 1.61 $\pm$ 1.06 2.89 $\pm$ 1.10 2.17 $\pm$ 1.73 2.04 $\pm$ 1.16

Values presented as no. patients (%) for each score given by a reviewer.

Cumulative score 2.0 ($\kappa = 0.06$).

### DISCUSSION

The overall mortality for this 10-year review was only 2.4%; far less than that reported from the national burn registry. As to be expected, there was a significantly greater extent of burn injury and a higher incidence of inhalation
injury in those dying at our institution. However, the mean value for all deaths was a body surface area burn of only 66% and an incidence of inhalation injury of only 60%. Furthermore, 19 children died with burns of less than 50% body surface area of which only 8 were noted to have an inhalation injury. These values demonstrate that some deaths were the result of neither devastating skin nor lung damage. This shows that, regardless of the extent of burns, something other than the actual injury must have contributed to the demise of many of these children. One probable assumption would be that a deficit in care, either as an omission or delay in providing appropriate care or possibly inappropriate care, may be a factor in some deaths.

In this review, experts in pediatric burn care identified lung damage as the most frequent cause of death in these injured children. In general, these reviewers thought that death from pulmonary failure, a consequence predominantly of either the initial smoke injury or as sequelae from sepsis, was largely not preventable. Conversely, these physician reviewers in aggregate considered hypovolemia or inadequate resuscitation as the second, and failure of airway control or aspiration as the third, most common cause of death. It was their opinion that such deaths were likely preventable. Death from infection, noted separately as pneumonia or burn wound sepsis, was also considered a frequent primary cause of death. Reviewers generally scaled these infectious deaths as potentially preventable, but with a varied opinion as to the responsibility of the medical community regarding infection control versus a feeling of pessimism for any intervention in an individual patient with severe sepsis.

The main goal of this study was to categorize failures in the care of injured children and thereby provide a guide to direct future quality care initiatives and ultimately improve patient care and survival. One presumption is to focus on those failures deemed most preventable; for example, an educational initiative aimed at optimizing fluid resuscitation and airway control of a severely burned child. With the findings of this study demonstrating that hypovolemia and loss of airway, a common facet in the death of some children, such a quality assurance directive would intuitively be beneficial. However, an acutely burned child is relatively infrequent for even an experienced emergency room physician, thus any postevent education is unlikely to have much impact in the future care of burn children as a rarely repeated event. Likewise, pre-emptive education such as that provided by the Advanced Burn and Trauma Life Support courses designed to reduce errors in resuscitation and airway management may fail to have a prolonged impact with possibly many years preceding an occurrence. As an alternative to a traditional continuing medical education initiative, advances in information technology, such as telemedicine, may provide an avenue for improving the emergency care and transfer of burn victims by allowing closer, more timely interaction of a burn expert to the initial care of an injured child. A key aspect of any such interaction is the prompt contact from the initial emergency room to the burn specialist and the ready availability of the technology. Furthermore, a concentrated effort at education and training for personnel dedicated to repeatedly providing safe transport would also likely be beneficial. Likewise, many physicians who work at a burn center are residents in training who lack experience in fluid resuscitation and airway intubation, especially for severely burned children. Emerging facilities such as the Human Patient Simulator may greatly aid in resident physician training by providing a manner for skills acquisition before such a physician is thrust into a life-or-death situation. In contrast to emergency resuscitation, death from pulmonary failure was generally considered nonpreventable. Yet, considering the prominent contribution of pulmonary damage to the demise of these patients, any improvements in this regard may have a substantial impact on outcome. However, considering health care negligence was not deemed to have a substantive influence regarding these respiratory deaths, therapeutic advances, not educational, quality assurance initiatives, are likely to be a more viable avenue for improving outcome from this cause of death.

There was no significant agreement between reviewers as to either the cause of death or the relevance of medical error in the demise of these children, despite having both autopsy records and a summary of their clinical course. Such a discrepancy between well-trained experts in a clearly defined specialty of care in a single specialized hospital setting emphasizes the difficulty and subjectivity in deciding on those factors contributing to the death of these injured children. Much of this disparity resulted from our inability to distinguish the relative contribution to a child’s demise from the initial injury versus any exacerbation of that injury related to an inadequate or delayed resuscitation or damage related to sepsis. Furthermore, because children have such an extensive physiologic reserve and the vast majority have excellent cardiac function, the progression through multiple organ failure to death was often prolonged. This common scenario of prolonged, multiorgan failure often precluded a clear interpretation of the exact inciting factor in the child’s death. Autopsy findings did little to relieve this uncertainty because the postmortem examination almost universally showed a combination of extensive inflammatory damage within the lung, bacterial and fungal infiltration within the lungs (i.e. pneumonia), and infection or contamination within any residual wound. Thus, autopsies were not particularly helpful in identifying either a predisposing cause of death or any associated medical error. Because autopsies are known to disagree with the clinical diagnosis as much as 40% of the time, any study with the intent of determining the nature and preventability of death would be expected to have substantial error without inclusion of the autopsy findings. Yet, this disparity between the pre- and postmortem cause of death is largely evident in review of adult patients. Furthermore, this review of injured children circumvents any variable of a “natural” death rate because the vast majority of these burn
victims were in good health before their injury, which negates much of the uncertainty by a reviewer as to the influence of the disease process versus error in the demise of these children. Therefore, a finding of this study suggests that, at least in regard to injured children, accurate records of a child’s clinical care, and not the autopsy, are of utmost importance in assessing any medical misadventures.

REFERENCES

A Fentanyl-Based Pain Management Protocol Provides Early Analgesia For Adult Trauma Patients

Kevin M. Curtis, MD, Horace F. Henriques, MD, Gilbert Fanciullo, MD, Cecily M. Reynolds, MD, and Freeman Suber, MD

**Background:** In the past two decades, a number of reports have identified inadequate treatment of pain among emergency department patients. No study has evaluated the frequency or effectiveness of early analgesia in the trauma patient. The objective of this study was to determine the effect of a protocol-driven pain management scheme on time to initiation of analgesia among trauma patients.

**Methods:** A fentanyl-based protocol was developed with patients being assigned to one of three treatment arms based on hemodynamics and Glasgow Coma Scale (GCS) score. Using an institutional review board-approved before and after study design, patients over the age of 14 and meeting trauma system activation criteria at the Dartmouth-Hitchcock Medical Center were eligible. Results were compared with a retrospective chart review of eligible patients treated during a matched preprotocol time period in 2002. The primary outcome measure was time to initiation of analgesia. Secondary outcome measures included (1) the proportion of patients receiving their first analgesia dose within 30 minutes, (2) the number of patients receiving multiple doses of analgesia in the trauma bay, and (3) adverse events. Pain level was assessed using either a Numeric Pain Scale (for patients with a GCS score of 15) or a Behavioral Pain Assessment Scale (GCS score <15).

**Results:** Implementation of the protocol resulted in a decrease in the mean time to initiation of analgesia from 53.61 minutes ± 6.88 minutes to 27.94 minutes ± 3.34 minutes ($p = 0.001$). The protocol also increased the percentage of patients receiving analgesia within the first 30 minutes of arrival from 44.4% to 74.6% ($p < 0.001$). There were no differences between the two groups in terms of baseline characteristics or adverse events.

**Conclusions:** The implementation of a fentanyl-based pain management protocol resulted in a marked reduction in time to initial analgesia among trauma patients. There was no evidence of an increase in adverse events. This tool has the potential to be easily extrapolated and applied to other trauma systems.

**Key Words:** Trauma, Analgesia protocol, Fentanyl, Pain management.

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For all these reasons, early pain management of patients with multiple injuries is particularly critical. However, inadequate analgesia in the trauma bay still occurs as a result of focused attention on acute injuries, failure to assess pain adequately, concerns over masking the underlying diagnosis, and fear of inducing respiratory depression or hemodynamic compromise. It has also been suggested that insufficient analgesic administration stems from (1) a lack of quality improvement programs evaluating pain management, and (2) insufficient translation of pain relief evidence into clinical practice.

The persistence of insufficient pain management, even in 2004, is supported by an article by Rupp and Delaney demonstrating inadequate analgesia among emergency department (ED) patients. Evaluation of analgesia in patients with major trauma is an area that has been neglected, with no studies specifically addressing the frequency or effectiveness of early pain management in this population.

In an effort to evaluate the trauma analgesia standard at Dartmouth-Hitchcock Medical Center (DHMC), Suber et al. conducted a pilot study evaluating analgesia among patients meeting established DHMC trauma activation criteria as well as >16 years of age, Glasgow Coma Scale (GCS) score of 14 to 15, systolic blood pressure >90 mm Hg with rib, spine, extremity, or pelvic fractures. (Suber F, Fanciullo G, Kispert P. Pattern of pain management and hemodynamic effects of pain medication in the trauma patient: data from Dartmouth-
Hitchcock. Unpublished data, 2002.) Despite having obviously painful fractures in addition to a high GCS score and acceptable hemodynamics, these patients waited an average of 72 minutes (range, 10–315 minutes) for the first administration of analgesia (n/H11005/47), with a dose that was often insufficient to relieve their discomfort. Furthermore, 15% of patients never received pain medication in the trauma bay. Based on our pilot data and the literature supporting protocol-based methodology,11 we developed a formalized, fentanyl-based analgesia protocol for pain management among adult patients treated in the DHMC trauma unit. The primary objective of this study was to determine the effect of this protocol on time to initiation of analgesia.

PATIENTS AND METHODS

Using an institutional review board-approved before and after study design, we evaluated patients over the age of 14 and meeting trauma system activation criteria at DHMC. DHMC is a rural Level I trauma center with an annual trauma volume of 1,200 patients, 50% of who meet trauma activation criteria (Table 1). Ninety-three percent of DHMC trauma patients are victims of blunt trauma, with motor vehicle crashes and falls predominating.

From September 15, to January 31, 2003, all eligible patients were prospectively enrolled according to the approach provided in Figure 1. Patients were assigned to group A, B, or C based on systolic blood pressure, heart rate, and GCS score. Group A included those patients with unstable physiology; group B patients exhibited stable but abnormal physiologic findings; and group C patients had normal or near-normal physiologic findings (Table 2). Results were compared with a retrospective chart review of eligible patients treated in a matched preprotocol time period in 2002 (during which a trauma analgesia quality improvement effort had already been initiated). The primary outcome measure was time to initiation of analgesia. Secondary outcome measures included (1) the proportion of patients receiving their first analgesia dose within 30 minutes, (2) the number of patients receiving multiple doses of analgesia in the trauma bay, and (3) adverse events.

Table 1 DHMC Protocol for Trauma System Activation

<table>
<thead>
<tr>
<th>Decision to call a trauma alert (limited response)—significant mechanism of injury (MOI) (see consult policy) with below physical criteria would prompt an alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>1. Respiratory distress</td>
</tr>
<tr>
<td>2. GCS score between 9 and 13 (GCS score &lt;9 requires a Trauma Nine activation)</td>
</tr>
<tr>
<td>3. Transient hypotension</td>
</tr>
<tr>
<td>4. Penetrating injuries to the head, neck, or trunk or extremities proximal to the elbow or knee</td>
</tr>
<tr>
<td>5. Injury to two or more body systems</td>
</tr>
<tr>
<td>6. Hemodynamically stable, intubated patients transferred from outside facility</td>
</tr>
<tr>
<td>7. Documented fractured femurs or severe pelvic fractures</td>
</tr>
<tr>
<td>8. Documented spinal cord injuries</td>
</tr>
<tr>
<td>9. At discretion of ED triage (MD, RN), trauma attending, trauma resident, or DHART helicopter team</td>
</tr>
</tbody>
</table>

Decision to call a Trauma Nine (full response)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trauma arrest</td>
</tr>
<tr>
<td>2. Blood pressure ≤90 mm Hg</td>
</tr>
<tr>
<td>3. Interfacility transfer requiring blood transfusion</td>
</tr>
<tr>
<td>4. Uncontrolled external hemorrhage</td>
</tr>
<tr>
<td>5. Severe respiratory compromise (inability to obtain/maintain airway; inability to oxygenate; inability to ventilate)</td>
</tr>
<tr>
<td>6. All intubated patients who are transferred in from the field or meet other criteria as above</td>
</tr>
<tr>
<td>7. GCS score ≤8</td>
</tr>
<tr>
<td>8. Gunshot wound to chest, neck, abdomen</td>
</tr>
<tr>
<td>9. Any patient with trauma mechanism arriving for aortic injury evaluation</td>
</tr>
<tr>
<td>10. Multiple patients meeting trauma alert criteria</td>
</tr>
<tr>
<td>11. At the discretion of ED triage (MD, RN), trauma attending, trauma resident, or DHART helicopter team</td>
</tr>
</tbody>
</table>

Serious consideration should be given to taking the hemodynamically unstable Trauma Nine patient directly to operating room 1 (trauma room) if they are not in full cardiac arrest.

Study inclusion criteria were as follows: (1) age >14 years (DHMC adult trauma patient); and (2) meet established criteria for trauma activation (Table 1). Exclusion criteria were (1) allergy to fentanyl; (2) acute change in mental status that complicates trauma assessment; (3) GCS score of 15 with patient refusal of analgesia; and (4) GCS score of 15 and Numeric Pain Scale ≤4.

For all enrolled patients, the following data were recorded: (1) time of patient arrival; (2) heart rate and systolic blood pressure (initial and subsequent); (3) GCS score (initial and subsequent); (4) time of administration of each dose of analgesia; (5) dosage of each administration of analgesia; (6) time of pain assessments (initial and subsequent); (7) results of pain assessments; (8) estimate of patient weight; and (9) adverse events within 30 minutes of analgesia administration.

Assessment of pain was performed using either (1) an 11-point Numeric Pain Scale for patients with a GCS score of 15 or (2) a Behavioral Pain Assessment Scale (BPAS) for...
patients with a GCS score <15 (Table 3). The BPAS has been validated for pain assessment among intensive care unit patients with a GCS score <15.12 Before implementation of the protocol, a formal presentation was provided to all DHMC physicians and nurses involved in the ED care of trauma patients. During the study, for each eligible patient, initiation of the protocol occurred by the order of one of the treating physicians. After the “fentanyl protocol initiation order” was given, subsequent nursing pain assessments and analgesia administration occurred without additional orders within the constraints of the protocol.

Vital signs and pulse oximetry were continually monitored and were recorded each 15 minutes according to the institutional policy for patients meeting trauma activation criteria.

Adverse events were defined as (1) ED intubation, (2) allergic symptoms (e.g., hives, bronchospasm, or angioedema), or (3) a deterioration in hemodynamic criteria or GCS score requiring a downgrading of physiologic stability (e.g., group C downgrading to group B, or group B downgrading to group A).

**Statistical Analysis**

A two-tailed t test for independent samples with unequal variance was used to compare the overall mean time to initiation of analgesia, as well as the mean time to second
Analgesics should be administered in individual doses with continuous assessment of physiological status.

**GROUP A: Unstable Physiology:**
- Glasgow Coma Scale (GCS) < 9 (indication for intubation)
- Heart Rate (HR) < 60 or > 120 without a chronic explanation
- Systolic Blood Pressure (SBP) < 90 mmHg without a chronic explanation
- Acute Mental Status (MS) changes, including psychosis, intoxication, head injury or metabolic changes which complicate trauma assessment

**Intervention:**
Analgesics are not recommended.
Re-evaluation every 15 minutes.

**GROUP B: Stable Physiology:**
- Patient does not have Group A criteria and has:
  - GCS 9–12 and
  - HR 60–120 beats/min with
  - SBP 90–120 mmHg
- No MS changes complicating surgical/trauma assessment

**Intervention:**
Analgesics should be administered in individual doses with continuous assessment of physiological status.

For weight >40kg: Fentanyl 25-50 mcg IV q 15 minutes prn pain
(For weight <40kg: Fentanyl 10-25 mcg IV q 15 minutes prn pain)

**GROUP C: Normal Physiology:**
- Patient does not meet criteria of Groups A or B, and has all of:
  - GCS 13
  - HR 60–120 beats/min
  - SBP > 120 mmHg or (<120 if documented normal for patient)
  - Injury mechanism which would require narcotic analgesia

**Intervention:**
Analgesics should be administered in individual doses with continuous assessment of physiological status.

For weight >40kg: Fentanyl 25-50 mcg IV q 5 minutes prn pain
(For weight <40kg: Fentanyl 10-25 mcg IV q 5 minutes prn pain)

**RESULTS**

Patient baseline characteristics are described in Table 4. A total of 243 patients were identified as meeting DHMC adult trauma activation criteria during the study periods. In the preprotocol period, 102 patients were potentially eligible. Fourteen met exclusion criteria, leaving 88 who would have qualified for group assignment. Of those 88 patients, 66 patients were appropriate for fentanyl administration (22 were in group A). Fifty-four of those 66 patients (81.8%) received fentanyl at some point while in the trauma bay (Fig. 2).

In the protocol period, 142 patients were potential study candidates. Twelve were initially excluded, leaving 130 patients...
for assignment to an analgesia group. Twenty-six additional patients were excluded, most of whom had a low pain score in addition to a GCS score of 15 (19 of 130). Of the remaining 104 who met inclusion criteria, 74 qualified for fentanyl administration (30 in group A). Sixty-seven of those 74 patients (90.5%) had appropriate initial treatment per the analgesia protocol.

Implementation of the protocol resulted in a decrease in the mean time to initiation of analgesia from 53.61 minutes ± 6.88 minutes to 27.94 minutes ± 3.34 minutes ($p < 0.001$), or an absolute reduction of 25.67 minutes (95% confidence interval, 25.66–25.68 minutes) (Figs. 3 and 4). The protocol also increased the percentage of patients receiving analgesia within the first 30 minutes of arrival from 44.4% to 74.6% ($p < 0.001$) (Fig. 5). In addition, in the protocol period, more patients received multiple doses of fentanyl while in the trauma bay (Fig. 6).

There were three adverse events noted among patients treated according to the fentanyl protocol; none of these could be attributed to the actual pain management scheme. Two patients required intubation in the trauma bay. In both cases, the intubation was performed before any administration of fentanyl. The third patient developed hypotension resulting in a downgrading of treatment category; this event also occurred before analgesia.
In their 2003 report on Improving the Quality of Pain Management Through Measurement and Action, the Joint Commission of Health Care Organizations stated that, at "the most fundamental level, improving pain management is simply the right thing to do." Unfortunately, studies involving hospitalized patients with acutely painful medical and surgical conditions have found that more than half of these patients received no analgesic medication while in the ED. Contributing to this deficiency is the fact that physicians often underestimate patients' pain.

We found that implementation of a fentanyl-based pain management scheme among adult trauma patients resulted in a marked reduction in the time to initiation of analgesia. The choice of fentanyl as the analgesic was based on its relatively short half-life, minimal effect on hemodynamic parameters, and rare central nervous system effects. The algorithm was designed to provide potentially frequent administration of a relatively low dose of medication in an effort to adequately treat pain while minimizing adverse effects. We found no adverse events attributable to the analgesia protocol despite cumulative doses of fentanyl up to 150 μg.

Although a decrease in time was observed in all three treatment groups, statistical significance was noted only in groups B and C (Table 3). Although our protocol stated that analgesics were “not recommended” for the most critically ill group A patients, the trauma surgeons elected to administer the fentanyl-based protocol to 38% of those patients. Historically, this group is the least likely to receive analgesia during resuscitation because of (1) reluctance over further compromise of hemodynamic status, (2) the potential negative effects on an already altered mental status, or (3) the team’s attention to the treatment of multiorgan injuries. Among the group A patients treated with fentanyl according to the group B guidelines, there was a 24% reduction in time to initiation of analgesia (57.6 minutes vs. 43.6 minutes, p = 0.289). Although not statistically significant, this subset was found to have no analgesia-related adverse events, suggesting that these critically ill patients can also be treated with intravenous fentanyl without complications.

Protocol implementation had a significant effect on the attention to analgesia, as evidenced by a doubling in the mean pain assessments per patient (2.13 vs. 1.03; p < 0.001). This is also reflected in the increased number of patients receiving multiple doses of analgesia.

One of the potential benefits of the proposed protocol-based approach is that it should have considerable external validity with relatively easy implementation. The treatment groups to which patients were assigned (A, B, or C) were defined based only on data that are obtained during a standard primary survey. Trauma centers are generally quite comfortable with the use of fentanyl, and our medication doses and frequency are well defined. The relative ease with which the protocol was incorporated into our standard trauma resuscitation is evidenced by the fact that within 1 month of the initiation, completion of the primary survey in a typical resuscitation would include the trauma team leader requesting “initiation of the fentanyl protocol”. However, even in the protocol period, eight patients, (7 in group B and 1 in group C) were eligible for analgesia but did not receive any. The explanation for those oversights is unclear, but the result of a 90% implementation rate of a new protocol among trauma activation patients is still viewed as a success. The greatest implementation challenge may be with introduction and incorporation of the BPAS into the analgesia assessment for those patients incapable of performing the Numeric Pain Scale.

**DISCUSSION**

In their 2003 report on Improving the Quality of Pain Management Through Measurement and Action, the Joint Commission of Health Care Organizations stated that, at “the most fundamental level, improving pain management is simply the right thing to do”.

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This study had several potential limitations. Out of necessity, the study was performed as a before and after design rather than being purely prospective and randomized. Our retrospective analysis indicated that attention to analgesia was often a relatively low priority among trauma patients. However, the decision to implement a protocol to improve attention to analgesia did not lend itself to a control arm. Because simply performing a study to evaluate the protocol will increase the attention given to analgesia, the results would be flawed. Furthermore, it would be unethical to withhold or delay analgesia for patients in a control arm. Therefore, the improvement seen in this study could be entirely explained by better attention to analgesia, rather than a uniquely effective pain management protocol. However, Suber’s pilot study (unpublished data) resulted in a quality improvement effort, which only decreased initial analgesia time from 72 minutes to 53.6 minutes. Furthermore, in its most basic form, this study could be viewed as an early-phase drug study in which it establishes safety in the disease group without definitive evidence of durable efficacy or optimal dosing.

This study also did not address adequately the effectiveness of the protocol in terms of extent or duration of analgesia. Subgroup analysis was performed for those patients who had adequate documentation of a reassessment of pain 30 minutes to 90 minutes after arrival. Using a definition for clinically significant analgesia a ≥2-point reduction on an 11-point scale, only 52% of those analyzed had achieved a significant reduction in pain in this window of time. Among those patients, the mean reduction in pain level was 1.7 (SD 1.71). Although the results are based on only 21 patients, they suggest that the protocol resulted in an insufficient level of analgesia for a substantial number of patients. There are a number of potential explanations for the apparent insufficient analgesia. One is that despite an early focus on analgesia, our attention to pain decreased significantly after the first 30 minutes. As attention shifts away from the initial resuscitation period to more detailed diagnosis and patient disposition, the importance of continued analgesia may be subverted until actual patient admission to an inpatient.

Furthermore, despite the protocol defining the administration of fentanyl as every 5 minutes to 15 minutes, after the early resuscitation phase, this was often not strictly adhered to. Among patients receiving repeat doses of analgesia, there was a notable improvement in time to the second dose of fentanyl between the two treatment periods (57.50 minutes ± 6.38 minutes vs. 83.11 minutes ± 9.53 minutes; \( p = 0.03 \)). However, only 20% of group B and C patients had their second pain assessment within 15 minutes of the initial evaluation. Although fentanyl has clear advantages over other opioid analgesics in terms of its minimal effect on hemodynamics and relatively short duration, the detriment is that it requires frequent reassessments and redosing. That is, although it clearly decreased the time to initiation of analgesia with minimal side effects, the extent and duration of analgesia may have been inadequate.

It is also possible, but less likely, that the individual doses of fentanyl are insufficient for some trauma patients. It would be surprising to find that, when dosed frequently, the average patient would not achieve adequate analgesia at this dose. However, a substantial number of trauma patients may develop early neuropathic pain, which would be characterized by inadequate control by narcotic analgesia. Our study did not attempt to evaluate the prehospital chronic use of narcotics in this patient population, which may have a marked impact on opioid requirements.

By design, the administration of prehospital analgesia was not included in our analyses for two reasons. From a practical standpoint, the exact timing of prehospital analgesia administration, as well as the use, timing, and accuracy of pain assessments was expected to be significantly less reliable than in those the trauma bay. More importantly, because an essential component of our pain management protocol was an initial evaluation of pain, the use of prior analgesia was somewhat irrelevant. In other words, the safety and efficacy of the algorithm should be assessed on its ability to manage patients according to their level of pain and physiology grouping, independent of the preceding events or interventions.

Finally, because the patient population studied involved only victims of blunt trauma, the ability to extrapolate this protocol to patients with penetrating trauma has not been demonstrated.

In conclusion, implementation of this safe fentanyl-based pain management protocol can significantly reduce the time to initiation of analgesia among adult trauma patients. The protocol-driven nature should allow easy implementation in other trauma centers. Future studies will evaluate (1) a similar fentanyl-based protocol for pediatric trauma patients, (2) a dose-response analysis of the using fentanyl in adult trauma patients, and (3) alternative methods of analgesia administration such as continuous infusion or patient-controlled delivery systems.

REFERENCES

Transarterial Embolization for Intractable Oronasal Hemorrhage Associated With Craniofacial Trauma: Evaluation of Prognostic Factors

Cheng-Chih Liao, MD, Yu-Pao Hsu, MD, Chien-Tzung Chen, MD, and Yuan-Yun Tseng, MD

Background: This study analyzed the outcomes for clinical application of transarterial embolization (TAE) to treat intractable posttraumatic oronasal hemorrhage in patients who suffered from craniofacial injuries.

Methods: The charts and radiologic and operative records of 34 patients from January 2002 to December 2007 were retrospectively reviewed. Inclusion criteria focused on the patients whose intractable posttraumatic oronasal hemorrhage associated with craniofacial trauma required TAE treatment. The patients’ survival was correlated with prognostic factors with Spearman’s rank correlation coefficients. Wilcoxon signed ranks test was used to analyze the differences between the severity of shock before and after TAE, and Fisher’s exact test was used to analyze unvaried factors.

Results: TAE successfully stopped the posttraumatic oronasal hemorrhage in 27 of 34 patients (79.4%). The internal maxillary artery was the most common hemorrhaging vessel requiring embolization. Successful hemostasis by TAE significantly contributed to patient survival (p = 0.001). In addition, higher Glasgow Coma Scale score (≥8) at presentation, lower shock index (calculated as heart rate/systolic blood pressure; ≤1.1 and 0.8, before and after TAE, respectively), and injury severity score ≤32 positively contributed to the patients’ higher survival rate (p < 0.05). During the acute treatment of posttraumatic oronasal hemorrhage, need for craniotomy was not correlated with patient survival, but need for laparotomy to treat the second abdominal hemorrhagic source decreased the rate of patient survival (p = 0.023).

Conclusions: TAE may stop intractable posttraumatic oronasal hemorrhage when conventional packing fails to achieve hemostasis. Glasgow Coma Scale at presentation, shock index before and after TAE, injury severity score, and need for emergent laparotomy can be used to predict the patient prognosis.

Key Words: Craniofacial trauma, Posttraumatic oronasal hemorrhage, Transarterial embolization, Shock index, Glasgow Coma Scale.


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DOI: 10.1097/TA.0b013e31814b9466
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Table 1 Summary of Spearman’s Correlation Coefficients Between Patient Demographic Characteristics and the Survival (N = 34)

<table>
<thead>
<tr>
<th>Range</th>
<th>Median</th>
<th>95% CI</th>
<th>Coefficients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y/o)</td>
<td>16–91</td>
<td>30</td>
<td>29.1–41.8</td>
<td>−0.29</td>
</tr>
<tr>
<td>Success of TAE</td>
<td></td>
<td></td>
<td></td>
<td>0.537</td>
</tr>
<tr>
<td>Laparotomy in peri-TAE period</td>
<td></td>
<td></td>
<td></td>
<td>−0.388</td>
</tr>
<tr>
<td>Hemorrhaging artery</td>
<td>0–3</td>
<td>1</td>
<td>1.08–1.68</td>
<td>−0.177</td>
</tr>
<tr>
<td>Transfused blood (mL)</td>
<td>1,000–17,500</td>
<td>2,500</td>
<td>2,659–5,384</td>
<td>−0.246</td>
</tr>
<tr>
<td>ISS</td>
<td>16–59</td>
<td>32</td>
<td>28.4–36.4</td>
<td>−0.464</td>
</tr>
<tr>
<td>SI before TAE</td>
<td>0.54–2.5</td>
<td>1.12</td>
<td>1.02–1.36</td>
<td>−0.596</td>
</tr>
<tr>
<td>SI after TAE</td>
<td>0.39–2.02</td>
<td>0.83</td>
<td>0.79–1.01</td>
<td>−0.696</td>
</tr>
<tr>
<td>GCS score at ER</td>
<td>3–15</td>
<td>7</td>
<td>6.72–9.57</td>
<td>0.531</td>
</tr>
</tbody>
</table>

* P < 0.05.

GCS score, Glasgow Coma Scale score at admission; 95% CI, 95% confidence interval of mean; ISS, injury severity score; SI, shock index; TAE, transarterial embolization; ER, emergency room.

rank correlation coefficient was used to analyze the relation between the patients’ survival and demographic characteristics such as age, gender, calculated injury severity scores (ISS)\(^{11}\) of the patients at admission, associated trauma and emergent operations other than hemostasis of facial bleeding, volume of blood transfusion during the peri-TAE periods for resuscitation and success of hemostasis by TAE, numbers of hemorrhaging arteries, Glasgow Coma Scale (GCS) score at emergency room (ER), and shock index (SI) before and after TAE. Wilcoxon signed ranks test was used to compare the SIs before and after TAE. For the fluctuation of the blood pressure during the resuscitation and embolization, we used the SI (calculated as heart rate/systolic blood pressure), before and 1 hour after TAE, to evaluate the effectiveness of TAE.\(^{12,13}\) Normally, the SI ranges from 0.5 to 0.7, and it indicates shock when the value is greater than 0.9. The peri-TAE interval was defined as the time before and after TAE when fluid and blood resuscitation was maintained to reverse hemorrhagic shock, to reduce the heart rate to <100 beats/min, to increase the systolic blood pressure to over 90 mm Hg, or increase the hematocrit to over 30%. TAE, combined with endonasal packing and resuscitation, was considered to be successful to achieve hemostasis, if there was decrease in the amount of arterial hemorrhage on angiography with the oronasal hemorrhage grossly controlled, post-TAE systolic blood pressure >100 mm Hg and heart rate <100 beats/min, 1 hour after TAE. For all statistical tests, \(p < 0.05\) (two-tailed) was considered statistically significant.

RESULTS

Between January 2002 and December 2006, 35 patients (31 men and 4 women) fulfilled the indication to use angiography to identify the origin of intractable posttraumatic oronasal hemorrhage associated with craniofacial injuries in Chang Gung Memorial Hospital. One patient was excluded from the study, because he had cardiac arrest during the angiography and did not undergo complete study and TAE. The age of the 34 patients, which ranged from 16 to 91 years (median, 30 years), was not correlated with patients’ survival. The follow-up period for survival ranged from 3 months to 5 years (median, 1.0 and 95% confidence interval, 0.6–1.5). Table 1 summarizes the Spearman’s correlation coefficients between the demographic parameters and patients’ survival. GCS score at the ER and successful hemostasis by nasal packing, with or without TAE, were positively correlated with patient survival, but ISS and SIs before and after TAE, were negatively correlated to patient survival. In addition, the patients whose GCS score was \(\geq 8\) at presentation, ISS was \(\leq 32\), SI was \(\leq 1.11\) before TAE, and SI was \(\leq 0.8\) after TAE had significantly higher survival rate than their respective counterparts (Table 2). The median volume of blood transfusion used for peri-TAE resuscitation was 2,500 mL (95% confidence interval, 2,659–5,384), but it was not correlated with patient survival (\(p > 0.05\)).

Conventional or superselective carotid angiography identified 48 hemorrhaging arteries in 29 patients (range, 1–3 vessels per patient) and contrast pooling or blush in 5 patients. Twenty patients (58.8%) had unilateral and 9 patients (26.5%) had bilateral hemorrhaging arteries. Table 3 displays the cumulative counts and frequencies of each hemorrhaging artery. The internal maxillary artery (47.2%, 25 of 53) was the vessel that most commonly bled and required TAE in this study and was followed by branches of the superficial temporal, external carotid, and sphenopalatine arteries.

Table 2 Comparison of Patient Survival According to the Median of GCS Score, ISS, and SI Before and After TAE (N = 34, Fisher’s exact test)

<table>
<thead>
<tr>
<th>Value</th>
<th>Survival/Subtotal</th>
<th>Survival (%)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS score at presentation</td>
<td>(\geq 8)</td>
<td>15/17</td>
<td>88.2</td>
</tr>
<tr>
<td></td>
<td>(\leq 7)</td>
<td>7/17</td>
<td>41.2</td>
</tr>
<tr>
<td>SI before TAE</td>
<td>(&gt;1.1)</td>
<td>8/19</td>
<td>42.1</td>
</tr>
<tr>
<td></td>
<td>(\leq 1.1)</td>
<td>14/15</td>
<td>93.3</td>
</tr>
<tr>
<td>SI after TAE</td>
<td>(&gt;0.8)</td>
<td>6/17</td>
<td>35.3</td>
</tr>
<tr>
<td></td>
<td>(\leq 0.8)</td>
<td>16/17</td>
<td>94.1</td>
</tr>
<tr>
<td>ISS</td>
<td>(&gt;32)</td>
<td>7/16</td>
<td>43.8</td>
</tr>
<tr>
<td></td>
<td>(\leq 32)</td>
<td>15/18</td>
<td>83.3</td>
</tr>
</tbody>
</table>
Hemorrhaging Artery in the Study (N = 34)

<table>
<thead>
<tr>
<th>Hemorrhaging Artery</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast pooling</td>
<td>5</td>
<td>3.8</td>
</tr>
<tr>
<td>Ascending pharyngeal</td>
<td>2</td>
<td>9.4</td>
</tr>
<tr>
<td>Descending palatine</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>External carotid</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>Facial</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Superior alveolar</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Middle meningeal</td>
<td>5</td>
<td>9.4</td>
</tr>
<tr>
<td>Sphenopalatine</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>Superficial temporal</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>

had significantly negative correlation to patient survival ($p = 0.023$).

**DISCUSSION**

Treatment for life-threatening oronasal hemorrhage associated with craniofacial fracture is principally based on the therapeutic options proposed by Ardekian et al.: aggressive resuscitation combined with anterior and posterior nasal packing should be performed in the ER as soon as possible. Tight nasal packing or tamponade with balloon catheters are frequently effective in hemostasis of mild to moderate posttraumatic oronasal hemorrhage, but its effectiveness is questioned in severe bleeding. Because posttraumatic oronasal bleeding frequently originates from lacerated arteries deep in the fractured facial skeleton and far from the nasal cavity, nasal packing occasionally cannot compress tightly enough to stop bleeding. If oronasal hemorrhage persists and blood pressure remains unstable after resuscitation and nasal packing, TAE of the hemorrhaging artery that originated from branches of external carotid artery can be a hemoatonic option. Although potential risks exist for inadvertent migration of emboli through abundant anastomoses between the external and internal carotid arteries, and more and more authors consider that the risk can be minimized by the technique of coaxial microcatheterization and superselective embolization. Furthermore, Komiyama et al. recommended that early TAE performed in the preshock state would be effective in decreasing blood transfusion volume and minimizing the adverse effect of massive transfusion and prolonged shock. In our study, combined with endonasal packing, superselective TAE successfully stopped the intractable posttraumatic oronasal hemorrhage in 27 patients, whose survival rate was significantly better than that of those in whom TAE failed (77.8% vs. 14.1%, respectively; $p = 0.001$). Therefore, successful hemorrhage of posttraumatic oronasal hemorrhage by combined TAE and nasal packing could significantly ameliorate hemorrhagic shock and reduce mortality in specific condition that conventional treatment with nasal packing has failed.

In addition to successful TAE, GCS score at presentation was also positively correlated with patient survival, i.e., higher GCS score at the ER implies less severity of brain injury and eventual higher probability of survival. In the study, all patients were endangered by shock and hypotension during the acute treatment. Because the conventional hallmarks of shock, such as heart rate and blood pressure, frequently fluctuated inconsistently in response to resuscitation during the course of acute treatment, it was difficult to monitor and record the real-time variation to represent severity of shock and responsiveness to resuscitation. Compared with the conventional signs of shock, hypotension, and tachycardia, the SI is suggested to be more sensitive and accurate to reflect the status of early shock. Therefore, we used the SI to quantify the severity of shock before and after TAE. Normally, the SI (heart rate/systolic blood pressure) ranges from the bilateral distribution of bleeding vessels nor the numbers of hemorrhaging arteries per patient were correlated with patient survival or blood transfusion in the study ($p > 0.05$). Five patients who had only contrast pooling on angiography did not undergo TAE, and, except one who died of pneumonia 2 weeks after trauma, all of them survived the acute hemorrhagic episodes. In these five patients, TAE combined with nasal packing was considered successful for hemostasis. TAE, combined with nasal packing and resuscitation, succeeded in controlling posttraumatic oronasal hemorrhage in 27 patients (79.4%) and yielded a survival rate of 77.8% (21 of 27 survived), and it was significantly better than that of 14.1% (1 of 7 survived) in patients in whom TAE failed to achieve hemostasis ($p = 0.001$). In seven patients, TAE failed because of small-caliber hemorrhaging arteries in five patients and severe arterial vasospasm in two patients.

In total, TAE reduced the median SI significantly from 1.13 to 0.82 (Wilcoxon signed ranks test, $p < 0.001$, N = 34). Twenty-two patients survived, but 13 patients died after the traumatic ictus: eight patients died of trauma-related hypovolemic shock, one died of both shock-induced intravascular coagulopathy and uncontrolled intracerebral hematoma, one died of delayed cerebral infarction associated with internal carotid artery dissection, and three died of pneumonia associated with prolonged unconsciousness. In addition, 22 patients (62.9%, n = 35) had concomitant traumatic brain injuries detected by positive brain computed tomography scan findings of traumatic subarachnoid hemorrhage, brain contusion, subdural hematoma, epidural hematoma, or brain swelling. Nine patients (28.6%) had associated chest injury and six patients had blunt abdominal trauma with torso organ injury. Seven patients (3 before and 4 after TAE) required craniotomy for intracranial hypertension or mass lesion. All the patients who had chest injury could be managed successfully with close thoracostomy but five of six patients with abdominal injury required laparotomy for associated hemoperitoneum. Only the patients who had to undergo laparotomy for severe hemoperitoneum with shock in the peri-TAE period...
0.5 to 0.7, and it is considered to signal potential shock when the SI is greater than 0.9. In contrast to the GCS score, both SIs before and after TAE were negatively correlated with patient survival; (1) SI >1.1, before the patients were sent for TAE, implied severer hemorrhagic shock with poorer responsiveness to resuscitation than those with SI ≤1.1; (2) SI >0.8, 1 hour after TAE, implied poorer effect of TAE and resuscitation and, potentially, other hemorrhagic source participating in persisting high SI, despite successful hemostasis by TAE. In our study, isolated single injury to the abdomen, chest, or brain that did not result in exsanguinating hemorrhage and did not reduce the chance of survival. Only those patients requiring laparotomy in the peri-TAE period who suffered from two major origins of hemorrhage had extremely high mortality (p = 0.023). In the study, the more extensive injuries of anatomic body parts, represented by higher ISS, did correlate with the less chance of patient survival (coefficient, −0.464, p = 0.006). Furthermore, the patients with ISS >32 have less probability of surviving than the patients with ISS ≤32 have (p = 0.03). Although some clinicians’ early experiences discouraged the application of emergency TAE by questioning the high possibility of unintended migration of the emboli to internal carotid systems, such a complication was not encountered in the analyzed patient series. Successful TAE could correct the shock and decrease the median SI from 1.12 to 0.83 (Wilcoxon signed ranks test, p < 0.001). Therefore, it is recommended that, in cases of intractable posttraumatic oronasal hemorrhage, TAE should be performed as early as possible when patients are endangered by shock and conventional hemostasis is expected to be ineffective.

CONCLUSION

Intractable posttraumatic oronasal hemorrhage is rare but life threatening. TAE of the oronasal bleeding may help to achieve hemostasis, if conventional packing is expected to fail. Successful hemostasis by TAE could reduce the median SI and significantly increase the probability of patient survival. Higher GCS score (>8) and less extensive systemic injury, represented by ISS <32, were both correlated with higher survival rate. If patients need laparotomy in cases of uncontrollable hemoperitoneum in acute stage, they bear extremely high mortality.

REFERENCES

Concomitant Injuries in Patients With Panfacial Fractures

Keith E. Follmar, MD, Marklieke DeBruijn, MS, Alessio Baccarani, MD, Anthony D. Bruno, MD, Srinivasan Mukundan, PhD, MD, Detlev Erdmann, MD, PhD, and Jeffrey R. Marcus, MD

Background: Patients with panfacial fractures comprise a small portion of the overall facial fracture patient population. Because of the forces necessary to cause panfacial injury, these patients often have other concomitant injuries. The timing of operative facial fracture management remains controversial.

Methods: A 3-year review of all patients with facial fractures was conducted at Duke University Medical Center (2003–2005, 437 total patients). All patients with panfacial fractures, defined as fractures involving at least three of the four facial segments (frontal, upper midface, lower midface, and mandible), were analyzed.

Results: Panfacial fractures were present in 38 patients (9% of overall facial fracture population). Twenty (53%) of these patients suffered concomitant injuries. The most common mechanism of trauma was motor vehicle collision, and the most common category of concomitant injury was intracranial injury or hemorrhage. Other commonly occurring categories of injury included abdominal organ injury, pneumothorax, pulmonary contusion, spine fracture, rib or sternum fracture, extremity fracture, and pelvic fractures. There was no significant difference in day of operation for the management of facial fractures between those with isolated facial injuries and those with other concomitant injuries (hospital day 2.1 vs. hospital day 2.9, not significant).

Conclusions: Concomitant injuries to all parts of the body are found in patients with panfacial trauma. In our experience, these injuries do not significantly delay or have an adverse effect on the treatment of facial fractures. A treatment strategy for consistent timely management of facial fractures is described.

Key Words: Facial fracture, Concomitant injury, Multidisciplinary, Craniomaxillofacial.


Panfacial fractures are relatively rare injuries that comprise a small subset of the overall facial fracture patient population. The management of these patients is challenging and frequently requires a multidisciplinary team approach. Advances in radiographic diagnosis and in open reduction or internal fixation (ORIF, Fig. 1) during the past several decades have greatly improved outcomes in these devastating injuries. Despite such improvements, the management of these patients remains challenging and is frequently complicated by the presence of injuries elsewhere in the body.

Because of the high-energy nature of the traumatic forces necessary to cause a panfacial bony injury, patients frequently have other concomitant injuries. These concomitant injuries can be very severe and may be life threatening. The extent to which management of these other injuries affects or delays treatment of facial fractures is unclear.

A recent review performed at Mount Sinai Hospital in Chicago, IL, investigated the types of facial fractures that are most commonly seen in the population of severely injured trauma patients. The converse question, however, has never been studied: namely, what is the incidence of other concomitant injuries in all patients with severe facial injury? An investigation into this issue will allow for a candid evaluation of the population of patients with panfacial injury and for analysis of how concomitant injuries effect their management.

Patients and Methods

This study was approved by the Institutional Review Board. A retrospective chart review of all patients presenting to Duke University Medical Center for acute management of facial fractures during a 3-year period (2003–2005) was performed. A total of 437 such patients were identified.

Definition of Panfacial Fractures

The term “panfacial” is poorly defined, and there is no single accepted definition. Thus, we have proposed our own definition of this term and used it for the purposes of this study. We have defined “panfacial” fractures as fracture patterns that involve at least three of the four axial segments of the facial skeleton: frontal, upper midface, lower midface, and mandible (Fig. 2). This definition is not a precise measure of severity of facial injury, and other measures, such as the recently described Facial Injury Severity Score, do exist. Nonetheless, we have chosen to use this definition in this study because of its simplicity and intuitive nature.

The fractures present in each patient were determined by reviewing radiology reports and other clinical records. In
those patients in whom the radiology report was unclear or vague, the fracture pattern was reviewed by a board-certified neuroradiologist.

Fractures of the frontal sinus and orbital roof were included in the “frontal” category. Lateral orbital wall fractures, medial orbital wall fractures, orbital floor fractures, nasal fractures, nasoethmoid orbital fractures, and zygomatic arch fractures were included in the “upper midface” category. Maxillary sinus fractures, bony palate fractures, and pterygofacial (Le Fort) I fractures were counted in the “lower midface” category. Zygomaticomaxillary complex fractures and pterygofacial (Le Fort) II and III fractures were counted as fractures of both the upper and lower midface. All mandible fractures were counted in the “mandible fracture” category. The presence or absence of fractures in each of the four segments of the face was evaluated for each patient. Patients with fractures in at least three of the four segments were classified as having “panfacial” fractures, and were thus included in this study.

**Collection of Patient Data**

For each patient with a panfacial fracture, the emergency department chart, all clinic notes, all operative reports, the discharge summary, and all relevant radiology reports were reviewed. The following data were collected for each patient: age, gender, mechanism of trauma, facial fractures present, concomitant injuries, modality of treatment (operative vs. nonoperative), and time of operative treatment. In addition, each patient’s clinical course was carefully reviewed to subjectively judge the effect of concomitant injuries on management of the patient’s facial fractures. Lacerations, contusions, and other soft-tissue injuries were not counted as “concomitant injuries”. Neither were joint sprains, strains, nor other ligamentous injuries. Intracranial injuries, fractures (other than those of the face), pneumothorax, damage to thoracic or abdominal organs, and vascular injuries were counted as concomitant injuries.

**RESULTS**

Of the 437 patients with facial fractures during the 3-year period analyzed, 38 suffered panfacial fractures (Table 1). Mean age was 35 years (SD: 17); 26 patients were male (68%), and 12 were female (32%). The most common cause of trauma was motor vehicle collision (MVC) (23 patients,
61%), followed by assault (5 patients, 13%), gunshot wound (4 patients, 11%), fall (2 patients, 5%), occupational (2 patients, 5%), and sports (2 patients, 5%).

Concomitant injuries were present in 20 of the 38 patients (53%). The injuries present in each patient are listed in Table 2. The most common category of injury was intracranial hemorrhage or injury, which was present in seven patients (18%). Other common categories of injury and their prevalence are summarized in Table 3.

### Table 1: Demographic Information and Facial Fractures Present in 38 Patients With Panfacial Fractures

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Gender</th>
<th>Mechanism</th>
<th>Facial Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/F</td>
<td>Assault (domestic violence)</td>
<td>L ZMC, L maxillary sinus, L orbital floor, L coronoid process</td>
</tr>
<tr>
<td>2</td>
<td>35/M</td>
<td>Assault (metal pipe)</td>
<td>L ZMC, L mandibular ramus, R parasymphyseal</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
<td>Assault (multiple persons)</td>
<td>R orbital floor, B maxillary sinus, L mandibular angle fx</td>
</tr>
<tr>
<td>4</td>
<td>48/M</td>
<td>Assault (kicked and punched in face)</td>
<td>B pterygofacial I fx, B ZMC fx, nasal fx, R mandibular angle, L mandibular body</td>
</tr>
<tr>
<td>5</td>
<td>42/M</td>
<td>Assault (beaten w/object)</td>
<td>Frontal sinus fx, palatal fx, B pterygofacial I fx, R ZMC, L orbital floor fx</td>
</tr>
<tr>
<td>6</td>
<td>28/M</td>
<td>Fall (hit rocks while hiking)</td>
<td>R ZMC fx, R mandibular ramus, R mandibular coronoid, L parasymphyseal</td>
</tr>
<tr>
<td>7</td>
<td>76/F</td>
<td>Fall (down stairs)</td>
<td>R maxillary sinus, R mandibular angle, NOE</td>
</tr>
<tr>
<td>8</td>
<td>14/F</td>
<td>GSW</td>
<td>L ZMC, L mandibular condyle, L mandibular ramus, R parasymphyseal</td>
</tr>
<tr>
<td>9</td>
<td>35/M</td>
<td>GSW</td>
<td>R maxillary sinus, R parasymphyseal</td>
</tr>
<tr>
<td>10</td>
<td>40/M</td>
<td>GSW (shot by friend in face)</td>
<td>R zygomatic arch, R maxillary sinus, R coronoid, R condyle, R mandibular ramus</td>
</tr>
<tr>
<td>11</td>
<td>36/F</td>
<td>GSW (self inflicted)</td>
<td>L orbital roof, L orbital floor, NOE, B maxillary sinus, palate, R mandibular body</td>
</tr>
<tr>
<td>12</td>
<td>24/F</td>
<td>MVC (head-on, unrestrained)</td>
<td>Nasal, B maxillary sinus, L symphyseal, R parasymphyseal</td>
</tr>
<tr>
<td>13</td>
<td>54/M</td>
<td>MVC (truck driver)</td>
<td>Frontal sinus fx, nasal, R zygomatic arch, L pterygofacial I</td>
</tr>
<tr>
<td>14</td>
<td>19/M</td>
<td>MVC (hit tree)</td>
<td>Frontal sinus, nasal, R maxillary sinus</td>
</tr>
<tr>
<td>15</td>
<td>51/F</td>
<td>MVC</td>
<td>L ZMC, R subcondylar</td>
</tr>
<tr>
<td>16</td>
<td>27/M</td>
<td>MVC (motorcycle vs. truck, head on, wearing helmet)</td>
<td>NOE, B ZMC, B pterygofacial I, B rami fx, B subcondylar</td>
</tr>
<tr>
<td>17</td>
<td>20/F</td>
<td>MVC</td>
<td>B pterygofacial I, B ZMC, NOE, palate, B condyle</td>
</tr>
<tr>
<td>18</td>
<td>38/M</td>
<td>MVC (unrestrained, ATV)</td>
<td>R zygomatic arch fx, R maxillary sinus, R ramus, R body fx</td>
</tr>
<tr>
<td>19</td>
<td>42/F</td>
<td>MVC (rollover)</td>
<td>Frontal sinus, NOE, B pterygofacial I, NOE</td>
</tr>
<tr>
<td>20</td>
<td>54/F</td>
<td>MVC (hit tree)</td>
<td>R lateral orbital wall, R orbital floor, NOE, R maxillary sinus, B rami</td>
</tr>
<tr>
<td>21</td>
<td>18/F</td>
<td>MVC (unrestrained, rollover)</td>
<td>L orbital floor, L pterygofacial I, B body</td>
</tr>
<tr>
<td>22</td>
<td>37/M</td>
<td>MVC (hit tree, ejected)</td>
<td>Frontal sinus, L pterygofacial III, R pterygofacial I</td>
</tr>
<tr>
<td>23</td>
<td>25/M</td>
<td>MVC (ejected)</td>
<td>B pterygofacial II, B lateral orbital wall, B rami</td>
</tr>
<tr>
<td>24</td>
<td>75/M</td>
<td>MVC (head on, ejected)</td>
<td>Frontal sinus, L orbital roof, L lateral orbital wall, L orbital floor, NOE, B maxillary sinus</td>
</tr>
<tr>
<td>25</td>
<td>17/M</td>
<td>MVC (ejected)</td>
<td>L pterygofacial II, R pterygofacial I, L body, L parasymphyseal</td>
</tr>
<tr>
<td>26</td>
<td>18/F</td>
<td>MVC (hit tree)</td>
<td>Frontal sinus, L orbital floor, NOE, R ZMC, R pterygofacial I, L maxillary sinus, R ramus</td>
</tr>
<tr>
<td>27</td>
<td>16/M</td>
<td>MVC (unrestrained, ejected)</td>
<td>R frontal sinus fx, L orbital floor L pterygofacial I</td>
</tr>
<tr>
<td>28</td>
<td>19/M</td>
<td>MVC</td>
<td>Nasal fx, R ZMC fx, R coronoid process</td>
</tr>
<tr>
<td>29</td>
<td>31/M</td>
<td>MVC (ATV vs. tree, no helmet)</td>
<td>Nasal fx, R ZMC, L maxillary sinus, palate, B mand rami, L mand subcond, L mand condyle</td>
</tr>
<tr>
<td>30</td>
<td>36/M</td>
<td>MVC (unrestrained rear passenger)</td>
<td>Frontal sinus, R orbital roof, R medial orbital wall, R orbital floor, R maxillary sinus</td>
</tr>
<tr>
<td>31</td>
<td>17/M</td>
<td>MVC (ATV vs. tree)</td>
<td>Frontal sinus, L pterygofacial III, R pterygofacial II</td>
</tr>
<tr>
<td>32</td>
<td>34/F</td>
<td>MVC (ATV rollover)</td>
<td>Frontal sinus, NOE, R orbital roof, R orbital floor, B pterygofacial I, L palate</td>
</tr>
<tr>
<td>33</td>
<td>27/M</td>
<td>MVC (hit tree)</td>
<td>L ZMC, L ramus</td>
</tr>
<tr>
<td>34</td>
<td>4/M</td>
<td>MVC (back seat, improperly restrained)</td>
<td>Nasal, maxillary alveolar ridge, L mand subcondyle</td>
</tr>
<tr>
<td>35</td>
<td>51/M</td>
<td>Occupational (cutting trees, hit my branch in head)</td>
<td>Frontal sinus, B orbital roof, NOE, L ZMC</td>
</tr>
<tr>
<td>36</td>
<td>54/M</td>
<td>Occupational (pile of ladders landed on face)</td>
<td>Frontal sinus, R orbital roof, NOE, L ZMC, B pterygofacial I</td>
</tr>
<tr>
<td>37</td>
<td>20/M</td>
<td>Sports (rock climbing, approximately 50 ft fall)</td>
<td>Nasal, L ZMC, L symphyseal, angle</td>
</tr>
<tr>
<td>38</td>
<td>58/M</td>
<td>Sports (golfing, hit in face with club)</td>
<td>L ZMC, L coronoid process</td>
</tr>
</tbody>
</table>

F, female; M, male; GSW, gunshot wound; fx, fracture; MVC, motor vehicle collision; ATV, all-terrain vehicle; L, left; ZMC, zygomatico-maxillary complex; R, right; B, bilateral; NOE, nasoorbital ethmoidal.

Concomitant injuries were present in 20 of the 38 patients (53%). The injuries present in each patient are listed in Table 2. The most common category of injury was intracranial hemorrhage or injury, which was present in seven patients (18%). Other common categories of injury and their prevalence are summarized in Table 3.

### Operative Management

Operative management of facial fractures was necessary in 31 of the 38 patients (82%). This included 16 patients with...
Concomitant injuries and 15 patients without concomitant injuries. The day between presentation to Duke University Medical Center and first operation for treatment of facial fractures was determined for each of these patients. Among patients without concomitant injuries, the mean time of first operation was hospital day 2.1 (SD). Among those with concomitant injuries, mean time to first operation was hospital day 2.9 ± 2.7 (SD). Among those with concomitant injuries, mean time to operating room was hospital day 2.9 ± 2.3. This difference was not significant (two-tailed t test).

Detailed analysis of each patient’s clinical records revealed no situations in which concomitant injuries caused significant delays in the treatment of facial fractures. Similarly, there were no adverse outcomes or complications that could be attributed to the presence or the management of facial fractures. There were no mortalities in this series.

**DISCUSSION**

The fact that panfacial fractures are commonly associated with concomitant injuries is obvious and well known. Trauma that involves sufficient energy to fracture the bones of the facial skeleton is also likely to distribute a substantial amount of force to other parts of the body, and thus cause injury. The increased prevalence of concomitant injuries in MVC is intuitively logical (concomitant injuries were present in 70% of MVC patients with panfacial fractures, but only 27% of patients with other mechanisms of panfacial fracture). MVC causes a more random pattern of mechanical trauma, with forces distributed to the entire body, which is conducive to injury to multiple parts of the body. Alternatively, assault (no patients with concomitant injuries) is generally targeted to a smaller portion of the body, causing isolated injury to the facial skeleton.

Cervical spine injury is the most widely recognized injury that occurs concomitantly with facial fractures.7–10 Because of the potential for spinal cord injury, all patients with facial fractures are assumed to have cervical spine injury unless proven otherwise. If a clinical disposition cannot be obtained, it is our practice to require at least a radiographic disposition (computed tomography) of the cervical spine before taking a patient to the operating room. This does not rule out ligamentous injury, but these patients are not stable enough for magnetic resonance imaging. Therefore, they are treated as if they have a possible ligamentous cervical spine injury with immobilization in the operating room. This precaution clearly makes operative treatment of facial fractures more challenging and likely leads to somewhat longer total operating times, although we did not specifically look at this issue.

Intracranial injury is another class of concomitant injury that has the potential to delay treatment of facial fractures. It is our practice not to operate on facial fractures until any increased intracranial pressure is controlled.

No other class of injury is routinely treated as a contraindication to operative facial fracture management. We do not routinely operate concurrently with general surgeons performing intra-abdominal procedures or with orthopedic surgeons repairing long bone injuries because of the length of such procedures. Long operating times have greater potential for blood loss and are associated with intraoperative hypothermia, which is a documented contributor to postoperative complications.11 Having multiple procedure sites also limits the use of intraoperative warming devices, further exacerbating the potential for hypothermia. The one exception to this rule that we commonly make is the application of intermaxillary fixation (IMF) concurrently with other operations. Operative time required for IMF is relatively short. If the patient will require subsequent ORIF, the initial IMF will acutely stabilize the occlusion and limit the length of the subsequent procedure.

**Table 2 Concomitant Injuries Present in Series of 38 Patients With Panfacial Fractures**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Concomitant Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Pharyngoesophageal laceration, damage to carotid vessels, R pneumothorax</td>
</tr>
<tr>
<td>11</td>
<td>Frontal bone fracture, traumatic lobectomy</td>
</tr>
<tr>
<td>12</td>
<td>B pulmonary contusions, liver lac, rib fxs, R pneumothorax, acetalubar fx</td>
</tr>
<tr>
<td>14</td>
<td>Subarachnoid hemorrhage, R tibial fx, R and L toe fxs</td>
</tr>
<tr>
<td>15</td>
<td>R LE fxs, L UE fxs, liver lac, innominate artery rupture</td>
</tr>
<tr>
<td>17</td>
<td>B LE fxs, R hand fx, L pulmonary contusion, liver lac</td>
</tr>
<tr>
<td>18</td>
<td>C2 fx, midbrain hemorrhage</td>
</tr>
<tr>
<td>20</td>
<td>C7 fx, splenic laceration, bilateral pulmonary contusions</td>
</tr>
<tr>
<td>21</td>
<td>Liver lac, acetalubar fx, pneumothorax, thoracic/lumbar/ sacral spine fxs</td>
</tr>
<tr>
<td>22</td>
<td>Pelvic fx</td>
</tr>
<tr>
<td>24</td>
<td>R tib/fib fx, L femur fx, C6–C7 fx</td>
</tr>
<tr>
<td>25</td>
<td>Pneumothoraces, B pulmonary contusions, rib fxs, B clavicle fxs</td>
</tr>
<tr>
<td>26</td>
<td>Sternal fx, B pneumothoraces, C7 process fxs,</td>
</tr>
<tr>
<td>27</td>
<td>Epidural hematoma, subarachnoid hemorrhage, splenic lac, B pulmonary contusions, R wrist fx, T1 and 2 fxs</td>
</tr>
<tr>
<td>28</td>
<td>C6 fx, L2–4 fxs</td>
</tr>
<tr>
<td>30</td>
<td>Epidural hematoma</td>
</tr>
<tr>
<td>31</td>
<td>Dural laceration, thyroid cartilage fracture</td>
</tr>
<tr>
<td>34</td>
<td>R distal radius fx</td>
</tr>
<tr>
<td>35</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>37</td>
<td>Multiple rib fxs</td>
</tr>
</tbody>
</table>

R, right; B, bilateral; lac, laceration; fx, fracture; LE, lower extremity; UE, upper extremity; C, cervical vertebrae; T, thoracic vertebrae.

**Table 3 Prevalence of Concomitant Injuries by Category in Series of 38 Patients With Panfacial Fractures**

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Prevalence, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial injury/hemorrhage</td>
<td>18 (7 patients)</td>
</tr>
<tr>
<td>Abdominal organ injury</td>
<td>16 (6 patients)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>13 (5 patients)</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>13 (5 patients)</td>
</tr>
<tr>
<td>Cervical spine fx</td>
<td>13 (5 patients)</td>
</tr>
<tr>
<td>Rib/sternum fx</td>
<td>11 (4 patients)</td>
</tr>
<tr>
<td>Lower extremity fx</td>
<td>11 (4 patients)</td>
</tr>
<tr>
<td>Upper extremity fx</td>
<td>11 (4 patients)</td>
</tr>
<tr>
<td>Pelvic fx</td>
<td>8 (3 patients)</td>
</tr>
<tr>
<td>Noncervical spine fx</td>
<td>8 (3 patients)</td>
</tr>
</tbody>
</table>

fx, fracture.
operation. This treatment strategy requires the ability of the patient to be nasotracheally intubated (usually using fiberoscopic intubation equipment) or to have a tracheostomy. We will also routinely perform concomitant operative procedures with other services if the other operation is of a shorter duration. The most common procedures performed concomitantly with ORIF of facial fractures in our series were gastrostomy tube placement and tracheostomy placement.

Some plastic surgeon might argue that postponement of facial fracture management is justified if there are concomitant injuries (especially neurosurgical) that carry a very poor prognosis. Anecdotally, we have seen multiple such patients who did recover, often against all odds. These patients’ fractures had not been treated in the manner that they otherwise would have been, and they ended up with severe secondary facial deformities as a result. The treatment options for these secondary deformities are never ideal, and the long-term outcome is often poor. Thus, we do not consider long-term prognosis a contraindication to optimal facial fracture management, as long as it can be performed safely.

It has been shown that, in our experience, the presence of concomitant injuries does not have to cause significant delay in the treatment of panfacial fractures. Consistent timely management of facial fractures has been demonstrated using the above described protocol to ensure patient safety. A number of authors have advocated prompt treatment of facial fractures to maximize esthetic and functional outcomes. Kelly et al.12 advocated performing “Bone reconstruction . . . as early as possible to minimize soft tissue shrinkage, stiffness and scarring of soft tissues in nonanatomic positions”. We agree with this argument and treat our patient accordingly.

The relatively high prevalence of serious concomitant injuries in this series serves as a reminder of the acuity of these patients and the importance of a multidisciplinary approach to the trauma patient.1 The absence of any mortality in this case series does not indicate that no patients with panfacial fractures died at this institution during the time period studied. More likely, it indicates that any such patients were of sufficiently high medical acuity that their facial fractures never came to clinical attention.

CONCLUSIONS

Panfacial fracture is a rare injury, seen in approximately one patient per month at our institution during the time period reviewed. Half of patients with panfacial fractures had other serious concomitant injuries, many of which were of a life-threatening nature. Common injuries in this population include intracranial injury, intra-abdominal injury, intrathoracic injury, spine fractures, and extremity fractures, indicating that all parts of the body are at risk for injury. Concomitant injuries are often more serious than facial fractures and can be life threatening. Nonetheless, review of patient charts revealed that concomitant injuries did not significantly delay or complicate the treatment of patients with severe facial fractures. The data presented in this report provide a current picture of concomitant injuries in patients with severe facial fractures at a representative urban United States Level I trauma center.

REFERENCES

Background: Head, face, and neck injuries (HFNIs) are an important source of combat mortality and morbidity. The objective of this study was to document the characteristics and causes of HFNIs during Operation Iraqi Freedom II.

Methods: A retrospective review of HFNIs sustained by US military casualties between March 1, 2004 and September 30, 2004 was performed. Data were collected from the Navy-Marine Corps Combat Trauma Registry.

Results: During the study period, 39% of all injury casualties in the registry had HFNIs. Of the 445 HFNI patients, one-third presented with multiple wounds to the head, face, and neck. Four percent of battle HFNI patients died from wounds, and nearly 40% of the surviving wounded were evacuated for treatment. Improvised explosive devices (IEDs) were the most frequent cause of battle HFNI. Nonbattle HFNI were most often the result of motor vehicle crashes. The majority (65%) of all HFNI were to the face. Head injuries, overall, were more severe than face or neck wounds according to the Abbreviated Injury Scale.

Conclusions: The proportion of combat-related HFNI is increasing and is primarily caused by IEDs. Improved protection for the vulnerable facial region is needed. Continued research on the changing nature of warfare and distribution of HFNI is necessary to enhance the planning and delivery of combat casualty medical care.

Key Words: Military, Combat, Head Injury, Operation Iraqi Freedom.

nonhostile causes. Battle injury casualties were further defined as “died of wounds” (i.e., those who died from wounds received in action after treatment) or “wounded in action” (i.e., those who survived wounds sustained in action). Wounded in action and nonbattle injury casualties were analyzed as a function of their disposition: returned to duty from a Level I (e.g., battalion aid station) or Level II MTF (e.g., surgical company); or evacuated to a Level III MTF (i.e., combat support hospital) or higher level of care.

Injury severity was assessed with the AIS and the Injury Severity Score (ISS). The AIS provided anatomically specific severity scores for each injury. The ISS was used to assess the overall injury severity of each patient. Analyses were also performed for age, gender, branch of service, patient disposition, anatomic location of injury, and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes.

Differences in AIS scores were compared between the evacuated and returned to duty populations among wounded in action and nonbattle injury patients. The two-sample t test for independent samples was used. Statistical analyses were performed using SPSS software version 12.0.2 (SPSS Inc., Chicago, IL); tests were two-tailed and \( p \leq 0.05 \) was used to determine statistical significance. Mean values are presented as mean ± SD unless otherwise indicated.

RESULTS

There were 1,130 injury casualties in the Navy-Marine Corps CTR during the study period. Six hundred forty-three (57%) were battle injuries and 487 were nonbattle injuries. HFNIs accounted for 39% (n = 445) of all injury casualties, comprising 52% of all battle injury and 22% of all nonbattle injury patients.

Of the 445 HFNIs, 4 Marines incurred 2 separate injury events during the study period; each injury event was counted as 1 casualty. Average age (with 69 unknown) was 24 years ± 5.9 years, with a range of 18 years to 48 years. All but six patients were male. Three hundred eighty-one patients were US Marines, 45 were US Army Soldiers, 14 were US Navy Sailors, and 1 was from the US Air Force. Branch of service was unknown for four casualties. The median ISS for the study population was 2 (mean, 5; range, 1–57; with four unknown).

The majority (71%) of HFNIs (315 of 445) were wounded in action and 19 (4%) died of wounds. The remaining 111 (25%) patients sustained nonbattle HFNIs. About an equal proportion of the wounded in action were evacuated (46%) and returned to duty (54%). Most nonbattle injury patients were returned to duty with only 23% evacuated for treatment of their injuries. Improvised explosive devices (IEDs) were the leading cause of battle HFNIs (Table 1). As shown in Table 2, motor vehicle crashes were the primary cause of nonbattle HFNIs.

Most battle HFNIs (93%) were reported wearing body armor at the time of injury, including Kevlar helmets and vests. Fewer patients (80%) were reported wearing ballistic eye protection at the time of injury.

Thirty-one percent of HFNIs sustained multiple wounds to the head, face, and neck; 177 (40%) had head wounds; 336 (76%) had facial wounds; and 84 (19%) had neck wounds. The majority (65%) of HFNIs among all casualties were to the face (653 of 1,011), with the exception of patients who died of wounds in which the predom-
The distribution of specific injury descriptions and associated ICD-9-CM codes are presented in Table 4. Approximately 45% of all HFNIs were coded as open wounds.

### Table 4 Distribution of HFNIs and ICD-9-CM Codes by Anatomic Region by Disposition

<table>
<thead>
<tr>
<th>Injury Description</th>
<th>ICD-9-CM Code(s)</th>
<th>No. (%) Injuries*</th>
<th>No. (%) Injuries</th>
<th>No. (%) Injuries</th>
<th>No. (%) Injuries</th>
<th>No. (%) Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All (N = 1011)</td>
<td>Died of Wounds (n = 60)</td>
<td>Wounded in Action Evacuated (n = 478)</td>
<td>Wounded in Action Evacuated (n = 296)</td>
<td>Nonbattle Evacuated (n = 47)</td>
</tr>
<tr>
<td>Injuries*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial injury, excluding skull fracture</td>
<td>850–854</td>
<td>128 (13)</td>
<td>18 (30)</td>
<td>56 (12)</td>
<td>32 (11)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Other open wound of head</td>
<td>873</td>
<td>52 (5)</td>
<td>4 (7)</td>
<td>21 (4)</td>
<td>14 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fracture of base and vault of skull</td>
<td>800, 801</td>
<td>33 (3)</td>
<td>6 (10)</td>
<td>24 (5)</td>
<td>2 (&lt;1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Injury to other cranial nerve(s)</td>
<td>951</td>
<td>26 (3)</td>
<td>1 (2)</td>
<td>7 (2)</td>
<td>18 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Other conditions of the brain</td>
<td>348</td>
<td>1 (&lt;1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Face</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other open wound of head</td>
<td>873</td>
<td>184 (18)</td>
<td>7 (12)</td>
<td>90 (19)</td>
<td>60 (20)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Open wound of ear</td>
<td>872</td>
<td>94 (9)</td>
<td>2 (3)</td>
<td>40 (8)</td>
<td>49 (17)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fracture of face bones</td>
<td>802</td>
<td>65 (6)</td>
<td>1 (2)</td>
<td>57 (12)</td>
<td>0</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Open wound of ocular adnexa and eyeball</td>
<td>870, 871</td>
<td>64 (6)</td>
<td>4 (7)</td>
<td>47 (10)</td>
<td>6 (13)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Superficial injury of the eye and adnexa</td>
<td>918</td>
<td>39 (4)</td>
<td>0</td>
<td>24 (5)</td>
<td>5 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Contusion of eye and adnexa</td>
<td>921</td>
<td>36 (4)</td>
<td>3 (5)</td>
<td>22 (5)</td>
<td>2 (1)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Foreign body on external eye</td>
<td>930</td>
<td>5 (&lt;1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Burn confined to eye and adnexa</td>
<td>940</td>
<td>5 (&lt;1)</td>
<td>1 (2)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Injury to optic nerve and pathways</td>
<td>950</td>
<td>3 (&lt;1)</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Other disorders of the eye</td>
<td>379</td>
<td>3 (&lt;1)</td>
<td>0</td>
<td>3 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open wound of neck</td>
<td>874</td>
<td>56 (6)</td>
<td>7 (12)</td>
<td>30 (6)</td>
<td>19 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Sprains and strains of neck</td>
<td>847.0</td>
<td>22 (2)</td>
<td>0</td>
<td>2 (&lt;1)</td>
<td>5 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fracture of vertebral column</td>
<td>805.0–1, 806.0–1</td>
<td>6 (1)</td>
<td>0</td>
<td>6 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other, multiple, and ill-defined dislocations</td>
<td>839.0–1</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other, multiple, and ill-defined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial injury of face, neck, and scalp</td>
<td>910</td>
<td>61 (6)</td>
<td>0</td>
<td>12 (3)</td>
<td>26 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Injury, other and unspecified</td>
<td>959.0</td>
<td>54 (5)</td>
<td>0</td>
<td>3 (1)</td>
<td>48 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Burn of face, head, and neck</td>
<td>941</td>
<td>35 (3)</td>
<td>2 (3)</td>
<td>16 (3)</td>
<td>5 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Contusion of face, scalp, and neck</td>
<td>920</td>
<td>27 (3)</td>
<td>0</td>
<td>9 (2)</td>
<td>6 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Injury to blood vessels of head and neck</td>
<td>900</td>
<td>7 (1)</td>
<td>3 (5)</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burns according to extent of body surface</td>
<td>948</td>
<td>4 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Because of rounding, percentages may not total 100.

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; RTD, returned to duty.

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The dominant location of injury was the head. The neck accounted for the smallest proportion of HFNIs among all groups (Table 3).
Dispositions* arms and other explosives such as landmines.9 The most common facial injury diagnosis was “other open wounds of the head”, which included only those ICD-9-CM codes specific to the face (873–873.9).

A higher AIS score, on a scale of 1 to 6, indicates more severe injury. The overall mean AIS scores (with 13 unknown) were 2.1 ± 1.3 for the head, 1.1 ± 0.3 for the face, and 1.2 ± 0.7 for the neck. Comparisons of injury severity by AIS body systems across dispositions are shown in Table 5. Among the wounded in action, the mean AIS scores for head, face, and neck body systems were significantly higher for the evacuated than returned to duty patients. Mean AIS scores did not differ between evacuated and returned to duty nonbattle injury casualties.

**Discussion**

During the study period, more than 50% of all battle injury patients in the Navy-Marine Corps CTR incurred one or more injuries to the head, face, or neck. The majority were caused by IEDs. The prevalence of battle HFNIs in OIF-II is remarkably high compared with that in OIF-I (19%–25%) and military conflicts of the 20th century (15%–25%). Emerging enemy tactics, such as the use of IEDs, have been implicated as a cause of this new pattern of combat injuries.15 In past conflicts, including OIF-I, the use of small arms weapons was common and caused a large proportion of combat injuries.2,3,7,9,10 IEDs, however, were the principal mechanism of injury during OIF-II and are now the hallmark of the Iraq war. IEDs also cause more HFNIs than small arms and other explosives such as landmines.9

Multiple HFNIs per patient were common and expected, given the effects of explosive munitions.15 The widespread use and efficacy of modern body armor technology, including Kevlar helmets and vests, in preventing penetrating head and chest injuries during this conflict is well recognized.15 However, the face remains exposed and may aid future military medical planning, it also presents a few limitations including the retrospective nature of the data, missing data, and lack of denominator data (i.e., population at risk). Although each of the US Armed Forces was represented in this examination, most casualties were Marines. Because of differences in force operations and body armor requirements, these data may not generalize to the other branches of military service.

Although the majority of all HFNIs in the study population were to the face, casualties who died of wounds sustained the largest proportion of injuries to the head. This is not surprising, as wounding patterns among battle injury deaths often differ from that of battle injury survivors and the head is, historically, the primary site of injury among battle injury deaths.2–4,17

Although the primary mechanisms of battle injuries have changed, causes of nonbattle injury seem to be largely consistent with the data from prior conflicts. Vehicle crashes cause the majority of nonbattle injuries during hostile action2,10 and result in the highest number of nonbattle injury hospital admissions.2 In the present study, nearly one-third of nonbattle HFNIs were injured in a motor vehicle crash. It is important to note that 22% of all nonbattle injury patients in the registry sustained HFNIs during the study period, indicating that the head, face, and neck are disproportionately injured during both combat and noncombat events.

Though this broad-based analysis provides important information in the ongoing assessment of the types of HFNIs and may aid future military medical planning, it also presents a few limitations including the retrospective nature of the data, missing data, and lack of denominator data (i.e., population at risk).

Table 5 Comparison of Mean Abbreviated Injury Scale (AIS) 2005 Scores for Injuries by Body System Across Dispositions*  
<table>
<thead>
<tr>
<th>AIS Body System</th>
<th>Died of Wounds</th>
<th>Wounded in Action</th>
<th>Nonbattle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Evacuated</td>
<td>RTD</td>
</tr>
<tr>
<td>Head</td>
<td>4.1 (1.7)</td>
<td>2.6 (1.3)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>Face</td>
<td>1.1 (0.2)</td>
<td>1.2 (0.4)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>Neck†</td>
<td>2.0 (1.3)</td>
<td>1.3 (0.8)</td>
<td>1.0 (0.0)</td>
</tr>
</tbody>
</table>

* Values are mean (SD). A score of 1 is considered minor injury; the maximum score is 6 (maximal injury).
† Includes spine (cervical) AIS.
RTD, returned to duty.
REFERENCES


Marked Improvement in Adherence to Traumatic Brain Injury Guidelines in United States Trauma Centers

Dale C. Hesdorffer, PhD, and Jamshid Ghajar, MD, PhD

**Background:** Prior surveys of acute medical management of severe traumatic brain injury (TBI) indicate that care is fragmented and inconsistent, although Guidelines for the management of severe traumatic brain injury (guidelines) were distributed and endorsed by the American Association of Neurologic Surgeons. We conducted a survey of US trauma centers to evaluate guideline adherence, to examine predictors of adherence, and to compare our results with similar surveys conducted in 1991 and 2000.

**Methods:** A Web-based survey was conducted in 413 designated trauma centers admitting patients with severe TBI. Good adherence was defined as adherence to the median number of guidelines (median = 6, interquartile range 5–7).

**Results:** In adjusted analysis, good adherence was predicted by Level I trauma center designation and presence of treatment protocols. Compared with trauma centers without these predictive factors, the likelihood of good guideline adherence increased 2.4-fold with each additional predictor (95% confidence interval = 1.8–3.3).

Routine intracranial pressure monitor use increased from 32.4% in 1991 and 50.8% in 2000 to 77.4% in the current survey (p < 0.0001). Avoidance of steroids in TBI rose from 47.8% in 1991 and 52.4% in 2000 to 86.0% in 2006 (p < 0.0001). Lack of guideline adherence decreased significantly from 67% in 2006 to 34.5%.

**Conclusions:** Adherence to evidence-based guidelines for severe TBI has improved dramatically since 1991. Trauma center level and treatment protocols were associated with good adherence, suggesting that directing patients with severe TBI to Level I and Level II trauma centers with treatment protocols will improve outcome for these patients.

**Key Words:** TBI, Guidelines, US trauma centers.

S evere traumatic brain injury (TBI), a major cause of death and disability among young people, costs an estimated $45 billion a year.1,2–3 Severe TBI is defined as a Glasgow Coma Scale score ≤8. Both primary and secondary brain injuries are major causes of brain damage and death after severe TBI,4–6 making optimal early intervention critical. Each year in the United States, there are an estimated 1.4 million TBI-related injuries and approximately 50,000 deaths.7 Approximately 230,000 survivors of TBI (i.e., mild, moderate, and severe TBI) in the United States experience long-term disability, making TBI a major public health problem.8

In 1991, a United States survey documented considerable variability in the management of patients with severe TBI.9 This survey led to the development of Guidelines for the management of severe traumatic brain injury (guidelines)10 using methodology developed by the American Medical Association.11 These guidelines, first published in 1995, have been endorsed by the American Association of Neurologic Surgeons, the World Health Organization Neurotrauma Committee, and the New York State Department of Health, and were distributed to all neurosurgeons in the United States in 1995. Despite these extensive efforts, surveys of the management of patients with severe TBI indicate that care remains fragmented and inconsistent,12–13 with full guideline adherence reported in only 16% of US trauma centers.13

Recent publications comparing mortality before and after guideline implementation have demonstrated a marked reduction in mortality.14–16 These studies highlight the need for widespread adherence to the guidelines as protocol to improve outcome in patients with severe TBI.

A survey of nurse managers or trauma coordinators for the intensive care units (ICUs) was conducted at US trauma centers to determine adherence to guidelines, to determine predictors of good adherence, and to compare the 1991 and 2000 surveys with the current survey.

**MATERIALS AND METHODS**

Designated trauma centers in the United States were identified through multiple sources. First, the hospital list used in the 2000 survey13 was retrieved and updated, using information from state health departments and the American Trauma Society Trauma Information Exchange Program.17 The final list of hospitals for this survey included all state-designated and American College of Surgeons–verified Level I, Level II, and Level III trauma centers; self-designated hospitals; and hospitals that had been self-designated as Level I in 2000 but whose status was currently unknown.
Trauma coordinators or nurse managers in the ICU at each center were emailed to request that they complete a Web-based survey that was maintained by Zoomerang (MarketTools, Inc., San Francisco, CA). Respondents were ensured confidentiality of their responses. Centers that were difficult to contact by email also received a mailed letter, describing the purpose of the Web-based survey, and providing a copy of the survey questions as well as a stamped return envelope. After 2 months, centers that had not responded were telephoned, emailed again, and resent the survey by mail every 2 to 4 weeks for a total of 8 months. Those centers that had not responded after this period were considered nonrespondents. Trauma centers were excluded from the survey if they accepted patients with TBI in the emergency department and then transferred them to another facility or if they admitted and treated only pediatric trauma.

The following predictors of guideline compliance were examined and are the same as those evaluated in the 2000 survey paper.13

**Trauma Center Level and Designation**: The source of the designation (American College of Surgeons [ACS] compared with state, self, and don’t know) was examined as a predictor of guideline adherence.

**Treatment Protocols**: Although the use of protocols was determined, their contents were not queried. Centers were classified as having treatment protocols or developing treatment protocol compared with the absence of treatment protocols.

**Specialized ICU Care**: The following types of ICUs were considered to be able to provide TBI care: Neurologic, Neurosurgical, Trauma, Surgical Trauma, and Neurotrauma, based upon the specialization of the physicians in these ICUs.18

**Monthly TBI Patient Volume**: The monthly volume of patients with TBI was categorized as ≤3, 4 to 15, and 16 or more patients per month.

**Neurosurgical Residency Program**: The presence of a neurosurgical residency program was validated against the American Association of Neurologic Surgeons register. Only the primary hospital listed in the residency program was categorized as having a neurosurgical residency program.

Adherence to each standard, guideline, option, and recommendation described in the guidelines was evaluated.10 For the guidelines for which adherence was assessed through a single question with six responses (never, rarely, some- times, very often, always, don’t know), adherence was defined as very often or always and centers answering don’t know were excluded from the analysis for that guideline. This approach was used to define adherence for indications for intracranial pressure (ICP) monitor insertion, ICP treatment threshold of ≥25 mm Hg, mannitol administration for ICP ≥25 mm Hg, barbiturate administration for ICP ≥25 mm Hg, avoidance of steroids for TBI without spinal cord injury, nutrition given before the seventh day after injury, and anti-epileptic drug discontinuation after the seventh day postinjury. For the guideline for type of ICP monitor inserted, adherence was considered to be the insertion of an intraparenchymal bolt or intraventricular catheter.

The degree of adherence was examined and good adherence was defined as adhering to the median or a greater number of guidelines. The following nine guidelines were assessed: indications for ICP monitor insertion, ICP monitor technology, ICP treatment threshold, mannitol, hypocarbia, barbiturates, antiepileptic drug (AED) discontinuation after 7 days, avoidance of steroids, and cerebral perfusion pressure (CPP) treatment threshold of <60 mm Hg. Missing information was classified as failing to adhere to that specific guideline because this was the most conservative approach. For comparison with the 2000 survey, trauma centers were classified as fully adherent to the guidelines if the center adhered to the six guidelines assessed in the 2000 survey13 and as partially compliant if the guidelines for indications for ICP monitoring and ICP technology were fulfilled.

Data were analyzed with SAS statistical software (SAS Institute, Inc., Cary, NC). The $\chi^2$ statistic was used for the analysis of categorical variables and Fisher’s exact test was used when cell frequencies were five or less.

Logistic regression was used to evaluate the impact of predictors of good guideline adherence versus poor guideline adherence. Univariate analysis was performed for each predictor of adherence. Based upon the results of the univariate analyses, all statistically significant predictors were entered into a multivariable logistic regression model and backward elimination was used to reduce the model to the final set of predictors of guideline adherence.

Adherence to the ICP monitor insertion and avoidance of steroids guideline was compared with parallel items from surveys conducted by the Brain Trauma Foundation in 19919 and 2000,13 reanalyzing the data if needed. The first survey was conducted in 1991,9 4 years before publication of the guidelines,10 the second in 2000,13 5 years after guideline publication, and the third in 2006, 11 years after guideline publication. The Mantel-Haenszel $\chi^2$ statistic was used to evaluate whether trends over time were statistically significant.

**RESULTS**

The final list of trauma centers consisted of 724 Level I, Level II, and Level III centers. The 140 centers (19.3%) that stabilized patients with TBI in their emergency departments and then transferred them to an appropriate facility were excluded. Of the remaining 584 adult US trauma centers, 413 (70.7%) treated patients with TBI and agreed to participate in the survey. After excluding the small number of Level III trauma centers (N = 25), there were 173 (41.9%) Level I centers and 215 (52.1%) Level II centers, representing a 90.0% participation rate. The current analyses exclude three centers without ACS or state designation, leaving 171 Level I and 214 Level II centers. Among the responding nurses, the highest degree was a doctorate in 33 (8.5%), a masters in 133
(34.3%), a registered nurse degree in 93 (24.0%), a bachelors in 88 (22.7%), a certificate in 2 (0.5%), and other in 39 (10.0%).

The state was the most common source of designation (Table 1, online only). Level I centers were more likely to be designated by the ACS ($p = 0.030$) and to have a specialized ICU care for patients with TBI ($p < 0.0001$), a neurosurgical residency program ($p < 0.0001$), and a higher monthly volume of patients with TBI ($p < 0.0001$). The overwhelming majority of trauma centers reported that most patients with severe TBI went to rehabilitation after discharge (41.9% to a facility affiliated with the trauma center and 49.7% to an unaffiliated facility).

Compared with Level II centers, Level I centers were statistically significantly more likely to adhere to guidelines for insertion of an ICP monitor, recommended ICP monitor technology, hyperventilation for an ICP $\geq 25$ mm Hg, CPP treatment threshold of 60 mm Hg, discontinuation of antiepileptic drugs after day 7 in the absence of seizures, and avoidance of steroids. ICP monitors were inserted by neurosurgery residents more often than by any other medical professional (93.6%) when trauma centers had a neurosurgery residency program. Among trauma centers without neurosurgery residency programs, ICP monitors were inserted most often by neurosurgery attendings (83.8%). The use of specific therapies for an ICP $> 25$ mm Hg did not differ by trauma center level, except for hypertonic saline and Lasix (Table 2). Hypertonic saline was used more in Level I centers (21.0%) than in Level II centers (7.4%; $p = 0.0002$). In contrast, paralytics were more common in Level II centers (44.9%) than in Level I centers (33.9%; $p = 0.03$). The use of specific therapies for a CPP $< 60$ mm Hg differed by trauma center level (Table 2) for Crystalloids ($p = 0.03$) and for Vasopressors ($p = 0.01$). Overall, crystalloids were used by 81.0% of trauma centers, vasopressors by 87.0%, and colloids by 52.7%.

In addition to ICP monitoring, trauma centers were surveyed about their monitoring of other parameters (Table 3). Level I centers were more likely than Level II centers to continuously monitor blood pressure by an arterial line ($p = 0.0004$), and to continuously monitor central venous pressure ($p < 0.0001$). There was no difference in continuous monitoring of end tidal CO$_2$, jugular oxygen content, or brain tissue oxygen by trauma center level. Interestingly, brain tissue oxygen tension monitoring was rarely used even at Level I trauma centers (8.2%, Table 3). The threshold for packed red blood cell transfusions was a hematocrit $< 21$% in 18.8% of centers, a hematocrit of 21% to 27% in 60.4% of centers, a hematocrit of 27% to 35% in 18.2% of centers, and a hematocrit of 35% to 40% in 0.8% of centers.

### Table 1 Characteristics of Surveyed Trauma Centers*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level I (N = 171)</th>
<th>Level II (N = 214)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Designation of level</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>State</td>
<td>93 (54.4%)</td>
<td>139 (64.9%)</td>
<td></td>
</tr>
<tr>
<td>American College of Surgeons</td>
<td>78 (45.6%)</td>
<td>75 (35.1%)</td>
<td></td>
</tr>
<tr>
<td>Specialized ICU care for TBI†</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>51 (30.0%)</td>
<td>152 (71.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes‡</td>
<td>119 (70.0%)</td>
<td>62 (28.9%)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgical residency programs</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>110 (64.3%)</td>
<td>212 (99.1%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (35.7%)</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Treatment protocols†</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No</td>
<td>48 (28.2%)</td>
<td>111 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>In development</td>
<td>21 (12.3%)</td>
<td>25 (11.7%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>101 (59.4%)</td>
<td>78 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>Volume each month§</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\leq$3 patients/mo</td>
<td>18 (11.2%)</td>
<td>76 (37.1%)</td>
<td></td>
</tr>
<tr>
<td>4–15 patients/mo</td>
<td>95 (59.4%)</td>
<td>111 (54.1%)</td>
<td></td>
</tr>
<tr>
<td>$\geq$16 patients/mo</td>
<td>47 (29.4%)</td>
<td>18 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Director of ICU treating most severe TBI†</td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Critical care intensivist</td>
<td>80 (47.1%)</td>
<td>112 (62.3%)</td>
<td></td>
</tr>
<tr>
<td>Anesthesiologist</td>
<td>3 (1.7%)</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Neurointensivist</td>
<td>7 (4.1%)</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgeon</td>
<td>22 (12.9%)</td>
<td>18 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>Neurologist</td>
<td>3 (1.8%)</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>General surgeon</td>
<td>36 (21.2%)</td>
<td>38 (17.8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>19 (11.2%)</td>
<td>41 (19.1%)</td>
<td></td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
† Includes self-designation and unknown source of designation.
‡ One center was missing information.
§ Twenty centers answered don’t know.

* Includes self-designation and unknown source of designation.
ocrit of 28% to 32% in 19.8% of centers, and a hematocrit of 32% in 1.0% of centers. Among surveyed trauma centers, half adhered to six or more guidelines (interquartile range 5–7 guidelines), which defined good adherence. Adherence to four or fewer guidelines was very rare (10%) as was adherence to all nine surveyed guidelines (1%). Among trauma centers with good guideline adherence, 99.2% treated ICP >25 mm Hg, 96.0% avoided the use of steroids, 87.2% inserted an ICP monitor, 90.8% used intraparenchymal or intraventricular ICP monitors, 79.3% used mannitol for ICP >25 mm Hg, 64.9% treated CPP <60 mm Hg, 62.4% used hyperventilation for ICP >25 mm Hg, 18.7% used barbiturates for ICP >25 mm Hg, and 83.7% discontinued AEDs after 7 days.

In univariate analysis, good guideline adherence was significantly more common for each predictor examined (Table 4). When all predictors were simultaneously entered into a model, only trauma center level and treatment protocols remained statistically significant. We then considered the impact of none, one, or both of these predictors on good guideline adherence. One hundred eleven trauma centers had no predictors (28.9%), 151 (39.3%) had one predictor, and 122 (31.8%) had two predictors. Compared with trauma centers with no predictors, trauma centers with one predictor were 2.8-fold more likely to have good guideline adherence (95% CI = 1.7–4.7) and trauma centers with both predictors were 5.9-fold more likely to have good guideline adherence (95% CI = 3.2–10.7). Thus, the likelihood of good guideline adherence increased 2.4-fold with each predictor (95% CI = 1.8–3.3).

When applying the definitions of full and partial guideline adherence from the 2000 survey to the current survey, lack of guideline adherence occurred in 133 centers (34.5%), partial guideline adherence in 172 centers (44.7%), and full guideline adherence in 80 centers (20.8%). The proportion of trauma centers routinely using ICP monitors in severe TBI has increased over time (p = 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1). Continuous monitoring of central venous pressure has risen over time (p < 0.0001, Fig. 1).

### Table 2 Therapies for Intracranial Pressure >25 mm Hg and for CPP <60 mm Hg by Trauma Center Level

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Level I, N (%)</th>
<th>Level II, N (%)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapies for high ICP†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF drainage</td>
<td>94 (56.6)</td>
<td>95 (49.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Paralytics</td>
<td>57 (33.9)</td>
<td>89 (44.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mannitol</td>
<td>112 (66.7)</td>
<td>135 (67.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>35 (21.0)</td>
<td>14 (7.4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>25 (15.0)</td>
<td>30 (15.1%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Lasix</td>
<td>9 (5.5)</td>
<td>19 (9.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>92 (58.2)</td>
<td>90 (48.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>39 (24.8)</td>
<td>37 (19.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Therapies for low CPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloids</td>
<td>147 (86.0)</td>
<td>165 (77.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Colloids</td>
<td>93 (54.4)</td>
<td>110 (51.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>157 (91.8)</td>
<td>178 (83.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Test for trend.
† Twenty six centers were missing information on CSF drainage, 19 on paralytics, 16 on mannitol, 28 on hypertonic saline, 19 on barbiturates, 26 on Lasix, 43 on hyperventilation, and 39 on hypothermia.

### Table 3 Types of Continuous Monitoring by Trauma Center Level*

<table>
<thead>
<tr>
<th>Type of Continuous Monitoring†</th>
<th>Level I, N (%)</th>
<th>Level II, N (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial line to monitor blood pressure</td>
<td>160 (94.1)</td>
<td>172 (81.9)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>130 (76.9)</td>
<td>118 (57.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End tidal CO₂</td>
<td>77 (45.8)</td>
<td>96 (47.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Jugular oxygen content or saturation</td>
<td>8 (4.9)</td>
<td>12 (6.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Brain tissue oxygen tension</td>
<td>13 (8.2)</td>
<td>10 (5.2)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Excludes ICP monitoring.
† Five centers were missing information on arterial lines to monitor blood pressure, 9 on central venous pressure monitoring, 14 on end tidal CO₂ monitoring, 28 on jugular oxygen content or saturation monitoring, and 35 on brain tissue oxygen tension monitoring.
DISCUSSION

There has been a dramatic improvement in the care of patients with severe TBI in US trauma centers since the first survey in 1991.9 Guidelines were first disseminated in 1995. It has, therefore, taken 11 years for more than two thirds of trauma centers to routinely insert an ICP monitor and for almost all trauma centers to avoid the use of steroids in patients with severe TBI. In addition, lack of adherence to guidelines fell more than 50% since the 2000 survey, from 67% in 200013 to 34.5% in the current survey. Why has it taken more than a decade to achieve this huge improvement in TBI care?

Table 4  Good Adherence* to the Guidelines by Characteristics of the Trauma Center

<table>
<thead>
<tr>
<th>Trauma Center Characteristic</th>
<th>N (% With Good Adherence)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I</td>
<td>171 (78.4)</td>
<td>3.1 (2.0–4.9)</td>
<td>2.6 (1.7–4.2)</td>
</tr>
<tr>
<td>Level II</td>
<td>214 (53.7)</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Designation of level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American College of Surgeons</td>
<td>153 (70.6)</td>
<td>1.55 (1.00–2.40)</td>
<td>NA</td>
</tr>
<tr>
<td>State and other</td>
<td>232 (60.8)</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>Specialized ICU care for TBI†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>181 (71.3)</td>
<td>1.7 (1.1–2.7)</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>203 (58.6)</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgical residency programs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (80.9)</td>
<td>2.7 (1.4–5.2)</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>322 (61.5)</td>
<td>1.0 (Referent)</td>
<td></td>
</tr>
<tr>
<td>Treatment protocols†‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>179 (73.7)</td>
<td>2.7 (1.7–4.3)</td>
<td>2.2 (1.4–3.5)</td>
</tr>
<tr>
<td>In development</td>
<td>46 (76.1)</td>
<td>3.1 (1.4–6.4)</td>
<td>2.8 (1.3–5.9)</td>
</tr>
<tr>
<td>No</td>
<td>159 (50.9)</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Volume each month§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 patients/mo</td>
<td>94 (52.1)</td>
<td>1.0 (Referent)</td>
<td>NA</td>
</tr>
<tr>
<td>4–15 patients/mo</td>
<td>206 (68.0)</td>
<td>1.9 (1.2–3.2)</td>
<td></td>
</tr>
<tr>
<td>≥16 patients/mo</td>
<td>65 (72.3)</td>
<td>2.4 (1.2–4.7)</td>
<td></td>
</tr>
</tbody>
</table>

* Good adherence is defined as the median or greater number of guidelines for which there was adherence among trauma centers. Trauma centers with missing information on adherence to a guideline were considered to be nonadherent to that guideline.
† One center was missing information.
‡ Includes neurologic/neurosurgical ICU, neurologic/trauma ICU, and surgical/trauma ICU.
§ Twenty two centers that answered “don’t know” are missing information on monthly volume of severe TBI.
NA, not significant in the multivariate model (including all predictors that were significant on univariate analysis; therefore, not included in the final model); ICU, intensive care unit.

Fig. 1. Trends in guideline compliance and continuous monitoring over time.
Previous studies have suggested that physician behavior is rarely changed simply by the publication of evidence-based guidelines.20 This is consistent with results of the US trauma center survey conducted in 2000,13 which reported that ICP monitor insertion increased little between 1991 and 2000. Lack of awareness, agreement, and familiarity with guidelines have been cited as common barriers to changing practice.19 Before conducting the last survey in 2000, only two studies20,21 had compared patient outcome before and after guideline implementation. Presently, there are a total of eight studies comparing patient outcome before and after implementation of guidelines as protocol, which have suggested that adherence to such protocols saves lives, improves patient outcome, and reduces the cost of acute care.14–16,20–24 These publications may account for some of the increased use of treatment protocols in US trauma centers over time. In 2000, 44.6% of US trauma centers had treatment protocols,13 but by 2006, 53.4% reported treatment protocols, parallel to the 57% observed in European centers.25 Also, strong new evidence supporting the guideline for avoidance of steroids in TBI was recently published. This evidence comes from the largest randomized, double-blind, placebo-controlled, multicenter trial ever conducted in TBI (N = 10,008) and demonstrated that intravenous corticosteroids significantly increase mortality.26 Collectively, these studies may constitute a critical mass of information, supporting guideline implementation and creating the necessary awareness and agreement needed to alter practice. Interestingly, hypertonic saline was used at 20.8% of Level I trauma centers, despite a small negative trial conducted in 1998.27

Trauma center level and treatment protocols were predictive of good guideline adherence. In addition, compared with Level II trauma centers, Level I centers were significantly more likely to have treatment protocols for severe TBI and were more likely to have a higher monthly patient volume. High trauma center volume has been variably associated with decreased mortality.28–30 However, the institution of treatment protocols has been associated with greatly improved outcome in multiple studies.14–16,20–24 These factors may suggest the need for increased regionalization of trauma centers.31

The concept behind regionalization of care is that non-trauma centers provide less optimal care compared with designated trauma centers with established treatment protocols and the resources to treat trauma, including neurosurgeons, neurosurgical residency programs, intensivists, and appropriate ICU care. Thus, regionalization shifts trauma care to the centers best able to manage these patients. Also, regionalization lowers the risk of death, particularly for the most severely injured patients.32 Even across trauma centers, there is variability in care by level of trauma center designation; treatment at Level I trauma centers has been shown to reduce mortality by 9% compared with treatment at Level II trauma centers.33 Other studies have discussed the difficulty of determining the reasons for a better outcome at Level I compared with Level II trauma centers.34 The data reported here suggest that guideline-directed treatment protocols may account for the improved outcome of patients with severe TBI treated in Level I trauma centers. These data suggest that better outcomes can be achieved through further regionalization of the care of severe TBI to high volume Level I trauma centers with treatment protocols or through the further implementation of guideline-directed protocols at Level II centers.

In the 2000 survey, the presence of a neurosurgery residency program was associated with full guideline adherence,13 but this tendency was not replicated in the current survey. One possible reason for the difference between surveys is that more than 95% of neurosurgery residents practiced at Level I trauma centers but not all Level I trauma centers had neurosurgery residency programs. Neurosurgery residents placed almost all ICP monitors in centers with neurosurgery residency programs whereas that work was shifted to neurosurgery attendings in almost all centers without neurosurgical residency programs.

The survey was completed by trauma coordinators or nurse managers in the ICU at each trauma center. It is possible that their responses do not reflect actual practice, because some respondents may not have been involved in direct patient care or because they had limited experience caring for TBI patients. This could lead to either an over- or underestimation of guideline adherence. It is also possible that neurosurgeons, ICU directors, and trauma surgeons may have responded differently, as has been suggested by Marion et al. in a survey of 40% of neurosurgeons in North America.35 These possibilities were impossible to evaluate directly. However, it was possible to compare the survey results with actual patient data from a New York State program.36 Parallel to data from the surveys reporting an increase in the frequency of ICP monitor insertion from 51.6% in 200013 to 77.4% in the current survey, ICP monitor insertion increased in New York State from 52.4% in 2000 to 71.3% in 2005.

Thus, it is possible that the surveys are detecting actual changes in practice over time.

Adherence to evidence-based guidelines for the acute management of patients with severe TBI has improved dramatically since 2000.13 In the current survey, trauma center level and presence of treatment protocols were associated with good guideline adherence in adjusted analyses. This suggests that implementation of guideline-directed protocols at Level I and Level II trauma centers or regionalization of TBI care to designated trauma centers with protocols, may be the best approach for optimizing outcome for these patients.

ACKNOWLEDGMENTS

Many thanks to Erica Filstien, Laura Iacono, Kerry Lyons, and Alicia Meyer for their invaluable help with the survey. We are also grateful to all of the trauma center personnel who participated in the survey.

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October 2007
REFERENCES


EDITORIAL COMMENT

This article surveyed trauma coordinators or nurse managers about patients with brain injuries at their hospitals, specifically asking about management practices and other characteristics. The authors quantified the extent to which the respondents at 385 designated Level I and II trauma centers reported that they followed nine practices recommended in the Brain Trauma Foundation’s (BTF) guidelines. The authors report that adherence to the BTF guidelines has significantly increased when the current results are compared with those from a 2000 survey.

It is difficult to separate the influence of the specific BTF guidelines from the larger movement toward evidence-based medicine and, particularly, toward the use of management protocols based on the best available evidence. Theoretically, the management recommendations in the BTF guidelines should be arrived at by any individual or group that performs a careful review of the available literature. Evidence that at
least some hospitals performed more widely ranging literature analyses to construct management algorithms that go beyond the BTF topics. These include the use of hypertonic saline, hypothermia, and brain tissue oxygen monitoring in some centers (Table 2), even though the BTF guidelines did not address these specific topics.

In terms of strict clinical trial methodology, it is extremely difficult, if not impossible, to demonstrate that adoption of any specific set of guidelines is responsible for improvements in clinical results. Any improvements more likely result from an institution’s introspective process of re-examining its current practices and eliminating unjustifiable variation by standardizing management according to the best available evidence. Carefully constructed documents like the BTF guidelines are excellent places to start.

**Dr. Alex B. Valadka, MD, FACS**

*University of Texas Medical School at Houston*

*Houston, Texas*
The Healing of Tibial Fracture and Response of the Local Lymphatic System

Grzegorz Szcześni, MD, PhD, Waldemar L. Olszewski, MD, PhD, Magdalena Gewartowska, MSc, Marzanna Zaleska, and Andrzej Gońcki, MD, PhD

Background: Damage of tissues by mechanical injury and inflammation is followed by reaction of the regional lymphoid tissue, lymphatics, and lymph nodes. In our previous lymphoscintigraphic studies, we showed that closed fractures of a lower limb cause reaction of the local lymphoid tissue. There was dilation of lymphatics draining the site of the fracture and enlargement of inguinal lymph nodes. These changes persisted even after clinical healing of the fracture. In the long-lasting nonhealing fractures, the lymphoscintigraphic pictures were different. The draining lymphatics became obliterated, and the lymph nodes disappeared.

Methods: In this study, we tried to correlate the lymphoscintigraphic images, reflecting the immune events at the fracture site, with the immunohistochemical observations of the biopsy specimens obtained during corrective operations from the healing and nonhealing fracture gaps. Thirty-eight patients with closed fracture of the tibia without traumatic skin changes were studied.

Results: We confirmed that closed tibial fracture evokes response of the regional lymphatic system. Normal fracture healing with immune cell infiltrates and foci of ossification was accompanied by dilated lymphatics and enlarged lymph nodes. Prolonged nonhealing fracture with lack of cellular reaction in the gap proceeded with decreased mass of lymph nodes.

Conclusion: This study provides evidence for existence of a functional axis between wound of bone and surrounding soft tissue and the local lymphatic (immune) system. We hypothesize that the fast healing is regulated by influx into the wound of lymph node regulatory cells, whereas prolonged healing causes gradual exhaustion of the regional lymph node functional elements, and reciprocally impairment in sending regulatory cells to the fracture gap.

Key Words: Tibia, Fracture, Lymph nodes, Lymphoscintigraphy, Healing.

of orthopedic surgery for the check-up. The inclusion criteria comprised closed fracture without traumatic skin changes. Exclusion criteria were leg dermatitis, chronic venous insufficiency, ulcers and additional injuries in the past as well as chronic atherosclerotic limb ischemia and diabetes. The patients' data and applied therapy are presented in Table 1. All patients were evaluated radiologically immediately after fracture and later at 2 months intervals. The delay in fracture repair was diagnosed clinically according to the pathologic mobility between bone fragments, and from X-ray films in the anteroposterior and lateral positions. The diagnosis was further confirmed on the basis of computed tomography scans as lack of callus formation between bone fragments. Routine lower limb isotope lymphography was performed before surgery. Ten patients had uneventful healing (group 1), and 28 had delayed healing or lack of union (group 2). Patients with indications for surgical correction (n = 28) were divided into two groups: group 1A, uneventful healing (21–42 days after fracture) (n = 7); and group 2A, nonhealing fracture (43 days to 15 months after fracture) (n = 21). All these patients were operated upon because of either lack of bone fragments alignment or nonunion. Tissue specimens were taken from the fracture gap for immunohistochemical investigations. The wounds were inspected daily. There was no wound suppuration or dehiscence during the follow-up period. The institute ethical committee approved the study.

**Lymphoscintigraphy**

Lymphoscintigrams were obtained on the day of appearance in the outpatient department, on both extremities after subcutaneous injection of 99mTc-Nanocol (3 mCi) into the first web space using a gamma camera (Orbiter ZLC 750, Siemens, Earlangen, Germany). The image of the lower leg and thigh lymphatics and lymph nodes was evaluated quantitatively. Lymphoscintigrams were scanned and analyzed using specialized PC software (Olympus Micro Image, Version 3.0.0., Olympus Optical, Hamburg, Germany). The surface area of the lymphatics (Lv) and inguinal lymph nodes (LN) of both extremities was evaluated in the inguinal area, thigh, and calf (Fig. 1). Data were expressed as indexes obtained from the equations $I_{Lv}$ or LN = $S_{TrLv}$ or LN/$S_{ClLv}$ or LN, where $S_{Lv}$ or LN were surface of lymph vessels or lymph nodes measured on the injured (Tr) and contralateral (C) extremity. The obtained data were compared between groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age Mean ± SD</th>
<th>Type of Fracture</th>
<th>Primary Treatment</th>
<th>Type of Surgery</th>
<th>Duration of Follow-up (mo)</th>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>41.3 ± 9.42</td>
<td>Tibial shaft (10)</td>
<td>Conservative</td>
<td>ORIF (7)</td>
<td>8.0 ± 6.5 (3–24)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>41.0 ± 17.4</td>
<td>Tibial shaft (28)</td>
<td>Surgical</td>
<td>ORIF (16), external fixation (7), bone transplantation (5)</td>
<td>28.6 ± 49.19 (3–204)</td>
<td></td>
</tr>
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</table>

ORIF, open reduction internal fixation.

**Immunohistochemical Investigations of Fracture Gap Tissue**

Tissue specimens from the fracture were snap-frozen at −70°C, sectioned, and stained immunohistochemically with antibodies against human leukocyte antigen (HLA)-DR (HLA class II), CD68 (monocytes/macrophages), CD4...
(helper) and CD8 (cytotoxic T lymphocytes), CD25 (receptor for interleukin-2), CD22 (B lymphocytes), CD34 (stem cells and thymocytes), and elastase (granulocytes) (all DAKO, Glostrup, Denmark). Staining with antibodies against bone morphogenetic proteins 2 and 4 (BMP-2 and 4), collagen type 1 and 2, SDF-1 (stromal derived factor-1), and OPG (osteoprotegerin) was performed (SantaCruz Biotechnology, CA). Stainings were performed using LSAB or LSAB-2 HRP kit (DAKO) according to the manufacturer’s procedures. Microscopical slides were analyzed under optical microscope (Olympus, BX40F, Nagano, Japan). Trichrome staining allowed visualization of collagen and elastin deposition.

Histologic scoring of cells from 0 to + + + (0–3) was performed, where 1 (1–25 cells), 2 (26–50 cells), and 3 (>50 cells/×200 magnification field). The intensity of staining of proteins in the intercellular space was scored 0 to 3, where 1 was weak, 2 intermediate, and 3 strong, compared with the strong in a control gap tissue.

Statistical Analysis

The lymph vessel and node surface area values of the affected and healthy limb were presented as means indexes (affected versus normal). The differences were analyzed using the Student t test for pairs. Differences between the union and nonunion groups were evaluated using the Mann-Whitney test for nonparamateric values. Two investigators blinded to the study evaluated the tissue sections. The mean densities of cells and intensity of protein staining were compared using the Monte Carlo permutation exact test. Differences were considered significant at the p level <0.05.

RESULTS

Lymphatic Response to Bone Fracture

Lymphoscintigraphies performed in patients from group 1 (bone union) revealed in the affected limb of all patients dilated lymphatics of the superficial system and enlarged inguinal lymph nodes (Fig. 1). The surface area of calf lymph vessels was 3.24 ± 3.25 times, of thigh lymphatics 3.14 ± 2.95 times, and of lymph nodes 1.76 ± 0.67 times larger than in the nonfractured limb (all p < 0.05). In group 2 (nonunion) lymphoscintigraphies revealed decrease of inguinal lymph node surface area in all patients, when compared with contralateral limb. The surface area of calf lymph vessels was 1.70 ± 2.28 times (not significant [NS]) of thigh lymphatics, 0.57 ± 0.50 times (NS) of lymph nodes, and 0.49 ± 0.40 times of that of the nonfractured limb (lymph nodes p < 0.001) (Fig. 2). Deep lymphatics and popliteal lymph nodes appeared on lymphoscintigrams in six patients (43%).

Phenotypes of Infiltrating Cells

The pictures of healing fractures showed cellular infiltrates and foci of ossification. In contrast, there was lack of chondrocytes and osteoblasts, and only a few fibroblasts could be seen in the nonhealing gap tissue. Trichrome staining was weak in this group.

Immunohistochemical Evaluation of Gap Tissue

Foci of Osteogenesis

The pictures of healing fractures showed cellular infiltrates and foci of ossification. In contrast, there was lack of chondrocytes and osteoblasts, and only a few fibroblasts with the healing cases; however, the intensity of this molecule on endothelial cells was decreased.
Fig. 3. Immunohistopathologic pictures of the tibial fracture gap tissue harvested during corrective surgery in a uneventful (A) and delayed healing (B). (a) hematoxylin-eosin staining, (b) trichrome staining for collagen and elastin, (c) expression of HLA-DR antigen on infiltrating cells, (d) CD68 macrophages, (e) staining for OPG (brown areas), and (f) SDF-1 (brown areas). Osteogenesis pictures were seen in all specimens from uneventful healing. There was no osteogenesis and little deposition of collagen as well as lack of OPG and SDF-1 in tissues from delayed healing. Also, there were fewer cells with HLA-DR and CD68 phenotype in the gap tissue (CD nomenclature of cellular populations clarified in text).
Cellular Proteins in the Gap Tissue

There was statistically less of BMP2, collagen II, SDF1, and OPG in the nonhealing group (Fig. 5). No difference in deposition of collagen I and BMP4 between groups was found.

Evaluation of Lymphoscintigraphic Images of Lymphatics and Inguinal Lymph Nodes and Histology of Gap Tissue

Dilated lymphatics and enlarged lymph nodes were accompanied by dense infiltrates and foci of ossification in the fracture gap. In all cases with decreased area of lymphatics and inguinal lymph nodes of the fractured limb, in comparison with the contralateral unaffected side, there was lack of osteogenesis, cellular depletion of the gap tissue, and low deposition of collagen I, SDF1, OPG, and BMP2.

DISCUSSION

This study has resulted in the following observations: (1) there is an increase in the area of lymphatics and lymph nodes on lymphoscintigrams and osteogenesis, cellular infiltrates in the gap tissue, and deposition of collagen I, SDF1, OPG, and BMP2 in cases with healing tibial fractures, (2) there is a decreased area of lymphatics and inguinal lymph nodes and lack of osteogenesis foci in gap tissue with cellular depletion and low deposition of proteins participating in osteogenesis in the nonhealing fracture group. The changes in lymph node lymphoscintigraphic images were analyzed in conjunction with the histologic pictures of the fracture gap tissue, whereas histologic findings of lymph nodes were not available, as biopsy of that tissue could not be performed because of ethical reasons.

There is a large body of evidence indicating that there is a functional relationship between the events at the site of bone fracture and response of the draining lymph nodes. Experiments performed under laboratory conditions of normally healing stable fracture showed increased mass of the regional lymph nodes at up to 16 weeks of follow-up and decreased node mass in animals with delayed healing of fractures. The fracture gap is first filled with blood, then follows the scavenging phase with accumulation of granulocytes, monocytes, and macrophages. Reconstruction starts with harrowing the mesenchymal cells. Subsequently, fibrous union is created, followed by focal bone formation. The response of the limb lymphatic system is observed immediately after injury. In our previously reported observations from intravital fluorescence microscopy, increased plasma extravasation with high lymph formation rate and outflow were observed during the first few hours after injury.

The nature of the activation and response of the lymphoid tissue to healing fracture remains unknown. In our previous investigations in rats, major changes in the lymph nodes were seen after fracture, muscle injury, and subcutaneous bone marrow but not blood injection. The weight of nodes increased by a factor of 1.4 to 2.1. The density of W3/13 (T cell), OX6 (Class II), OX7 (stem cells), and ED1 (macrophages) cells was found increased in the paracortex; however, most advanced changes were observed in the medulla. High frequency of B cells was seen in follicles and medulla. Endothelial cells stained strongly for OX6 and OX7. Interestingly, there were few HIS48 cells (granulocytes). Low concentrations of granulocytes pointed to a nonbacterial reaction. Increased responsiveness of lymph node lymphocytes to mitogens was also observed. It was concluded that closed bone trauma with bone marrow spillage and damage of muscles initiates mobilization of cells in the regional nodes. In dog experiments, bone marrow cells (BMC) evoked major inflammatory changes both in skin and lymph nodes. Autologous BMC and PBL stimulated lymph node lymphocytes in a 6-day culture.

These observations suggest activation of the regional lymph nodes by molecular mediators (cytokines and growth factors) and migrating cells drained from the site of injury. It has also been suggested that activation of microorganisms inhabiting deep tissues of the limb may occur in damaged tissues by cytokines produced by immune cells at the site of injury and provide a signal for stimulation of regional lymph nodes.

In a number of cases, the process of bone union does not proceed even in absence of infection. The pathomechanism of this condition remains unknown. Which cells and their products are lacking in the gap of the nonhealing fractures is unclear. We hypothesize that in the closed injuries of tissues, the extravasated blood and cellular debris from...
local tissue are phagocytosed by macrophages and incorporated by the migrating dendritic cells. The scavenging cells migrate to thefferent lymphatics and are dragged with lymph stream to the regional lymph nodes. This last has been documented in a large series of studies. In addition to the migrating cells, their fragments, including nuclei, flow with lymph to the nodes. In the nodes, presentation of self-antigens by dendritic cells to lymphocytes proceeds. This results in priming of node cells and mobilization of blood lymphocytes that enter the node via high endothelial venules. Enlargement of lymph node cellular mass is observed. The question arises as to whether the antigen-specific clones of lymphocytes to self-antigens are being raised. If so, the primed cells would leave the lymph nodes via efferent lymphatics, and having flown through the thoracic duct, enter blood circulation. Then the antigen-specific cohorts of lymphocytes home to the site of injury. There they may display their cytotoxic and regulatory function. The cytotoxicity is necessary for elimination of hyperproliferating granulation tissue cells. The regulatory CD4+/CD25+ cells may downregulate the process of uncontrolled growth of the granulation tissue. This is an autoimmune type of response ending up when there is no more exposure of damaged and proliferating cells to the infiltrating immune cells. Such a type of protective autoimmunity process has been observed after injury of the central nervous system and spinal cord. The T cells directed against myelin-associated proteins accumulated at the site of injury, activated effector macrophages and B cells, which resulted in neuronal survival.

As long as there is active healing of the wound, the draining lymph nodes remain enlarged. However, a prolonged healing process with cellular apoptosis and necrosis may lead to lymphocyte depletion and attenuation of node function (unpublished). This in turn may result in lack of production of antigen-specific lymphocytes and homing to the wound and subsequently impaired regulation of the healing mechanism. Whether the healing defect originates in the wound or the regional lymph node remains to be clarified. Nevertheless, observations indicate that there exists a functional axis between the wound and lymph nodes.

A number of causative factors may play a role in impaired wound healing of fractured bone. These may be excess of disintegrated cells by trauma and ischemia, impaired lymphatic drainage, and transfer of signals to the lymph node, overloading of nodes by cellular debris from the periphery resulting in apoptosis and necrosis of their cells, genetic defects as point mutations of genes for interleukins and growth factors. Not properly cleared dead cells are dangerous for the body. The dead cells accumulate, lose their membrane integrity, danger signals are released, and nuclear antigens get accessible in an inflammatory context. In times of increased apoptosis, tolerance can be broken, and a chronic inflammatory results, which can then lead to an autoimmune reaction against nuclear constituents. Many adaptor molecules and receptors are involved in the clearance of dying cells. Complement components, serum DNase I, phosphatidylycerine, and modified glycoproteins participate crucially in the clearance of apoptotic and necrotic cells. Accumulation of nuclear material in terminal centers of lymph nodes of some systemic lupus erythematosus (SLE) patients has been observed. The noningested nuclear material may provide survival signals for autoreactive B cells and consecutively antinuclear autoantibodies will be produced for wound cells.

Taken together, the tibial fracture evokes response of the regional lymphatic system. Normal healing with immune cell infiltrates and foci of ossification is accompanied by dilated lymphatics and enlarged lymph nodes. Prolonged nonhealing fracture with lack of cellular reaction in the gap goes with decreased mass of lymph nodes. We hypothesize that the prolonged healing process in the fracture gap causes gradual exhaustion of the lymph node functional elements, and reciprocal deficient lymph node cannot produce and send regulatory cells to the fracture gap.

REFERENCES
Knee Dislocations With Vascular Injury: Outcomes in the Lower Extremity Assessment Project (LEAP) Study

Brendan M. Patterson, MD, Julie Agel, MA, ATC, Marc F. Swiontkowski, MD, Ellen J. MacKenzie, PhD, Michael J. Bosse, MD, and the LEAP Study Group

Objectives: The purpose of this study is to report the clinical and functional results of a cohort of patients with knee dislocations associated with vascular injury.

Methods: Patients with knee dislocation and associated vascular injury were prospectively assessed for outcome of severe lower extremity trauma during 2 years. The Sickness Impact Profile was used to assess the functional recovery of the patient. Surgeon and therapist assessments documented clinical metrics and treatment, including salvage or amputation, neurologic recovery, knee stability, and knee motion.

Results: Eighteen patients sustained a knee dislocation and an associated popliteal artery injury. Seven patients were found to have an additional vascular injury. All patients underwent repair of the vascular injury. At the time of final follow-up, 14 knees were successfully salvaged and four required amputation (1 below knee amputation, 2 through knee amputation, and 1 above knee amputation). Eighteen patients had at least a popliteal injury and underwent repair of the vascular injury. The patients with a limb-threatening knee dislocation that was successfully reconstructed had Sickness Impact Profile scores of 20.12 at 3 months, 13.18 at 6 months, 12.08 at 1 year, and 7.0 at 2 years after injury.

Conclusions: Patients who sustain a limb-threatening knee dislocation have a moderate to high level of disability 2 years after injury. Nearly one in five patients who present to a Level I trauma center with a dysvascular limb associated with a knee dislocation will require amputation. Prolonged warm ischemia time was associated with a high rate of amputation. Patients who sustain vascular injuries associated with a knee dislocation need immediate transport to a trauma hospital, rapid assessment and diagnosis at presentation, and revascularization. Patients with these injuries can be effectively treated without angiography before surgery.

Key Words: Knee dislocation, Lower extremity trauma, Sickness impact profile (SIP), Vascular injury.

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The management of acute knee dislocation has evolved during the past 2 decades with the improvement in trauma care, particularly the care of severely injured patients in trauma centers. The management of knee dislocations associated with vascular injury remains a challenge, as the management demands early recognition, transport to an appropriate facility, expedient evaluation, the coordination of several services, and timely treatment. The outcomes of knee dislocation associated with vascular injury are variable, and it has been difficult to determine the important factors that contribute to the prognosis. Historically, amputation has been frequently required because of prolonged warm ischemia time. Green and Allen¹ reported that more than 85% of patients who sustained a knee dislocation with a dysvascular limb that had warm ischemia time of more than 6 hours ultimately required amputation. The purpose of this article is to report on the clinical outcome of limb-threatening knee dislocation with associated vascular injury and identify factors related to poor outcomes.

PATIENTS AND METHODS

This cohort of patients was derived from the Lower Extremity Assessment Project (LEAP),²³ a multicenter, prospective longitudinal study of patients with severe lower extremity injuries as a result of blunt trauma managed in Level I trauma centers. The LEAP study involved patients treated in eight Level I trauma centers in the United States and enrolled 585 patients during 2 years. Patients in the LEAP study were between the ages of 16 and 69 and sustained high-energy injuries distal to the mid femur. Specific injuries included Gustilo Type IIIB and IIIC tibia fractures, dysvascular limbs, and major degloving or soft tissue injury. Only those patients with a Glasgow Coma Scale score <15 at the time of discharge, concomitant spinal cord injury, or presumed difficulty in either being able to complete follow-up for distance or language reasons were excluded. The patients in this study were drawn from the much larger LEAP cohort and 2-year outcomes of knee dislocation with vascular injury that required limb salvage decision-making were compared with the outcomes for normal populations.
patients with an isolated below knee amputation, through knee amputation, and patients with an isolated above knee amputation. The latter groups were selected, as these represent the alternative treatments for patients with knee dislocations associated with vascular injury.

There were 11 men and 7 women with all but 1 of the patients younger than 55 years. The mechanism of injury was a motor vehicle crash in four patients, a pedestrian versus motor vehicle crash in three patients, a fall in five patients, and a motorcycle crash in three patients. Mechanism of injury was not reported in three patients.

At 24 months, range of motion was measured by physical therapists following a standard protocol. Knee flexion and extension strength measurements were made using a custom designed myometer. The myometer was designed at Carolinas Medical Center to accommodate the fact that not all centers had isokinetic strength-testing machines available and hand-held myometers were not of sufficient resistance to enable maximum force production in the lower extremity. The time to walk 150 feet was quantified in seconds, and patients were instructed to walk at their normal pace and use walking aids as needed. At 24 months, an orthopedic surgeon examined knee stability, which was classified as stable, mildly unstable, or grossly unstable. Outcomes were determined with the Sickness Impact Profile (SIP). The SIP is a well-validated multidimensional measure of overall health status quantified in 12 categories and 2 major domains of physical health and psychosocial health. SIP scores >10 represent significant disability.

RESULTS

In this study group of 18 patients, 14 patients were treated with limb salvage and 4 patients were treated with an amputation. All the amputations were performed at the time of the initial hospitalization, and no patients in the limb salvage group required late amputation.

Sixteen legs had at least a popliteal injury repair requiring repair. Five of the 18 popliteal injuries had other arterial injuries and 2 underwent additional repairs. In the two patients who had additional repairs, one patient had an isolated suprapopliteal arterial injury requiring repair and one patient had a combined posterior and anterior tibial artery injury.

Eleven of the patients received four compartment fasciotomies. Orthopedic stabilization of the initial injury included bridging external fixation in four patients and plating of an associated tibial plateau fracture in two patients. Four patients had saphenous vein grafts and one patient had a great saphenous artery graft. One patient had an unidentified shunt. Ligamentous repair was performed on a delayed basis after successful revascularization, as the restoration of circulation was the primary consideration in patients with knee dislocation and limb ischemia. In delayed reconstruction of the knees, a tourniquet was used in three of the seven cases. In the seven patients with delayed reconstruction, three patients had anterior cruciate ligament reconstruction and two patients had posterior cruciate reconstructions.

The warm ischemia time was 1 hour in two patients, 2 hours in one patient, 3 hours in two patients, 4 hours in two patients, 5 hours in three patients, 6 hours in three patients, and more than 6 hours in five patients. Two patients had no warm ischemic time documented in the records. The average warm ischemia time for those patients treated with amputation was 7.25 hours (range 3–11 hours). The average warm ischemia time for those patients treated without an amputation was 4.7 hours (range 1–9 hours) (p = 0.11). Two of the five patients with warm ischemia time of more than 6 hours required amputation. There were eight patients with absent plantar sensation identified at the time of presentation, and four of the eight patients had delayed amputation.

Fourteen of the 18 patients had an arteriogram as part of their evaluation. The diagnosis and treatment of the vascular injury was based upon plain radiographs and clinical assessment of the limb in the other four patients. The average warm ischemia time for patients who were evaluated by an arteriogram was 5.1 hours, and the average warm ischemia time for those patients treated without an arteriogram was 6 hours. The difference was not statistically different.

The SIP score for all patients with a limb-threatening knee dislocation was 9.11 at 24 months. In the larger cohort of patients in the LEAP study, the SIP scores at 2 years for 330 patients in the LEAP study who had limb salvage was 11.8, and for 130 patients who had an amputation in the LEAP cohort, the SIP score was 12.6. The average SIP score for the patients who had a salvage of the limb after a knee dislocation was 7.0, when compared with the patients who underwent amputation for whom the average score was 16.1. Assuming unequal variances, the difference between these two groups was not statistically significant (p = 0.32). There was no significant difference between the knee dislocation group treated with salvage and the overall LEAP population treated with salvage (p = 0.12). The lack of statistical significance may be caused by the small sample size in the amputated group (n = 4).

Knee flexion at 24 months was decreased 30% with an average arc of motion of 118 degrees (70–135 degrees) compared with 130 degrees in the unaffected leg (90–135 degrees). Flexion strength as measured by myometer averaged 228.6 lbs (94–300 lbs) on the affected side when compared with 390 (212–630 lbs) on the unaffected side, a 38% decrease in strength. Extension strength as measured by myometer averaged 454 lbs (142–963 lbs) in the affected knee when compared with 568 lbs (172–985 lbs) on the unaffected side, a 13% reduction in extension strength.

At 24 months, clinical knee examinations demonstrated that two knees were stable in all directions. Three knees were stable in three of four directions with mild residual instability in one direction. The remaining six knees that had clinical examination at 24 months were either mildly or grossly unstable in at least two directions.
Knee dislocations with associated vascular insult are generally the result of high-energy mechanisms of injury. The anatomy of the knee joint, the tethering of the artery above and below the knee, and limited collateral circulation around the knee contribute to the danger of a major vascular injury with a knee dislocation. The effective treatment of a knee dislocation with an associated vascular injury requires a system of care that includes prehospital rescue, rapid transport to an appropriate facility, timely evaluation, and a coordinated plan whose primary goal is to restore blood flow to the limb. A team composed of vascular surgeons, general surgery trauma surgeons, orthopedic surgeons, and interventional radiologists often develop the institutional protocols to facilitate expedient evaluation and care of these injuries.

The assessment of patients with a knee dislocation has changed during the past 2 decades, as the experience in the management of these varied and complex injuries has increased. Routine arteriography was strongly recommended for all knee dislocations after early studies that reported the association of vascular trauma with knee dislocation and the adverse outcomes related to the failure to identify an arterial injury. As the number of negative arteriographic evaluations mounted and cost-effectiveness became more important, later studies demonstrated the value of clinical examination and the benefit of selective angiography.

Treiman et al. advised selective angiography based upon clinical examination as all significant arterial injuries were identified based upon abnormal or absent pulses distal to the zone of injury. However, the role of arteriography remains controversial. Barnes et al. performed a meta-analysis in an effort to define the sensitivity and specificity of physical examination for the diagnosis of arterial injury in patients with knee dislocation. The meta-analysis concluded that the presence of abnormal pedal pulses on initial examination was not sufficiently sensitive to detect surgically important vascular injuries. Barnes et al. also questioned the use of arterial pressure index in cases of blunt trauma to the knee as the reports of its use were based largely on patients with penetrating injury. The authors strongly recommended a low threshold for arteriography in the setting of a knee dislocation. Alternatively, Miranda et al., in a prospective series of 35 knee dislocations, an investigation not included in the meta-analysis study by Barnes et al., reported that physical examination reliably identified patients with vascular injury, and none of the patients with a negative physical examination developed limb ischemia, needed an operation for treatment of a vascular injury, or suffered limb loss. Miranda et al. concluded that a normal physical examination reliably excluded significant vascular injury and routine arteriography was not indicated in all patients after knee dislocation. Miranda’s findings were confirmed by Stannard as their findings in patients with knee dislocations indicated the diagnosis of clinically significant vascular injury could be made on the basis of physical examination and angiography was not routinely required.

Restoring circulation in patients with an ischemic limb after knee dislocation is paramount for successful limb salvage and establishes the basis for a good outcome. It is important not to underestimate the value of a warm hand placed on a cold foot. In a patient with an absent pulse after reduction of a knee dislocation, the diagnosis is clear and the location of the vascular injury is defined by the zone of the injury, the popliteal fossae. Arteriogram has little value in this setting and usually prolongs the time to definitive treatment. Immediate surgical exploration by a vascular surgeon provides expedient restoration of blood flow. The surgical procedure often requires a saphenous interposition vein graft as the displacement of the knee joint places traction on the tethered vessels and simple end-to-end repair is frequently complicated by thrombosis. Prophylactic compartment release is warranted for most patients who require vascular repair; as the warm ischemia time, as measured from the time of injury, is frequently prolonged and there can be associated blunt injury to the muscle compartments in the lower leg adjacent to the knee.

Orthopedic management of the knee dislocation also remains controversial. Treatment recommendations include cast or brace immobilization, external fixation, primary repair of collateral ligaments with delayed reconstruction of one or both cruciate ligaments and primary repair and reconstruction of all soft tissue injuries. The surgical treatment of the knee injury depends upon institutional expertise, the age of the patient, the presence of other major injuries, and the status of the limb after vascular repair. Reconstruction and repair of multiple ligaments to restore stability and allow early range of motion is supported by several studies and most recommend surgery within 3 weeks of the injury. Multiply injured patients with an Injury Severity Score >26 are predisposed to the development of heterotopic ossification as reported by Mills and Tejwani. Early repair of the lateral and posterolateral ligamentous complex, spanning external fixation for up to 6 weeks and delayed arthroscopic cruciate reconstruction was advised for patients with Injury Severity Score >26.

Patients who had limb salvage after a knee dislocation with a limb threatening vascular injury had moderate levels of disability as measured by the SIP scores at 2 years. Those patients who had salvage of the knee had a SIP <10 suggesting modest disability, whereas those who had amputation were much greater than 10. Amputees in the knee dislocation group had an overall score of 16.4 compared with the overall LEAP study amputees whose score was 12.6. This may have been caused by the small sample size, but the trend toward...
higher disability in the knee dislocation group may be related to the higher proportion of through knee amputation patients. The small numbers failed to demonstrate statistical significance but there was a trend for less disability after successful revascularization and retention of the limb after knee dislocation with vascular injury. Patients who had a successful salvage of a dysvascular leg fared better than the salvaged limbs in the LEAP study (7.2 vs. 11.8). This can be attributed to the narrower zone of injury, less severe soft tissue trauma, and sparing of the distal lower extremity, especially the hindfoot, when compared with others in the LEAP group. Walking speed was reduced compared with normal patients, 90% had residual instability, and knee range of motion was reduced by 30%. Patients requiring amputation had warm ischemic time as the central factor determining the fate of the limb in this cohort. The knee dislocation needs to be quickly recognized and transported to a center with vascular repair capability.

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REFERENCES

Exchange Nailing for Aseptic Nonunion of Femoral Shaft: A Retrospective Cohort Study for Effect of Reaming Size

Chi-Chuan Wu, MD

Background: Exchange nailing has been the favored method to treat aseptic nonunions of the femoral shaft. The recommended amount of over-reaming is at least 2 mm. The purpose of this study was to determine whether the effectiveness of nonunion treatment is greatly reduced with less than 2 mm of over-reaming.

Methods: Aseptic nonunions of the femoral shaft were treated by exchange nailing with 1 mm (n = 37) or at least 2 mm (n = 44) of over-reaming. Union rates, union periods, and complications were compared. Indications for exchange nailing were aseptic nonunions of the femoral shaft with an inserted intramedullary nail, shortening of less than 1.5 cm, and a fracture gap of less than 5 mm.

Results: After a mean follow-up of 3.6 years (range, 1.1–7.1 years), union rates were 31 (91.2%) of 34 nonunions with over-reaming of 1 mm and 37 (92.5%) of 40 nonunions with over-reaming of 2 mm or more (p = 0.32). The mean union periods were 4.4 months (range, 2.5–8 months) and 4.4 months (range, 3–8 months), respectively (p = 0.83). Except for persistent nonunions, no significant complications occurred.

Conclusions: Exchange nailing can be considered the first choice to treat aseptic nonunions of the femoral shaft. The diameter of the new intramedullary nail should be as large as possible to reinforce the mechanical strength of the repair. The osteogenic potential stimulated by the reaming of cancellous bone graft was similar with over-reaming of 1 mm and with over-reaming of 2 mm or more.

Key Words: Exchange nailing, Femoral nonunion, Reaming size.

Although some skeptics still exist, most orthopedists have favored exchange nailing as the treatment of choice for aseptic nonunions of the femoral shaft and success rates of 53% to 100% have been reported. The main advantages of this technique are its possible high union rates, low complication rates, and relative technical simplicity. In addition, the incision is always small and a second wound is not needed to procure the cancellous bone graft. Therefore, the patient is usually able to walk early postoperatively and patient discomfort is often minimized.

The principles of treating aseptic nonunions are providing sufficient stability and stimulating the osteogenic potential of the bone during fracture healing. With advances in modern technology, current intramedullary nails generally provide sufficient stability. Therefore, the key factor for successful treatment is how to effectively stimulate the osteogenic potential. Although surgical or nonsurgical methods may be chosen, cancellous bone grafting has been reported to have the highest success rate.

The amount of over-reaming needed for successful exchange nailing is not well defined. Over-reaming of at least 2 mm is usually recommended. However, this amount can not always be achieved in clinical practice because previous reaming might have been maximal and the previous intramedullary nail might have been the largest possible. Whether exchange nailing can be performed in this situation is unclear. The purpose of this retrospective study was to determine whether the effectiveness of treating nonunion was greatly reduced with less than 2 mm of over-reaming and concomitantly to evaluate the feasibility of femoral exchange nailing.

Patients and Methods

Between January 1996 and December 2003, 79 consecutive adults (mean age, 34 years; age range, 18–73 years; male to female ratio, 2:1) with 81 aseptic nonunions of the femoral shaft were treated with exchange nailing at the author’s institution (the author performed all the procedures). All nonunions were caused by failed treatment of the fractures, all of which were resulting from motor vehicle crashes. The period between injury and revision surgery was 0.5 to 9 years (mean, 2.4 years) and patients underwent one to four operations (mean, 1.7 operations). Six fractures had been deeply infected but no recurrence was noted for at least 1 year after treatment with intravenous administration of antibiotics.

Patients were examined in the author’s outpatient department to carefully evaluate their wounds and healing of the fractures. Range of motion (ROM) of the knee was measured with use of a goniometer. Leg length discrepancy was evaluated by measuring the spinomalleolar distance with or without a scanogram. Patients with a leg length discrepancy of more than 1.5 cm were treated with a lengthening technique and excluded from this study. ROM of the knee was not concomitantly treated and was preserved until the nail was...
removed. Patients with a fracture gap of more than 5 mm, as shown on plain radiographs, were excluded; for these patients, open cancellous bone grafting was considered more appropriate than exchange nailing.

When the patients were admitted for revision surgery, their complete blood counts, erythrocyte sedimentation rates, and levels of C-reactive protein were routinely checked. For all patients, the laboratory data were within the normal range. Patients with suspected latent infection were treated with external fixation and excluded from this study.

Indications for exchange nailing were aseptic nonunion of the femoral shaft with an inserted intramedullary nail, shortening of less than 1.5 cm, and a fracture gap of less than 5 mm.

**Surgical Technique**

When the patient had a fracture that did not require the insertion of distal locked screws to maintain its stability, the patient was given spinal anesthesia and placed on the operating table in the lateral decubitus position. The previous intramedullary nail was removed. A flexible guide wire was inserted, and the marrow cavity was reamed as widely as possible (until the strong resistance against the reaming was felt). An intramedullary nail (Küntscher nail, Zimmer, Warsaw, IN; Grosse-Kempf locked nail, Howmedica, Kiel, Germany; or Russell-Taylor locked nail, Smith & Nephew, Memphis, TN), 1 mm smaller than the hole, was inserted.

When the patient had a fracture requiring the insertion of distal locked screws to maintain its stability, the patient was given general anesthesia with endotracheal intubation and placed on the fracture table in the lateral decubitus position. A 2.4-mm Kirschner wire was inserted in the femoral condyle for skeletal traction. As with the other patients, the previous intramedullary nail was removed and the marrow cavity was reamed as widely as possible. A Grosse-Kempf or Russell-Taylor locked nail, 1 mm smaller than the hole, was inserted. The dynamic mode of a locked nail was used if possible, and the proximal diagonal screw was not inserted.

The indications for using a static locked nail were narrowed. For the patient who had shortening of 1 cm to 1.5 cm, a static locked nail was reinserted to prevent further shortening. For the patient whose previous nail had been the maximal diameter (i.e., 14 mm), further over-reaming of 1 mm more than the previous reaming (i.e., 16 vs. 15 mm) was performed, and a static locked nail of the 14-mm diameter was inserted. In this series, the size of used nails was 12 mm to 14 mm and the majority was 13 mm.

After surgery, antibiotics were not administered, and walking with aids was encouraged as early as possible. Use of the aids was advised for 3 months, after which patients could stop using them as warranted.

Patients were followed up at the outpatient department every 1 to 1.5 months. Healing of the fracture was clinically and radiographically recorded. Complications were managed as necessary. After the fracture healed, the patient was advised to return for annual follow-up and whenever necessary. Removal of the nail was recommended at 2 years if the fracture had healed completely.

Union was defined as no pain or tenderness on clinical examination and the ability to walk without aids. On radiographs, a callus with cortical density had bridged both fragments.8,16 Nonunion was noted when the fracture did not heal after 1 year of treatment or when a repeat operation was needed to achieve union.8,15

Patients were divided into two groups (Tables 1 and 2). Group 1 comprised patients who received over-reaming of 1 mm more than the previous amount, and group 2 comprised those who received over-reaming of at least 2 mm more than the previous amount (i.e., 1 mm plus the diameter of the nail).

**Statistical Analysis**

The two groups of patients were compared to investigate the effect of the reaming size. For the convenience of comparison, the Fisher’s exact test, χ², and unpaired Student’s t test were used. p < 0.05 indicated a significant difference.

**RESULTS**

Seventy-two patients with 74 fractures were followed up for at least 1 year (mean, 3.6 years; range, 1.1–7.1 years) and seven patients were lost to follow-up despite best efforts to contact. Group 1 included 34 patients with 34 fractures, and group 2, 39 patients with 40 fractures (Tables 1–3). One patient was assigned to both groups (as patient 18 in group 1 and as patient 15 in group 2) and another patient had two fractures and was twice assigned to group 2 (as patients 26 and 27).

Union was achieved in 68 fractures, including 31 (91.2%) of 34 fractures in group 1 and 37 (92.5%) of 40 fractures in group 2 (p = 0.32) (Figs. 1–3). Therefore, the overall union rate was 68 (91.9%) of 74 fractures. Overall, the mean union period was 4.4 months (range, 2.5–8 months). Mean union periods were 4.4 months (range, 2.5–6 months) for group 1 and 4.4 months (range, 3–8 months) for group 2 (p = 0.83).

In group 1, seven nonunions were treated with a static locked nail and all fractures healed uneventfully. In group 2, 11 nonunions were treated with a static locked nail and 2 persisted (p = 0.36).

No perioperative complications occurred and patients were admitted for 3 to 5 days. No wound infections or malunions (shortening >2 cm, angular deformity >10 degrees, or rotational deformity >10 degrees) were observed.

Six fractures were considered nonunions because they did not heal after a period of 1 year. Because the patients had no complaints and because they hesitated in undergoing a second surgery, the nonunions were simply followed up on a regular basis. However, one of the nonunions unexpectedly healed after 2 years (as patient 31 in group 2) (Fig. 4).

Forty-two patients underwent implant removal after 2 years, and six patients were concomitantly treated with Judet...
quadricepsplasty to improve ROM of their knees. At last follow-up, all patients could flex their knees more than 110 degrees.

DISCUSSION

Factors that promote fracture healing are a minimal gap, adequate stability, and sufficient nutritional supply. After closed reamed nailing with a locked or unlocked intramedullary nail became the treatment of choice for closed or mild open fractures of the femoral shaft, nonunions gradually become uncommon. Even so, the nonunion rate for comminuted fractures can be as high as 10%, though most articles report a union rate of more than 95%. Currently, nonunions of the femoral shaft are most common in cases involving open reduction because intramedullary and periostal vascularity are severely destroyed. Therefore, the key factor for effective treatment is to stimulate the osteogenic potential of the bone.

To stimulate the osteogenic potential, surgical or nonsurgical methods can be used. Among the nonsurgical treatments, electrical stimulation, low-intensity pulsed ultrasound, and shock wave therapy have had clinical success. The highest success rate is around 80% to 86%. For surgical treatment, dynamization of a static locked nail, open cancellous bone grafting, and exchange nailing to provide an internal cancellous bone graft have been reported. A success rate of about 50% can be achieved with dynamization. However, open bone grafting or exchange nailing can achieve a success rate of 53% to 100%, as reported in most articles.

Table 1 Clinical Data of 37 Patients With 37 Aseptic Nonunions of Femoral Shafts Treated With Exchange Nailing by Over-Reaming of 1 mm

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<th>Method of Last Operation</th>
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A, upper-third; B, middle-third; C, lower-third; F, female; K, Küntscher nailing; M, male; N, nonunion; T, lost; DK, double Küntscher nailing; DL, dynamic locked nailing; OK, open Küntscher nailing; SL, static locked nailing; CDL, closed dynamic locked nailing; CSL, closed static locked nailing; ODL, open dynamic locked nailing; OSL, open static locked nailing.
In clinical practice, exchange nailing seems to be more convenient and more often advocated than the other options.\textsuperscript{3–6} Although exchange nailing has a variable success rate of 53\% to 100\%, a union rate of 91.9\% was achieved in this study.\textsuperscript{1–3,7–9} Because this technique has few complications except for persistent nonunions and because the surgical technique is relatively simple, it should be considered the first choice for most cases of aseptic nonunions of the femoral shaft. Should nonunions persist, many techniques can be tried.\textsuperscript{3,6–9,28,29} In this study, one of six persistent nonunions spontaneously healed after 2 years. Because the nonunion was treated with a dynamic locked nail, a weight-bearing effect undeniably played a role.

The most important aim of this study was to investigate the effect of reaming size on therapeutic success. In the literature, at least 2 mm of over-reaming is recommended, but no definite value has been established, to the author’s knowledge.\textsuperscript{1,5,9} Large-diameter intramedullary

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A, upper-third; B, middle-third; C, lower-third; F, female; K, Küntscher nailing; M, male; N, nonunion; T, lost; DK, double Küntscher nailing; DL, dynamic locked nailing; OK, open Küntscher nailing; SL, static locked nailing; CDL, closed dynamic locked nailing; CSL, closed static locked nailing; ODL, open dynamic locked nailing; OSL, open static locked nailing.
nails are theoretically stronger than small-diameter nails and may reduce the incidence of nail breakage. Therefore, patients usually receive intramedullary nails of the largest diameter possible. In practical terms, when a patient undergoes exchange nailing, a nail with a diameter larger than that of the previous one might not be available. In this situation, the surgeon may doubt if over-reaming of 1 mm is effective, and if a nail of appropriate size can be inserted after reaming is performed. Results of this study revealed that even 1 mm of over-reaming was effective and that a static locked nail can be used to stabilize the fragments with a 2-mm smaller nail.

In a nonunion site, fibrous tissues usually occupy the fracture gap. Whether over-reaming is 1 mm or 2 mm or more, the interface between the fibrous tissues and the marrow cavity should theoretically be coated with only a thin layer of cancellous bone. In this study, both groups of patients had similar union rates, suggesting that reaming size did not affect the ability to stimulate the osteogenic potential of the bone. In practical application, the success rate of even simply over-reaming by 1 mm was high. Additional over-reaming cannot supply more cancellous bone graft material for the fracture site.

The gap size that can still be treated with exchange nailing is unclear. The amount of reamed cancellous bone

Table 3 Comparison of the Effect of Over-Reaming Between 1 mm and 2 mm or More in the Treatment of Aseptic Nonunions of the Femoral Shaft

<table>
<thead>
<tr>
<th>Item</th>
<th>1 mm Over-Reaming (n = 34)</th>
<th>2 mm or More Over-Reaming (n = 40)</th>
<th>p Value</th>
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<tr>
<td>Age (yr)</td>
<td>32 (18–70)</td>
<td>36 (18–73)</td>
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<tr>
<td>Male/female</td>
<td>23/11</td>
<td>28/12</td>
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<tr>
<td>M/3 fracture (%)</td>
<td>76 (26/34)</td>
<td>73 (29/40)</td>
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<td>Previous operating times</td>
<td>1.8 (1–3)</td>
<td>1.7 (1–4)</td>
<td>0.49</td>
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<tr>
<td>Interval from injury (yr)</td>
<td>2.8 (0.5–9.0)</td>
<td>2.1 (0.6–9.0)</td>
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<tr>
<td>Union rate (%)</td>
<td>91.2</td>
<td>92.5</td>
<td>0.32</td>
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<tr>
<td>Union period (mo)</td>
<td>4.4 (2.5–6)</td>
<td>4.4 (3–8)</td>
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<tr>
<td>Complication rate (%)</td>
<td>8.8</td>
<td>7.5</td>
<td>0.32</td>
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<tr>
<td>Follow-up (yr)</td>
<td>3.6 (1.1–6.7)</td>
<td>3.6 (1.2–7.1)</td>
<td>0.88</td>
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</table>

* Statistical difference.

Fig. 1. Case 9 in group 1. A 31-year-old man sustained a left comminuted middle-third femoral shaft fracture and was treated with a static locked nail. Nonunion occurred for 1.5 years and was treated with exchange nailing. Over-reaming of 1 mm was performed and a static locked nail was inserted. The fracture healed uneventfully at 5 months.

Fig. 2. Case 12 in group 1. A 24-year-old man sustained a right middle-third femoral shaft nonunion with shortening of 3 cm for 16 months. One-stage lengthening with static locked nail insertion was performed. However, nail breakage at the proximal slot end (arrow) occurred at 8 months. Exchange nailing with over-reaming of 1 mm was performed and a static locked nail was inserted. The fracture healed uneventfully at 5 months.

Fig. 3. Cases 26 and 27 in group 2. A 21-year-old man sustained right middle-third and left lower-third femoral shaft nonunions for 1.5 years. Exchange nailing with over-reaming of 2 mm was performed and static locked nails were inserted. The fractures healed uneventfully at 4.5 and 4 months, respectively.
implant failure can be reduced.30,36 Second, parts of loads are transmitted through the nonunion site, and the fracture healing process was very slow. Although it was classified into the persistent nonunion, the fracture healed at 2 years finally.

Additional over-reaming of the marrow cavity has an advantage. An intramedullary nail with a diameter larger than that of the previous nail can be inserted. Therefore, nail strength can be reinforced and the incidence of nail breakage can be reduced.30–33 Of note, larger diameter locked screws must be used with locked nails of more than 12 mm in diameter. Thus, the incidence of screw breakage can also be reduced. In most cases, when nonunion of the femoral shaft persists for a long time, the intramedullary nail may be vulnerable to fatigue failure because of cracking of the metal.34,35 If the nail is not replaced, the nail or locked screws may break. The insertion of a new nail can prevent this complication.

In this study, the dynamic mode of the intramedullary nail was preferred for several reasons. First, a dynamic intramedullary nail is a load-sharing device, and the rate of implant failure can be reduced.30,36 Second, parts of loads are transmitted through the nonunion site, and the fracture healing process can be reinforced.37 Third, the insertion of distal locked screws may not be needed, and the surgical technique can thus be simplified.

The mechanisms of treating aseptic nonunion with exchange nailing may be multiple. (1) Dynamic nails allow bone impaction and latent osteogenic potential of the fibrous callus is stimulated.38 (2) Reaming serves as autogenous bone grafts.38 (3) Osteogenic stimulation is caused by the trauma of reaming rather than the graft.39,40 (4) The reinjury of reaming re-establishes medullary vascular continuity during repair.41 (5) Added stability is provided by the larger nail.38,40,42 (6) Renewed cortical revascularization comes from ingrowth of periosteal vessels.43–45 (7) Osteoinductive properties come from reamed bone fragments and marrow elements.40,46 The present study supported the concept that reamed cancellous bone grafting is not the main factor in the success of exchange nailing, although it may be more obvious presumptively.

Choosing different anesthetic techniques were completely referred to patient operating position to insert both distal locked screws. Because distal locked screws were inserted using the free-hand technique, the patient was placed on the fracture table in the lateral decubitus position. This position was uncomfortable for the patient. Therefore, general anesthesia was used. If the patient operative position was supine, spinal anesthesia could also be used.

In most patients, ROM of the knee was nearly normal on initial examination. A few patients had extension contracture of the quadriceps femoris. In this study, ROM of the knee was not corrected while exchange nailing was performed. Quadricepsplasty normally requires a large dissection wound and the risk of infection and impaired healing of the fracture because of extensive soft tissue destruction may reduce the success rate.47 Therefore, therapy to improve ROM of the knee might be delayed until the implant is removed.

In conclusion, exchange nailing had a 91.9% success rate in the treatment of aseptic nonunion of the femoral shaft and can be considered the first choice for treating this condition. The diameter of the newly inserted intramedullary nail should be as large as possible to enforce the mechanical strength of the repair. The osteogenic potential stimulated by reaming for a cancellous bone graft was similar with over-reaming of 1 mm and with over-reaming of 2 mm or more. Therefore, the effect of reaming size may need no special emphasis.

REFERENCES


Encouraging Results of Treating Femoral Trochanteric Fractures With Specially Designed Double-Screw Nails

Jinn Lin, MD, PhD

Background: Conventional intramedullary nails for trochanteric fractures have the disadvantages of intraoperative splintering resulting from large proximal section and postoperative femoral fracture caused by stress concentration at the nail tip. The present study reports the experience of using a specially designed double-screw nail with a smaller proximal section to avoid intraoperative splintering and a longer nail shank to avoid postoperative femoral fracture.

Methods: Between 2003 and 2005, 144 consecutive femoral trochanteric fractures in 143 patients with an average age of 78.2 years were treated with double-screw nails. The OTA fracture classification was 31-A1 in 51 cases, 31-A2 in 65 cases, and 31-A3 in 28 cases. Seventy-nine patients had more than one major medical disease. The operation was performed using fluoroscopic guide on the fracture table. A distal locking screw was applied in patients with 31-A2 and A3 fractures. At 1 year, 23 patients had died and 6 were lost to follow-up, leaving 114 fractures for functional evaluation.

Results: Patients with 31-A1 fractures tended to have better preoperative conditions than those with 31-A2 and A3 fractures. Lag screw breakage occurred in four patients with 31-A2 and A3 fractures, and two of these also had screw backout. Another three patients had lag screw cutout. Among these seven patients, only one with screw cutout underwent revision of the fixation. All 114 fractures at 12 months had eventual union. Preoperative mobility was recovered in 35 (85%) patients with 31-A1 fractures and 45 (61%) with 31-A2 and A3 fractures. The functional recovery among patients with 31-A2 and A3 fractures was significantly worse than their preoperative condition and that of patients with 31-A1 fractures.

Conclusions: The double-screw nail can yield acceptable treatment results for both 31-A1 and 31-A2 and A3 trochanteric fractures and is particularly useful in patients with a small proximal femur. Type 31-A1 and 31-A2 and A3 trochanteric fractures should be separately analyzed in terms of treatment planning or prognostic study.

Key Words: Femoral trochanteric fractures, Double-screw nails.

W ith the increasing number of aged people with osteoporosis, the incidence of peritrochanteric fractures has also risen.1,2 Because these fractures are associated with significant mortality and morbidity, they are rapidly increasing society’s health care expenditures. The standard treatment for femoral trochanteric fractures is internal fixation with a sliding screw plate,2 an approach introduced in the 1950s to replace the fixed-angle nail plate. The greatest advantage of the sliding screw device is that the sliding of the lag screws in the barrel of the side plates facilitates fracture impaction and healing and prevents lag screw cutout.1,2 In unstable fractures, however, this device does not perform as well.1–5 Excessive sliding of the lag screw may result in limb shortening, lag screw cutout, and significant functional impairment. The intramedullary device has been used in an attempt to improve treatment results.6–11 It provides a better biomechanical environment with a shorter lever arm to reduce the hardware load, as well as the risk of mechanical failure, and offers an effective control of lag screw sliding to prevent femoral shortening and hip deformity. Percutaneous insertion of the nail may further reduce the soft tissue trauma and lower the risk of infection or nonunion. However, the intramedullary devices for trochanteric fractures, either first or second generation, have the disadvantages of intraoperative splintering as a result of the bulky proximal part and postoperative femoral fracture via the nail tip because of stress concentration.2,7,8,12,13 A third-generation nail with a smaller proximal part and multiple lag screws has been introduced,9 but there are still few clinical reports of using this kind of nail,10 especially the use of long versions of the nail.11

This prospective cohort study reports our experience of using specially designed double-screw nails, which are long version nails with a small proximal section. The study tested the hypothesis that this nail could be effectively used for femoral trochanteric fractures.

MATERIALS AND METHODS

Nail Design

The double-screw nail (United, Taipei, Taiwan) made from ASTM138 stainless steel is a cannulated straight tube with a proximal curvature of 7 degrees located 8 cm from the threaded end (Fig. 1). The proximal part of the nail is 13 mm...
in diameter, and the distal part is either 10.5 or 9.5 mm with a wall thickness of 2 mm. Proximally, there are two oblique lag screws with a 6.5-mm diameter and a 45-degree angle to the axis of the nail. The lag screws have a round neck collar to exert compression and prevent medial migration. The distance between the lag screws is 1.5 cm. The diameter of the transverse locking screw at the distal nail end is 4 mm. The nail length is 300, 320, or 340 mm.

**Patients**

From July 2003 to January 2005, 144 consecutive femoral trochanteric fractures in 143 patients with an average age of 78.2 years were treated with the use of double-screw nails and prospectively followed up. The inclusion criteria were an age of at least 60 years, no history of fractures or operations involving the ipsilateral hip, a femoral anatomy that allowed intramedullary nailing, and a general condition that could tolerate anesthesia and operation. The exclusion criteria were pathologic fractures, Paget diseases, fractures involving the femoral neck, and fractures for more than 2 weeks. The Institute Review Board approved the investigation plan, and all patients provided informed consent. The preoperative parameters that were recorded included age and gender, body mass index, bone mineral density, medical history, mental status, social functioning status, and mobility (Table 1). Preoperative surgical risk was classified according to ASA (American Society of Anesthesiologist) classification (I–V). Mental status was assessed with the Abbreviated Mental Test Score (0–10). Social functioning was defined according to the Jensen index (1–4). Mobility was assessed with the mobility score of Parker and Palmer (0–9). The fractures were classified on the basis of OTA/AO classification: A1, simple two-part pertrochanteric fracture (51 cases); A2, pertrochanteric fracture with intermediate fragments (65 cases); A3, intertrochanteric fracture (28 cases). In total, 79 patients—of whom 23 had 31-A1 and 56 had 31-A2 and A3 fractures—had more than one major medical disease, such as dementia, brain stroke, Parkinsonism, endocrine diseases (including diabetes mellitus, hypothyroidism, etc.), ischemic heart disease, renal failure, liver cirrhosis, multiple compression fracture of the spine, malignancy, or some other major medical disease requiring active treatment. Spinal anesthesia was used in 131 patients, and endotracheal general anesthesia was used in the rest. The intraoperative blood transfusion, operative time, and intraoperative complications were recorded, as were data pertaining to the

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### Table 1 Preoperative and Perioperative Conditions

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<tr>
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<th>Stable Fracture (n = 51)</th>
<th>Unstable Fracture (n = 59)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>75.3 ± 8.8</td>
<td>79.5 ± 10.4</td>
<td>0.018*</td>
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<tr>
<td>Men:women</td>
<td>16:35</td>
<td>26:67</td>
<td>0.79</td>
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<td>Body mass index (kg/m²)</td>
<td>24.3 ± 7.6</td>
<td>27.7 ± 8.2</td>
<td>&lt;0.01*</td>
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<td>Bone mineral density (T-score: SD)</td>
<td>-2.01 ± 0.73</td>
<td>-2.32 ± 0.85</td>
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<td>ASA classification</td>
<td>2.7 ± 0.9</td>
<td>3.0 ± 1.1</td>
<td>0.10</td>
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<tr>
<td>More than one major medical diseases</td>
<td>23</td>
<td>56</td>
<td>0.16</td>
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<td>Mental score</td>
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<td>6.5 ± 2.6</td>
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<td>Jensen index</td>
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<tr>
<td>Mobility score</td>
<td>6.5 ± 2.3</td>
<td>5.9 ± 2.6</td>
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<td>Operation time (min)</td>
<td>41.2 ± 9.9</td>
<td>63.6 ± 15.2</td>
<td>&lt;0.01*</td>
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<td>Without walking aid</td>
<td>35</td>
<td>50</td>
<td>0.12</td>
</tr>
<tr>
<td>Fracture reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>39</td>
<td>72</td>
<td>0.94</td>
</tr>
<tr>
<td>Acceptable</td>
<td>12</td>
<td>16</td>
<td>0.49</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>5</td>
<td>0.11</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>6.8 ± 2.5</td>
<td>10.1 ± 3.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Preoperative delay (days)</td>
<td>1.6 ± 1.1</td>
<td>1.9 ± 1.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, unless otherwise indicated.
* Statistically significant.
mode of fixation, including the diameter and length the nail, and the use of distal locking screws. The type of reduction was graded as good, anatomic reduction or slight valgus position compared with the contralateral side; acceptable, <10 degrees varus position; or inadequate, >10 degrees varus position. All patients received antibiotic prophylaxis with one dose of intravenous first-generation cephalosporin before induction of the anesthesia and one more dose 12 hours after operation. Patients were permitted to get out of bed and sit on a wheel chair on the second postoperative day. Walking with assistance was encouraged as early as tolerable. If the patients could not walk because of poor medical condition or a 31-A2 or A3 fracture, active exercise of hip joints was instructed. The patients were regularly followed up every 2 weeks during the first 3 months, and then every 1 to 2 months until 1 year. The radiographs and the patients were examined at each follow up. Average follow-up time was 19.5 months (range 15 to 25 months). Mental status, social functioning, and mobility score were reevaluated at 12 months and compared with preoperative data. Leg length was evaluated by scanogram. A surgeon blinded to the radiologic findings evaluated the functional recovery.

Pre operative conditions and postoperative treatment results were compared between 31-A1 fractures and 31-A2 and A3 fractures. Statistical methods were Student’s t tests for continuous variables and \( \chi^2 \) tests or Fisher exact tests where appropriate for binary variables. Multiple regression tests were used to examine the relationship of femoral shortening to age, preoperative mobility index, bone mass index, and bone mineral density in 31-A2 and A3 fractures.

**Operative Technique**

The patient is placed in supine position on a radiotransparent fracture table. The trunk is tilted toward the nonoperated side and the hip joint is adducted to ensure sufficient room for antegrade nailing (Fig. 2). Pelvis obliquity is important to avoid the obstruction of the iliac crest. The fracture is first reduced in a closed manner by applying an axial traction to the leg. The fracture reduction is examined with a fluoroscope in both anteroposterior and lateral views. Then a longitudinal skin incision about 3- to 5-cm long is made proximal to the greater trochanter. The fascia lata is incised and the wound is carried down bluntly to expose the piriformis fossa. An awl is used to create the entry portal right medial to the greater trochanter and anterior to the piriformis tendon. A 3-mm guide wire is inserted into the intramedullary canal, passing through the fracture site. The femoral canal is gently reamed with flexor reamers sequentially. After adequate reaming, the nail is manually inserted with use of fluoroscopic guide until the distal lag screw hole is lined up with the inferior cortex of the femoral neck. Then 3-mm predrill holes for lag screws are made with use of the guide of a targeting device attached to the proximal nail end. The predrill hole for the distal lag screw should be as close as possible to the inferior cortex of the femoral neck in the

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**Fig. 2.** Schematic diagram of ideal position of patient for nailing. (A) adequate pelvic obliquity, (B) insufficient pelvic obliquity and the iliac crest may obstruct the nailing. The arrows indicate the nailing direction.
posteroanterior view and at the center of the femoral neck in the lateral view. Two lag screws are inserted sequentially with the screw tip at a distance about 10 mm from the subchondral bone of the femoral head. During screw insertion, the screw cap is tightened against the lateral femoral cortex for interfragmentary compression. In patients with 31-A2 and A3 fractures or a wide medullary canal, one distal locking screw is applied with the use of the guide of the targeting device or fluoroscope.

RESULTS

The patients with 31-A1 fractures tended to have better preoperative conditions (Table 1), but with the available number of patients, only age, bone mineral density, and body mass index were significantly different at the level of \( p < 0.05 \). No blood transfusion was necessary for the operation. The operation time and hospital stay were significantly shorter for 31-A1 than for 31-A2 and A3 fractures. Seven 31-A2 and A3 fractures required a semi-open approach to achieve reduction. The nail diameter used was 9.5 mm in 85 fractures and 10.5 mm in 59. The nail length was 300 mm in 23, 320 mm in 108, and 340 mm in 13. Distal locking was performed in 16 31-A1 fractures and all of the 31-A2 and A3 fractures. Immediate postoperative radiographs showed good reduction in 99 fractures, acceptable in 38, and poor in 7. The accumulated mortality rate was 3 in the hospital, 16 in the first 6 months, and 23 at 1 year. At discharge, 102 patients could walk at least a short distance with the assistance of walkers. All other patients, except the 13 originally bedridden patients, could sit on wheel chairs. Fifty-five patients were admitted to the intensive care unit for more than 1 day because of pneumonia, heart failure, brain stroke, or other severe medical complications. In our early experience, lag screws backed out in four fractures at 3 to 8 months (Fig. 3), and two of them were associated with screw backout (Fig. 5). However, the fractures went on to union with different degrees of femoral shortening. Lag screw cutout of the femoral head occurred in another three 31-A2 and A3 fractures at 2, 6, and 12 months. Among these seven patients, one with lag screw cutout underwent revision of the fixation (Fig. 6). The other six patients, among whom two had implant removal, could still walk with aids and refused further revisional operation. Excluding 23 deaths and six losses to follow-up, the functional recovery could be assessed in a total of 114 patients with 114 fractures at 12 months after operation, including 41 31-A1 fractures and 73 31-A2 and A3 fractures (52 A2 and 21 A3). Eventual fracture union (defined as visible solid bridging callus across the fracture site on the radiographs and the subjects being able to close as possible to the inferior cortex of the femoral neck. Lag screw breakage occurred in four 31-A2 and A3 fractures at 3 to 7 months (Fig. 4), and two of them were associated with screw backout (Fig. 5). However, the fractures went on to union with different degrees of femoral shortening. Lag screw cutout of the femoral head occurred in another three 31-A2 and A3 fractures at 2, 6, and 12 months. Among these seven patients, one with lag screw cutout underwent revision of the fixation (Fig. 6). The other six patients, among whom two had implant removal, could still walk with aids and refused further revisional operation. Excluding 23 deaths and six losses to follow-up, the functional recovery could be assessed in a total of 114 patients with 114 fractures at 12 months after operation, including 41 31-A1 fractures and 73 31-A2 and A3 fractures (52 A2 and 21 A3). Eventual fracture union (defined as visible solid bridging callus across the fracture site on the radiographs and the subjects being able to
move their hip without significant pain) was achieved in all these patients (Fig. 7). The mean Jensen index and mobility scores were decreased as compared with those of the prefracture condition (Table 2). The difference reached a significant level only in 31-A2 and A3 fractures (p < 0.01 for Jensen index and p = 0.02 for mobility score). The mental scores did not differ significantly. The proportion of patients who walked unaided 1 year after operation was significantly higher in those with 31-A1 fractures. In the 41 patients with 31-A1 fractures, preoperative mobility was recovered in 35 (85%) and preoperative social functioning was recovered in 34 (83%). By contrast, in the 73 patients with 31-A2 and A3 fractures, preoperative mobility was recovered in 45 (61%) and preoperative social functioning was recovered in 43 (59%). Both of these differences were statistically significant (p < 0.01). Additionally, the patients with 31-A1 fractures had significantly better postoperative clinical results, including time to union, Jensen index, and mobility score (Table 2). At the same time, femoral shortening was significantly less severe in 31-A1 fractures than in 31-A2 and A3 fractures. Sixteen fractures had femoral shortening more than 1.5 cm, two of which were 31-A1 fractures and 14 were 31-A2 and A3 fractures (p = 0.013). In multiple regression analyses, the correlation coefficients of femoral shortening to age, preoperative mobility index, body mass index, and bone mineral density in 31-A2 and A3 fractures were 0.51, −0.46, 0.76, and −0.71 (p < 0.05), respectively. There were no intraoperative or postoperative femoral fractures. No patients had infection or notable venous thromboembolism.

**DISCUSSION**

Debate about the ideal fixation device for treatment of proximal femoral fractures continues. Similar to sliding screw plates, intramedullary devices allow telescoping of lag screws to facilitate fracture impaction, but they can also act as a lateral buttress to prevent excessive sliding. The conventional intramedullary nails for femoral trochanteric fractures, such as the gamma nail (Howmedica, Rutherford, NJ), intramedullary hip screw (Smith & Nephew, Memphis, TN), or proximal femoral nail (Synthes-Stratec, Oberdorf, Switzerland), have in common a bulky proximal part (17–17.5 mm) and a short nail length. The bulky proximal part requiring extensive over-reaming carries a risk of intraoperative trochanteric split and difficulty in later hip arthroplasty. It may also jam in the femoral canal, preventing insertion of the lag screw in a more ideal lower part of the femoral neck, and substantially prolong the operation. A short nail may cause intra- or postoperative femoral fracture because of the stress concentration around the nail tip at the isthmic part of the proximal femur. This complication may persist, no matter how the nail design or surgical technique is improved, if the patients have severe osteoporosis. However, whether to use nails or compression hip screws remains controversial. Some articles report similar final results, but others have found...
better walking ability in 31-A2 and A3 fractures treated by nails, especially after the surgical skills were improved.8,12,19

Third-generation nails with a smaller proximal part and two lag screws were developed to improve the weakness of conventional nails. Kubiak et al.23 conducted a biomechanical study comparing trochanteric antegrade nails (Smith & Nephew, Memphis, TN) with a proximal diameter of 13 mm and an intramedullary hip screw. They were similar with respect to screw sliding or femoral head displacement under cyclical loading, but trochanteric antegrade nails were better with regard to load to failure because the bulky intramedullary hip screw might cause more bone destruction. The double screw nail used in this study has a proximal diameter similar to that of trochanteric antegrade nails, but has a longer length. The nail can be manually inserted as deep as desired to place the lag screw at the proper position. With adequate reaming, the nail can snugly fit in the proximal femur without causing trochanteric split. The small proximal section can furthermore decrease the risk of disruption of hip abductors.9,24 The observation that no patients had intra- or postoperative femoral fractures in this study could be attributed to the length of the nail, which had passed the isthmic part of the femur and could effectively avoid the stress concentration on the femur.2 However, longer nails pose a potential problem of impingement on or even penetration through the anterior cortex of the distal femur, because of the disproportionate anterior bowing of the femur.2,25 In our experience, during operation, the surgeons might encounter

**Table 2** Data from Patients Who Could be Evaluated at 12 Months

<table>
<thead>
<tr>
<th></th>
<th>Stable Fracture (n = 41)</th>
<th>Unstable Fracture (n = 73)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to union (weeks)</td>
<td>12.3 ± 3.8</td>
<td>16.5 ± 4.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Simple screw backout</td>
<td>1</td>
<td>5</td>
<td>0.10</td>
</tr>
<tr>
<td>Screw breakage and backout</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Screw cutout</td>
<td>0</td>
<td>2</td>
<td>0.29</td>
</tr>
<tr>
<td>Jensen index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretrauma</td>
<td>1.7 ± 1.1</td>
<td>2.0 ± 1.2</td>
<td>0.19</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>2.2 ± 1.1</td>
<td>2.8 ± 1.3</td>
<td>&lt;0.014*</td>
</tr>
<tr>
<td>Mental score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretrauma</td>
<td>7.2 ± 2.1</td>
<td>6.7 ± 2.4</td>
<td>0.27</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>7.1 ± 2.5</td>
<td>6.5 ± 2.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Mobility score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretrauma</td>
<td>6.4 ± 2.2</td>
<td>6.1 ± 2.7</td>
<td>0.55</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>6.2 ± 2.1</td>
<td>5.1 ± 2.5</td>
<td>0.019*</td>
</tr>
<tr>
<td>Walking without aids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretrauma</td>
<td>27</td>
<td>41</td>
<td>0.42</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>23</td>
<td>26</td>
<td>0.026*</td>
</tr>
<tr>
<td>Femoral shortening (mm)</td>
<td>4.2 ± 3.3</td>
<td>9.8 ± 6.1</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, unless otherwise indicated.
* Statistically significant.
high nailing resistance when the nail tip abuts the distal femur. Converting to shorter or smaller nails could relieve this impingement. Although Robinson et al.25 have reported five cases of metaphyseal fractures distal to the tip of the long gamma nails with abutment of the nail tip against the distal anterior cortex,25,26 in the present study no patients had distal femoral fractures or significant knee pain resulting from this problem.

Theoretically, two lag screws could provide better rotational control of the femoral head fragment2,11 and decrease the cutout of femoral head by prevention of head fragment toggling.23 We considered that smaller screws might also decrease the likelihood of postnailing avascular necrosis of the femoral head27 and subcapital femoral neck fracture caused by big lag screws before or after implant removal.6,7,28 Although Loch et al.29 reported that the lag screw sliding is less effective in intramedullary nails than in sliding screw plates, the two parallel lag screws used in the present study did provide effective sliding and fracture impaction. Although excessive sliding could be limited by the nail (Fig. 8), in our study, femoral shortening was still high in 31-A2 and A3 fractures (average 9.8 mm; >15 mm in 20%). This femoral shortening was more severe in patients with osteoporosis and heavy weight. Besides poor preoperative functions, substantial femoral shortening with deformity of hip joints and weakness of hip abductors could explain the low proportion of patients, as low as 17%,30 who could recover the same level of prefracture daily activities. For the patients with 31-A2 and A3 fractures in the present study, preoperative mobility was recovered in 61% and social functioning was recovered in 59%.

Similar to previous reports,4,31 the patients with 31-A1 fractures in this study had more favorable preoperative conditions and better postoperative functional recovery than those with 31-A2 and A3 fractures. Many 31-A1 fractures with mild fracture displacement or comminution had quick and satisfactory functional recovery. We agree with Cornwall et al.31 that different fractures without equivalent outcome should not be grouped together. The need to improve the treatments and analyze the outcomes should be individually evaluated. We think the difference of the ratio of the stable or unstable fractures might be one of the causes responsible for the widely varying percentage of patients who could recover their pretrauma activities reported in the literature.32 It is widely accepted that a sliding screw plate is preferable to an intramedullary nail, especially for stable fractures, because of easier technique, lower complication rate, and lower cost.21 However, we think intramedullary nails with a small proximal section could also achieve satisfactory results for 31-A1 fractures with few complications. They have the further advantages of minimal tissue destruction and blood loss. Surgical technique is easier than that for conventional nails with a big proximal part, and the cost is relatively lower.

With an incidence ranging from 4% to 20%,2 lag screw cutout of the femoral head greatly threatens the results of trochanteric fracture treatment. The risk of screw cutout includes inadequate screw position, malreduction of the fractures, and osteoporosis. It is strongly recommended that the best position of the lag screw is at the lower part of the femoral neck because the compression trabeculae and tensile trabeculae of the proximal femur intersect at the lower part of the femoral neck and constitute the strongest architecture.7 Furthermore, the lower the lag screw is, the more the bone can resist cutting out. In the present study, screw cutout occurred in only 31-A2 and A3 fractures, especially those with varus fracture reduction. Varus displacement of the proximal femur may increase the load on the lag screw, decrease sliding capability, and decrease the bone mass to resist screw cutout. Rechecking the fracture reduction with the fluoroscope during operation is strongly recommended to prevent malreduction. To prevent screw loosening, we emphasize inserting the inferior lag screw as close as possible to—or even right on—the inferior cortex of the femoral neck. Doing so could prevent the so-called Z or reversed Z effects2 and could also increase the bone mass to resist screw cutout.

The entry portal of the nail has been controversial.33,34 In fact, the adequate entry portal depends on the nail’s design elements, such as angle of the proximal bend, the distance between nail tip and the bend, the length of the nail, and the size of the proximal part. Too lateral insertion of the nail on the trochanteric tip tends to cause trochanteric split, varus deformity, and damage to the gluteus medius tendon. We prefer inserting the nail right medial to the trochanteric tip and anterior to the piriformis tendon. This medial entry portal has the advantages of more linear insertion of the nail to decrease the nailing resistance, facilitation of fracture reduction in valgus position,33 and decrease of muscle and vessel injury.33,34 Furthermore, a medial entry portal could stop the sliding of the head fragment earlier than could a trochanteric

Fig. 8. (A) A 72-year-old man suffered an OTA type A2 trochanteric fracture. (B) Postoperative radiograph showed telescoping of lag screws within the nail. Abutment of the femoral head and neck fragment against the intramedullary nail (arrows) could prevent excessive sliding.
tip entry portal and prevent femoral shortening more effectively. Pelvic obliquity to prevent obstruction of the iliac wing during operation is very important for a medial entry portal (Fig. 2), especially in obese patients.

The present study had some limitations that should be noted. The first was limitation of the follow-up time. The functional recovery was reported at 12 months after operation, which is the most commonly used time for eventual functional evaluation reported in the literature. Although it has been reported that improvement of hip functions seems to level off after approximately 6 months, in our observation, the patients’ daily functions might continue to improve for longer than 6 months. However, these functions might also be aggravated after 12 months, especially in patients with a poor general condition or hip joint deformity. Therefore, the time point selected for reporting the functional recovery is critical, especially in comparison with historical studies. However, radiologic finding usually didn’t change much after fracture healing, though some patients might have a certain degree of hip osteoarthritis at final follow-up. A second limitation is that pain, range of hip motion, and muscle power, which are important indicators of hip function, were not included in this study because of the difficulty of evaluating them in old patients with mental impairment. Social functional index and mobility score could be more objectively evaluated. The third limitation is that this was a single arm study without a concurrent control. The relative risks and benefits as compared with other devices were not demonstrated.

CONCLUSIONS

Preinjury conditions and postoperative functional recovery were significantly better in 31-A1 fractures than in 31-A2 and A3 fractures. These two kinds of fractures should be separately analyzed in terms of treatment planning or prognostic study. The double-screw nail can yield acceptable treatment results for both 31-A1 and 31-A2 and A3 fractures and is particularly useful in patients with a small proximal femur. However, implant design and surgical technique can be further improved to prevent femoral shortening and implant failure. A prospective randomized comparative study with other fixation devices is warranted.

REFERENCES

24. McConnell T, Tornetta PI, Benson E, Manuel J. Gluteus medius wing during operation is very important for a medial entry portal (Fig. 2), especially in obese patients.

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Prevalence of Pelvic Fractures, Associated Injuries, and Mortality: The United Kingdom Perspective

Peter V. Giannoudis, MD, EEC (Ortho), Martin R. W. Grotz, MD, Christopher Tzioupis, MD, Haralambos Dinopoulos, MD, Gareth E. Wells, MRCS, Otmar Bouamra, PhD, and Fiona Lecky, MD, FRCS

Background: We wished to determine the characteristics of patients with pelvic ring fractures (PGs) in England and Wales, and determine factors predicting mortality, including the impact of the presence of pelvic reconstruction facilities in the receiving hospitals on outcome.

Methods: Prospective data from 106 trauma receiving hospitals forming the Trauma Audit and Research Network database were studied. Between January 1989 and December 2001 data of 159,746 trauma patients were collected in the Trauma Audit and Research Network database. Because of incomplete data, 1,610 pelvic fracture patients and 13,499 patients without pelvic injury were excluded from the final analysis.

Results: There were statistically significantly more patients with an Injury Severity Score >15 in the PG group (n = 3,576; 32.1%) than in NPG group (n = 19,238; 14.4%) (p < 0.001), indicating that pelvic injuries were more often associated with other injuries. The majority of patients sustained Abbreviated Injury Score (AIS) 2 pelvic injuries (65.0%), whereas AIS 4 and 5 injuries were found in less than 10% of patients. Pelvic ring injuries were most commonly associated with chest trauma with >AIS 2 severity in 21.2% of the patients, head injuries (>AIS 2) in 16.9%, liver or spleen injuries in 8.0%, and two or more long bone fractures in 7.8%. The 3-month cumulative mortality rate of the patients with pelvic injuries was 14.2% (1,586 patients) versus 5.6% (7,465 patients) of the NPG group.

Conclusion: Age, early physiologic derangement, and presence of other injuries (head or trunk) were associated with reduced survival rates. When the expertise to deal with such a group of patients is not available, early transfer under safe conditions should be considered to improve survival rates.

Key Words: Pelvic fractures, Prevalence, UK perspective.

agement of serious injury in the United Kingdom. Patients that are included in the TARN database are those who are admitted to receiving hospitals for more than 3 days, referred to receiving hospitals and fulfill the aforementioned hospitalization length criterion, those who are transferred or admitted to intensive care units regardless of the presence of a pelvic injury, as well as those patients who have died from their injuries. The TARN database excludes patients aged more than 65 years with isolated fractures of the proximal femur or pubic rami. Up to December 2001, a total of 159,746 patients with injury admitted to 106 hospitals all over England and Wales were included in the TARN database. Data are collected by staff of the member hospitals on dedicated data collection forms relating to the care and outcome of trauma patients. The cases are validated and scanned into the TARN database (which currently holds around 200,000 cases). Analysis includes anonymous comparison of the performance of each system of care against others in the database. For each patient, all injuries are documented according to the Abbreviated Injury Score (AIS), which is then used to generate the injury severity score (ISS). Recordings of the respiratory rate (RR), systolic blood pressure (SBP), and Glasgow Coma Scale score (GCS) are used to calculate a Revised Trauma Score (RTS). Further documentation includes demographic and prehospital data, admission physiologic findings, initial resuscitation, interhospital transfers, operative intervention, duration of intensive care and length of hospital stay, and time of death. This statistical analysis is called the “Ws” and the data are adjusted to account for the confounding factors of age, ISS, physiologic change, RTS, and method of injury. Previous TARN publications have indicated a lack of reporting bias.

**Study Population and Study Design**

Data of all patients included in the TARN database between January 1989 and December 2001 were analyzed. Pelvic ring injuries were classified according to the AIS. Patients were divided in two groups: PG (patients sustaining injuries of the pelvic ring, including symphysis pubis and sacroiliac joint disruptions); and NPG (all patients without pelvic ring injuries, representing the control group). TARN did not distinguish between open comminuted and displaced fractures before June 2001. To determine the prevalence of open pelvic fractures, a subset of cases submitted after June 2001 was analyzed.

For both patient groups, demographic details (age and gender), mechanism of injury, injury severity according to ISS and injury pattern, initial physiologic findings (heart rate, SBP, and pulse rate), operative interventions, length of intensive care or hospital stay, and mortality were compared. Factors affecting mortality in patients with pelvic injuries were analyzed by comparing data of survivors and nonsurvivors in the PG.

To assess the impact of the presence of pelvic reconstruction facilities in the receiving hospitals on outcome, patients with pelvic fractures were separated in one group that was treated in or transferred to a hospital with known pelvic reconstruction facilities (PRF) and another group, which was treated in a hospital without pelvic reconstruction facilities (NPRF). Seven hundred randomly selected patients from both the PRF group and the NPRF group with pelvic ring injury according to the AIS were compared for the evaluation of this variable on patients’ outcome using a logistic regression model to adjust for any variations in age, ISS, and RTS.

**Statistical Analysis**

All statistical analyses were performed using a commercially available statistics software package (SPSS, Version 11.0, Chicago, IL). Continuous data were assessed for normal distribution. Unless stated otherwise, values are expressed as median (interquartile range) and then analyzed by the Mann-Whitney U test. Categorical data were evaluated by the χ² test. To identify factors predicting mortality in pelvic fractures, a univariate analysis was performed. Significant variables were used in a logistic regression multivariate analysis to determine relationship with outcome. Data were considered significant when probabilities were less than 0.05.

**RESULTS**

**Patient Population**

Between January 1989 and December 2001 data of 159,746 trauma patients were collected in the TARN database. Of these patients, 12,759 (8.0%) had sustained a pelvic fracture. However, 1,610 (1.01%) patients with pelvic fracture and 13,499 (8.45%) patients without pelvic fracture were excluded from detailed analysis because of transfer, and their final outcome was not recorded in a hospital that submits data to TARN. Therefore, there were a total of 11,149 patients in the PG group for further analysis. The remaining 133,486 patients formed the NPG (control) group.

**Comparison of PG and NPG Patients**

**Demographics**

In both groups (PG and NPG) there was a male predominance concerning the percent of patients that sustained the injuries (Table 1). In the PG population, the patients that have sustained a pelvic injury were mostly younger and predominantly male. However, in the NPG group, the patients that were injured were predominantly older and more often of male gender.

**Mechanism of Injury**

In patients with pelvic fractures, road traffic crashes (RTC) were the most common mechanism of injury with an incidence of 62.9% followed by falls, with an incidence of 30.6%. In contrast, more than half of NPG patients (50.9%) sustained a fall and only 29.7% were involved in an RTC. Less common mechanisms included sports injuries and assaults with an incidence below 10% in both groups. If patients were involved in an RTC, PG patients were sig-
significantly more likely to be vehicle drivers or pedestrians, whereas NPG patients showed a higher incidence of bicycle and motorbike crashes (Fig. 1). Vehicle passengers and pedestrians were equally distributed in both groups (Fig. 1).

**Injury Severity and Injury Pattern**

The median ISS showed no significant difference for patients with and without pelvic injuries (Table 1; \( p > 0.05 \)). However, there were statistically significantly more patients with an ISS >15 in the PG group (\( n = 3,576; 32.1\% \)) than in the NPG group (\( n = 19,238; 16.9\% \) (\( p < 0.001 \)), indicating that pelvic injuries were more often associated with other injuries, although the median ISS did not reflect this. The severity of pelvic injuries according to the AIS is shown in Figure 2. The majority of patients sustained AIS 2 pelvic injuries (65.0%), whereas AIS 4 and 5 injuries were found in less than 10% of patients (Fig. 2). Pelvic ring injuries were most commonly associated with chest trauma >AIS 2 severity in 21.2% of the patients, head injuries (>AIS 2) in 16.9%, liver or spleen injuries in 8.0%, and two or more long bone fractures in 7.8%. Urogenital injuries were noted in 3.7%, and spinal injuries in only 2% of the PG patients. From the 17,424 cases submitted between June and December 2001, 1,177 (6.8%) had sustained a pelvic fracture, of which 59 (5%) were open, and 4.3% (694) of the 16,247 patients without pelvic fracture had sustained an open limb fracture.

**Initial Physiologic Data of Both Groups**

Patients with pelvic ring injuries more commonly presented with a tachycardia (pulse >100 bpm) compared with NPG patients (21.9% vs. 13.4%). The RTS\(^2\) was more frequently abnormal in the PG patients than in the NPG

![Fig. 1. Incidence (%) of position in road traffic crash in PG and NPG patients.](image)
patients (18.16% vs. 9.65%). RTS is the physiologic score that is used in TRISS (combines SBP, RR, and GCS), and it has a maximum value of 7.84; however, because of poor recording of RR values, RTS values were missing in 22.4% and 31.5% of PG and NPG patients, respectively. PG patients were almost three times as likely to be hypotensive at admission (SBP < 90 mm Hg) than were NPG patients (7.4% vs. 2.6%) (*p* = 0.04) and almost twice as likely to have an impaired conscious (GCS) level (21.0% vs. 11.9%) (*p* = 0.045); however, once again there were significant amounts of missing recordings.

**Intensive Care Unit and Hospital Stay**

Significantly more patients with pelvic injuries were admitted to an intensive care unit compared with the control group (24.5% vs. 11.7%) (*p* < 0.001). Their median total hospital stay was 15 days, which was significantly longer than that of the control group (8 days). However, in 30.3% of the NPG patients and 26.4% of PG patients, the presence or absence of an intensive care unit admission was not recorded.

**Mortality**

The 3-month cumulative mortality rate in the patients with pelvic injuries was 14.2% (1,586 patients), whereas only 5.6% (7,465 patients) of the NPG patients died within the first 3 months after the injury. The median time to death from admission was sooner in PG patients (6.22 hours vs. 40.25 hours). Sub analysis of the PG group data failed to illustrate any difference in the mortality rates relating to time of transfer.

**Factors Associated With Mortality in PG Patients**

Patients with pelvic injuries who subsequently died were significantly older and had a significantly higher ISS compared with that of survivors (*p* = 0.001; Table 2).** Mortality clearly increased with the severity of pelvic injuries (AIS) in these patients (Fig. 2). The fact that nonsurvivors showed significantly higher pelvic AIS levels supports this finding (Fig. 3). However, at the same time, nonsurvivors also showed significantly higher AIS levels of their associated injuries, such as head, thoracic, and abdominal injuries as well as long bone fractures (Fig. 4), indicating that not the pelvic injury alone but multiple injuries combined with pelvic injury lead to death in these patients. This observation is supported by the fact that 95.2% of nonsurvivors with pelvic injuries had other injuries, whereas this was the case, the same was true for only 68.7% of survivors with pelvic injuries (*p* = 0.01).

Additional factors that were associated with a higher mortality rate in this patient group included decreased level of consciousness on arrival (GCS < 15), hypotension on arrival (SBP < 90 mm Hg), an RTS < 7.84, and the amount of fluid transferred.

### Table 2 Comparison of Patients With Pelvic Ring Injuries Who Survived or Died After Trauma

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 9,563)</th>
<th>Nonsurvivors (n = 1,586)</th>
<th>Overall (n = 11,149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>37</td>
<td>53*</td>
<td>39</td>
</tr>
<tr>
<td>Mean ISS (points)</td>
<td>9</td>
<td>34*</td>
<td>9</td>
</tr>
<tr>
<td>GCS &lt;15 (%)</td>
<td>15.2</td>
<td>55.5*</td>
<td>21.0</td>
</tr>
<tr>
<td>SBP &lt;90 mm Hg (%)</td>
<td>3.3</td>
<td>31.3*</td>
<td>7.4</td>
</tr>
<tr>
<td>RTS &lt;7.84 (%)</td>
<td>13.3</td>
<td>47.1*</td>
<td>18.1</td>
</tr>
<tr>
<td>Median fluids in resuscitation room (mL)</td>
<td>1,000</td>
<td>2,750*</td>
<td>1,000</td>
</tr>
</tbody>
</table>

*Statistically significant difference.

ISS, Injury Severity Score;** GCS, Glasgow Coma Scale score on arrival;* SBP, systolic blood pressure on arrival; RTS, Revised Trauma Score on arrival.**
administered in the resuscitation room (Table 2). Multiple logistic regression analysis revealed age, physiologic derangement, and associated head, chest, and abdominal injuries as having an independent predictive ability of increased mortality \((p = 0.001)\) with the highest odds ratio for liver or spleen injuries.

## The Impact of Availability of Pelvic Reconstruction Facilities on Outcome

Twenty-one percent of the PG patients were treated in a hospital with known pelvic reconstruction facilities (availability of trauma and orthopedic surgeons with special interest in pelvic and acetabular reconstruction, providing a local and tertiary referral service) with most patients being transferred within the first 24 hours after injury (47.3%). Pelvic trauma patients who were admitted or transferred to a hospital with PRF showed a significant lower overall mortality rate (10.8% vs. 17.6%) compared with those not being treated or transferred to a hospital without NPRF \((p = 0.002)\). Further analysis of pelvic AIS subgroups illustrated that the higher the pelvic AIS the greater was the reduction of mortality rates when patients were managed in pelvic reconstruction facility (Fig. 5). However, in less severe pelvic injuries (AIS <3), the availability of pelvic reconstruction facilities had no impact on the mortality rate.

Multiple regression analysis adjusted for ISS, age, and RTS showed an odds ratio of 2.5 for mortality comparing patients treated in hospitals without and with pelvic reconstruction facilities.

## DISCUSSION

The aim of TARN in the United Kingdom is to collect and analyze clinical and epidemiologic data and thereby to provide a statistical base to support clinical audit, to aid the development of trauma services and to inform the research agenda (TARN leaflet).

The TARN database has been used for different research projects in the past, including nation-wide surveys and national and international comparisons.\(^9,15–21\) It is of note that participation in the TARN project initially led to a decline of the severity-adjusted odds of death by 40% from 1989 to 1997, and this has been attributed to the implementation of the advanced trauma life support (ATLS) protocol, senior surgeon involvement, and the increased awareness of the needs of the trauma patients with multiple injuries.\(^19\)

Although the TARN data have been used to evaluate specific populations of trauma patients, including those with brain and spine injuries, no data have been analyzed before to evaluate patients with pelvic injuries.\(^22,23\) The current study analyzes data of more than 11,000 patients with pelvic ring injuries, representing the largest ever documented patient group. Until now, the largest single series of patients with pelvic ring injuries ever published was from a German multicenter study by Gänsslen et al., analyzing data of 2,551 patients.\(^7\)

The overall incidence of pelvic ring injuries has been reported to range between 3% and 8% of all skeletal injuries.\(^24\) In the current study, the overall incidence was 8%. This figure might be artificially high, because the TARN database does not include a significant number of inpatient...
A comparison of the severity of pelvic ring injuries of recently published studies is difficult because of the high number of different classification systems. Some authors used very simple distinctions of stable versus unstable fracture patterns, closed versus open fractures, or simple versus complicated fractures.26–29 Other authors prefer more analytical classification systems, such as the Tile/AO, the Young-Burgess, or the Kane modification of the Key and Conwell classification (Table 3).2,3,7,29–36 These more detailed classification systems are based either on the vector of impact (Young-Burgess) or the stability of the pelvic ring (Tile). Because injuries in the TARN database are documented using the AIS code, patients could not be categorized in the above-described classification system. The AIS is a way of describing the injury, and on its own, is not designed to provide any outcome prediction. The AIS is also usually assigned rather than derived. It is not an injury scale, in that the difference between AIS 1 and AIS 2 is not the same as that between AIS 4 and AIS 5. The AIS, however, is a classification system for ranking and comparing injuries by severity developed and was published by the Association for the Advancement of Automotive Medicine.10

Only a few studies have used the AIS to describe the injury severity of the pelvic ring to date.25,26,37,38 Demetriades et al. found that the mortality rate markedly increased in patients with pelvic AIS ≥4.25 Similarly, in this study, a significant correlation between the pelvic ring injury severity according to the AIS and the mortality rate was found (Fig. 4). The question, however—whether the severity of the pelvic ring injury according to conventional classification systems (vector force or stability) is associated with an increased mortality—is still under vivid discussion. Although some authors suggested that increasing instability of the pelvis is related to increased mortality rates, other authors could not find a correlation between fracture severity and survival.2,3,7,30,31 In fact, Poole et al. reported that the severity of the pelvic ring injury is purely an indicator of injury severity as a whole and not related to final outcome.32 On the other hand, Eastridge and Burgess could correlate the vector force according to the Young-Burgess classification with mortality.33 Table 3 summarizes classification systems for pelvic ring injuries previously described in the literature and gives information whether a correlation with mortality could be observed in these studies.

The majority of pelvic ring injuries is caused by blunt trauma and is most commonly encountered after motor vehicle crashes. This is, in particular, true for the younger population, whereas pelvic injuries in elderly patients more often result from falls.39,40 Interestingly, in the current study, patients with pelvic injuries who were involved in an RTC were typically vehicle drivers, whereas NPG patients were more frequently bicycle and motorbike riders (Fig. 1). These data are supported by findings from technical reconstructions made of nearly 10,000 crashes in Germany, where the distribution of injury mechanism was exactly the same, with mostly car drivers or passengers and pedestrians being involved in crashes leading to pelvic ring injuries.37 Indeed, motor vehicle collisions (MVCs) remain the leading cause of pelvic fractures accounting for 44% to 64% of these injuries.38,41 There are numerous crash-related factors that may be related to this rise in pelvic injury. The final speed in MVCs has been increasing, which may result in more energy transfer to occupants of a vehicle involved in a collision.42 Compartment intrusion has been shown to be an important factor in pelvic injury.43 The discrepancy in vehicle sizes, with the popularity of subcompact cars and the increasing number of sport utility vehicles involved in MVCs may be resulting in increased compartment intrusion.38

The overall mortality rate of patients with pelvic ring injuries included in the present study was 14.2%. In previous studies, mortality rates ranged from 3% to 20% with no significant change during the past 20 years (Table 4).2–7,25,27–30,32,36,44–49 However, when applying the principle of “number correction”, the overall mortality rate was estimated to be 12.2% (Table 4). Only very few publications reported mortality rates greater than 20%.33,49,50 However, in these studies, all the patients had multiple injuries with a high injury severity score.33,49,50 In general terms, the wide range of mortality rates presented in Table 4 could be explained by patient selection, e.g., high incidence of multiple or associated injuries.

The 14.2% mortality rate in this study could be related to the inclusion criteria of the TARN database as previously discussed. For instance, most previous publications do not represent a nation-wide survey but rather are provided by centers with a special interest in pelvic trauma. When this is taken into account and the mortality rate is analyzed for

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**Table 3 Previous Clinical Studies Using Pelvic Injury Classification Systems and Correlation With Mortality Rates**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tile</th>
<th>Young</th>
<th>Kane Mod.</th>
<th>Correlation with Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rommens and Hessman</td>
<td>2002</td>
<td>+</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Parreira et al.</td>
<td>2000</td>
<td>+</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Chong et al.</td>
<td>1997</td>
<td>+</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Eastridge and Burgess</td>
<td>1997</td>
<td>+</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Gänsslen et al.</td>
<td>1996</td>
<td>+</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>van Veen et al.</td>
<td>1995</td>
<td>+</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Burgess et al.</td>
<td>1990</td>
<td>+</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Fox et al.</td>
<td>1990</td>
<td>+</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Poole et al.</td>
<td>1991</td>
<td>+</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Mucha and Farell</td>
<td>1984</td>
<td>+</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

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The Journal of *TRAUMA* Injury, Infection, and Critical Care

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patients treated in dedicated centers with pelvic reconstruction facilities, then it declined to a rate of 9.7%.

Early mortality is usually associated with hemorrhage from both pelvic and extrapelvic sources or severe closed head injury, whereas late mortality is secondary to sepsis or multiple system organ failure. In this study, using a multiple regression analysis model, it was found that factors contributing to an increased mortality rate included such variables as patient’s age, ISS, associated injuries, early physiologic derangement with a systolic blood pressure <90 mm Hg, and increased fluid resuscitation requirements (Table 2; Fig. 4). Most of these factors have been previously described in the literature (Table 5). Ismail et al.44 compared 722 pediatric patients with 532 adult patients with pelvic ring injuries and found that with hemodynamic instability (blood pressure <90 mm Hg) the mortality rate reached 78.3%.44 Similarly, other authors have also demonstrated early physiologic derangement as a risk factor.29,36,51 van Veen et al.34 described that mortality was closely related to the need for transfusion of blood products.34 Other authors quoted injury severity as an important cofactor for mortality.4,7,34,36 Parreira et al.3 retrospectively investigated a group of 103 patients with pelvic ring injuries and found that besides age and “shock upon admission”, associated head, chest, or abdominal injuries with an AIS >2 were the most important factors identified as related to the occurrence of complications or death.3 Mucha and Farnell29 also described an increased mortality caused by associated head and trunk injuries in their study regarding the management of 533 pelvic ring fractures.29 Allen et al. and Wubben again found that head injury has an impact on mortality.4,39

In summary, in accordance to the results of the herein study, the majority of the published studies have emphasized the utmost importance of early hemodynamic instability and the presence of associated injuries on mortality rates.

As a final point, this study supports the view that Level I trauma centers with pelvic reconstruction facilities in the United Kingdom could contribute to improving survival rates in patients with pelvic fractures by almost a rate of 30%. This finding is open to a number of interpretations. First, it could be caused by early senior input in the management of these patients, allowing early implementation of a treatment plan focusing on optimizing the resuscitation process as indicated by the principles of damage control orthopedics.52 Second, a multidisciplinary approach to the management of these patients is imperative because it prevents early pitfalls, which could lead to unexpected complications and dictates an appropriate treatment protocol throughout the patient’s clinical

### Table 4 Mortality Rates Reported in the Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>ISS</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demetriades et al.26</td>
<td>2002</td>
<td>1,545</td>
<td>15</td>
<td>13.5</td>
</tr>
<tr>
<td>Rommens and Hessman7</td>
<td>2002</td>
<td>222</td>
<td>NA</td>
<td>9.9</td>
</tr>
<tr>
<td>Parreira et al.3</td>
<td>2000</td>
<td>103</td>
<td>20</td>
<td>19.4</td>
</tr>
<tr>
<td>Allen et al.4</td>
<td>2000</td>
<td>75</td>
<td>23</td>
<td>14.7</td>
</tr>
<tr>
<td>Alost and Waldrop5</td>
<td>1997</td>
<td>205</td>
<td>NA</td>
<td>3.0</td>
</tr>
<tr>
<td>Chong et al.30</td>
<td>1997</td>
<td>343</td>
<td>20</td>
<td>10.5</td>
</tr>
<tr>
<td>Brennemann et al.8</td>
<td>1997</td>
<td>1,179</td>
<td>30</td>
<td>16.3</td>
</tr>
<tr>
<td>Eastrside and Burgess33</td>
<td>1997</td>
<td>111</td>
<td>29</td>
<td>23.4</td>
</tr>
<tr>
<td>Gänslien et al.7</td>
<td>1996</td>
<td>2,551</td>
<td>NA</td>
<td>13.4</td>
</tr>
<tr>
<td>Ismail et al.44</td>
<td>1996</td>
<td>532</td>
<td>21</td>
<td>17.5</td>
</tr>
<tr>
<td>van Veen et al.34</td>
<td>1995</td>
<td>39</td>
<td>32</td>
<td>12.8</td>
</tr>
<tr>
<td>Poole et al.32</td>
<td>1994</td>
<td>348</td>
<td>22</td>
<td>8.0</td>
</tr>
<tr>
<td>Riemer et al.27</td>
<td>1993</td>
<td>476</td>
<td>23</td>
<td>6.3</td>
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<tr>
<td>Davidson et al.45</td>
<td>1993</td>
<td>975</td>
<td>27</td>
<td>7.3</td>
</tr>
<tr>
<td>Burgess et al.35</td>
<td>1990</td>
<td>196</td>
<td>34</td>
<td>24.7</td>
</tr>
<tr>
<td>Fox et al.36</td>
<td>1990</td>
<td>175</td>
<td>24</td>
<td>16.0</td>
</tr>
<tr>
<td>Torode and Zieg46</td>
<td>1985</td>
<td>141</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Hesp et al.47</td>
<td>1985</td>
<td>111</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>Mucha and Farnell29</td>
<td>1984</td>
<td>533</td>
<td>NA</td>
<td>6.4</td>
</tr>
<tr>
<td>Naam et al.58</td>
<td>1983</td>
<td>102</td>
<td>NA</td>
<td>16.6</td>
</tr>
<tr>
<td>Gilliland et al.49</td>
<td>1982</td>
<td>100</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Rothenberger et al.26</td>
<td>1978</td>
<td>604</td>
<td>NA</td>
<td>11.9</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td>10,632</td>
<td>25.9 (mean)</td>
<td>12.4*</td>
</tr>
<tr>
<td>TARN study</td>
<td>2004</td>
<td>11,149</td>
<td>9 (median)</td>
<td>14.2</td>
</tr>
</tbody>
</table>

*Mortality rates were multiplied by the number of patients of each study and the sum was subsequently divided by the overall number of patients.
NA, not available.

### Table 5 Factors Associated With Increased Mortality in Patients With Pelvic Ring Injuries—Review of the Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Head Injury</th>
<th>Chest Injury</th>
<th>Abdomen Injury</th>
<th>Injury Severity</th>
<th>Hemodynamic Instability</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starr et al.51</td>
<td>2002</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ISS</td>
<td>+</td>
<td>RTS, transfusion requirements, AIS</td>
</tr>
<tr>
<td>Parreira et al.3</td>
<td>2000</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Base excess</td>
</tr>
<tr>
<td>Allen et al.4</td>
<td>2000</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ISS</td>
<td>+</td>
<td>Soft tissue damage</td>
</tr>
<tr>
<td>Gänslien et al.7</td>
<td>1996</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>RTS</td>
<td>+</td>
<td>PTT &gt;15 s</td>
</tr>
<tr>
<td>Wubben39</td>
<td>1996</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>Transfusion requirements</td>
</tr>
<tr>
<td>van Veen et al.34</td>
<td>1995</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ISS</td>
<td>+</td>
<td>Associated injuries/patient</td>
</tr>
<tr>
<td>Fox et al.36</td>
<td>1990</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ISS</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mucha and Farnell29</td>
<td>1984</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

AIS, Abbreviated Injury Score;10 ISS, Injury Severity Score;11,12 RTS, Revised Trauma Score;14 PTT, partial thromboplastin time; PTS, Hannover polytrauma score.56
course. Third, in addition to the initial surgical interventions, resources must include an increase in availability of intensive care unit (ITU) and high dependency unit (HDU) beds especially for multiple injury patients with pelvic ring injuries. An enhanced medical experience in the intensive care environment could aid in better management of posttraumatic complications such as adult respiratory distress syndrome or multiple organ dysfunction syndrome. Radical changes in the National Health System (NHS) are mandatory to ensure that patients with severe pelvic injury are provided with an efficient specialist trauma service. Although the above explanations are speculative, it has been shown in the past that experience levels of different trauma centers affect favorably the outcome as it has been shown by several authors in patients with blunt splenic injuries or multiple injuries. 53–55 Current reasons for failure to transfer PG patients to pelvic reconstruction facilities have not been explored in this study. However, the authors speculate that these may include underdeveloped regional trauma systems in the United Kingdom as well as resource issues.

Decisions regarding transport to the most appropriate specialized facility should be based on the patient’s physiology as well as the nature of the pelvic injury and the presence of other associated injuries. Thus, it is of paramount importance that the accepting physician, in a hospital without adequate resources or experience, identifies rapidly such patients and organizes transportation in an appropriately timely fashion after adequately stabilizing the patient’s condition. Early communication with the receiving facility and transport under safe conditions, especially, in the more severe pelvic injuries (AIS ≥3) is necessary to ensure patient survival.

CONCLUSION

In this prospective multicenter study in England and Wales of more than 11,000 pelvic ring injuries, it was found that the mechanism, injury pattern, and mortality are comparable to previously reported data from the United States, Germany, and other countries. 2,3,7,25,56 Furthermore, age, early physiologic derangement, presence of associated injuries (head or trunk), and the absence of pelvic reconstruction facilities on the receiving hospital were associated with reduced survival rates. When the expertise to deal with such a group of patients is not available, early transfer under safe conditions should be considered to improve survival rates.

REFERENCES

Long-Term Functional Outcome After Unstable Pelvic Ring Fracture

Takashi Suzuki, MD, Masateru Shindo, MD, Kazui Soma, MD, Hiroaki Minehara, MD, Koushin Nakamura, MD, Masataka Uchino, MD, and Moritoshi Itoman, MD

Purpose: In patients with unstable pelvic ring fractures, the factors related to poor outcome are still controversial. The purpose of our study was to evaluate the long-term functional outcome of patients with unstable pelvic ring fractures and correlate it with various other factors.

Methods: Fifty-seven patients who had a minimal follow-up of 2 years completed the three-view plain radiographs, physical examination, and functional assessment with questionnaire. There were 28 male and 29 female patients with an average age of 42.4 years and Injury Severity Score of 24.6 points. The mean time of follow-up was 47.2 months. Thirty-nine patients were Tile type B, and 18 were type C. Twenty-three patients were treated conservatively, 22 with external fixation, and 12 with internal fixation. The results were scored with the Majeed score, the Iowa Pelvic Score, and the Medical Outcomes Study Short-Form 36-item Health Survey (SF-36). Statistical analysis was performed by use of the Pearson correlation coefficient test and multiple regression analysis.

Results: The average Majeed score was 79.7, the average IPS was 80.7, and the average physical component summary of the SF-36 was 13.4 points worse than that of the population norm. These scores correlate significantly with each other. The average residual displacement was 7.3 mm anteriorly and 5.2 mm posteriorly. Multiple regression analysis revealed that the Majeed score and the physical component summary of the SF-36 correlated with the presence of neurologic injury, and the Iowa Pelvic Score correlated with the presence of a mental disorder, posterior displacement, and neurologic injury.

Conclusions: The long-term functional outcome after unstable pelvic ring fracture was not associated with Injury Severity Score, fracture location or fracture type. We discovered a close correlation between neurologic injury and functional outcome.

Keywords: Pelvic fracture, Functional outcome, Neurologic injury.

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Unstable pelvic ring fractures occur as high-energy injuries, and are usually associated with multiple, concomitant injuries.1–3 The mortality has been reported between 18% and 25%,4 and the aims of treatment of unstable pelvic ring fractures has focused on the survival of the patients for a long time.5 During the last decade, several authors reported functional outcomes that were based on patient-oriented systems and factors that deteriorated the outcomes.5–15 Most of them, however, had limitations, such as small populations, lack of radiographic evaluation, or less than ideal statistical analyses. We report three functional outcome scores of patients with unstable pelvic ring fractures and the factors that correlate with poor prognosis using multivariable analysis.

PATIENTS AND METHODS

Between 1995 and 2003, 114 patients with unstable pelvic ring fractures (Tile type B and C)16 were discharged after treatment in our emergency medical and trauma center. The medical records, plain radiographs, and computed tomography scans were reviewed. Six patients with concomitant acetabular fractures, four patients with severe head or spinal cord injuries that caused palsy, seven patients with schizophrenia, and six patients who died after being discharged were excluded. We tried to contact 91 patients meeting the inclusion criteria with a minimal follow-up of a 2-year period,7 but 22 patients were untraceable, and 12 patients refused to participate. Thus, the remaining 57 of 91 patients (62.6%) were recalled and underwent a standardized clinical and radiographic reevaluation. This clinical reevaluation included the patient-oriented questionnaire surveys of the Majeed score,17 the Iowa Pelvic Score (IPS),12 and the Medical Outcomes Study Short-Form 36-item Health Survey (SF-36),18 which were frequently used in previous studies.7–15 The Majeed score is a pelvic-injury-specific functional assessment divided into seven items, such as pain, work, sitting, sexual intercourse, standing, gait unaided, and walking distance. The IPS also a pelvic-injury-specific assessment divided into six items: daily-life activities, work history, pain, limping, visual pain line, and cosmesis. Each of the total Majeed score and IPS can range from 0 to 100 in order of decreasing disability. The SF-36 is a general health assessment survey consisting of 36 questions and has been...
established as well validated and reliable for the Japanese population.\textsuperscript{19} It can assess eight subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The first four subscales can be combined as the physical component summary (PCS) relating to physical health, and the last four can be combined as the mental component summary (MCS) relating to mental health. A transformed scale-score of 0 to 100 was calculated for each of the eight subscales and the two component summaries. The presence of neurologic deficiency of the lower extremities, sexual deficiency, urologic deficiency, and mental disorder were all examined. The social and occupational status was also recorded. The radiographic assessment included an anteroposterior, inlet, and outlet views for all patients. In these views, the largest displacement assessment included an anteroposterior, inlet, and outlet views for all patients. In these views, the largest displacement was recorded in millimeters anteriorly and posteriorly.

There were 28 male and 29 female patients with an average age of 42.4 (range, 16–72) years and an Injury Severity Score (ISS) of 24.6 (range, 9–50) points. Only two patients had no other significant injuries. The mean time of follow-up was 47.2 (range, 24.4–107.4) months. There were 39 patients with type-B pelvic fractures and 18 patients with type-C pelvic fractures. Four open fractures belonged to type C. According to the Young classification,\textsuperscript{20} there were 21 lateral compression (LC)-1, 10 LC-2, 7 LC-3, 4 anteroposterior compression (APC)-1, 4 APC-2, 4 APC-3, 6 vertical shear (VS), and 1 combined mechanism (CM). The posterior lesions were classified as follows: 31 sacral fractures, 15 pure sacroiliac dislocations, 14 sacroiliac fracture dislocations, and 9 iliac fractures. No formal treatment protocol for unstable pelvic fractures was used during the study period. Therefore, the initial treatment was based on the attending surgeon’s preference. Transcatheter arterial embolization (TAE) of pelvic arteries for persistent hemodynamic instability was performed in 31 patients. Among 57 patients, 23 were treated conservatively, 22 were treated with external fixation, and 12 were treated with internal fixation. The internal fixations of 17 posterior lesions were two sacral bars, four sacroiliac plates (invented for the fixation of the sacroiliac joint), five plate-and-screw fixations, and six sacroiliac screws. Two orthopedic trauma specialists (T.S., M.S.) made the decisions of the definitive treatment and performed the operations. There were no deep infections.

Statistical software programs (SPSS, version 10.0J, SPSS, Tokyo, Japan) were used for all statistical analyses. The statistical method used in the comparison of the results among the questionnaire surveys was the Pearson correlation coefficient test. To determine the independent factors influencing each functional outcome, multiple linear regression analyses were used. The variables were age, Injury Severity Score (ISS), type of fracture according to the Tile classification, force vectors of fracture according to the Young classification, amount of residual posterior displacement, performance of TAE, and presence of mental disorder, lower extremity fracture, and neurologic injury. Care was taken to avoid inclusion of pairs of variables with high internal correlations. The level of significance was considered at $p < 0.05$.

**RESULTS**

The average Majeed score was 79.7 (range, 30–100) points. For this score, a sexual disturbance of fewer than 3 points (maximum 4 points) was shown in 15 patients. The average IPS was 80.7 (range, 35–100) and the average pain score by visual analog scale was 6.9 points (0 as worst, 10 as best). There were 31 patients with excellent IPS, 11 patients with good IPS, 8 patients with fair IPS, and 7 patients with poor IPS according to Nepola.\textsuperscript{12} The average of the SF-36 was worse than that of the population norm in all eight subscales (Fig. 1). The average PCS of the SF-36 was 65.2 (range, 22.8–100) points, 13.4 points worse than population norm. The average MCS of the SF-36 was 67.6 (range, 9.4–100) points, 9.5 points worse than population norm. We defined the neurologic deficiency of the lower extremity as an existing sensory deficit, regardless of motor disturbance, at the examination. In the present study, 16 patients were suffering from neurologic deficiencies (Table 1). There was no relationship between the site of the posterior lesion and the type of the neurologic injuries. Two of the 16 patients apparently suffered from iatrogenic injuries judging from the admission records. Sixteen were suffering from urologic deficiency, and 11 presented with a mental disorder at the examination. Twenty patients were able to work as before, 28 returned to their previous jobs but reduced their activities, and 9 were unable to return to work.

The average of the largest residual displacement was 7.3 (range, 0–30) mm anteriorly and 5.2 (range, 0–40) mm posteriorly, which was classified as 29 excellent, 13 good, 9 fair, and 6 poor according to the Majeed radiographic score.\textsuperscript{21} Nonunion was not observed in all the patients. Radiographs from two patients can be seen in Figures 2 and 3.

There was a significant correlation between the Majeed score and the PCS of the SF-36 ($p < 0.001$), the Majeed score and the IPS ($p < 0.001$), and between the IPS and the PCS of the SF-36 ($p < 0.001$). Multiple linear regression analysis showed that (1) the Majeed score was found to be affected by the presence of neurologic injury ($p = 0.049$); (2) the IPS was found to be affected by the presence of mental disorder ($p = 0.013$), posterior displacement ($p = 0.005$), and neurologic injury ($p = 0.028$); and (3) the PCS of the SF-36 was found to be affected by the presence of neurologic injury ($p = 0.007$) (Table 2). Variables, such as age, ISS, type of fracture, force vector of fracture, performance of TAE, and presence of lower extremity fracture were of no significant value. In the patients with neurologic injuries, the outcome of “physical functioning” was significantly worse compared with the scores of all the patients by SF-36 subscales (Mann-Whitney $U$ test, $p = 0.018$) (Fig. 1).
DISCUSSION

Since the late 1980s, there have been several reports on the factors or predictors that affect functional outcome and disabilities, such as age, ISS, type of fracture, fracture location, residual posterior displacement, force vectors of fracture, open fracture, treatment method, performance of TAE, whether it was a work-related injury, lower extremity fracture, urologic injury, impotence, psychological problem, or neurologic injury.1,2,9,10,14,16 In general, anatomic reduction and internal fixation has been emphasized for good outcome. Henderson22 and McLaren et al.23 reported that displacement of more than 1 cm posteriorly was associated with increased long-term pain and disability. Tornetta et al.24 and Gruen et al.6 reported that open reduction and internal fixation of unstable pelvic ring fractures resulted in a high functional success rate. Dujardin et al. reported that exact reduction of pure sacroiliac dislocation was critical for good functional outcome compared with iliac or sacroiliac fracture dislocations.11 Lindalh and Hirvensalo described that an excellent radiographic result showed a clear association with excellent or good functional outcome.15 On the other hand, some authors have reported that there was no relationship between residual displacement and functional outcome. Ne-

Table 1 Neurologic Deficiency of the Lower Extremity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Type of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Left L5 nerve root</td>
<td>Sensory</td>
</tr>
<tr>
<td>3</td>
<td>Right lumbosacral plexus</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>8</td>
<td>Right sciatic nerve</td>
<td>Sensory</td>
</tr>
<tr>
<td>9</td>
<td>Left L5 nerve root</td>
<td>Sensory</td>
</tr>
<tr>
<td>13</td>
<td>Left L5 and S1 nerve root</td>
<td>Sensory</td>
</tr>
<tr>
<td>14</td>
<td>Right lumbosacral plexus</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>15</td>
<td>Left L5 and S1 root</td>
<td>Sensory (L5 and S1) and motor (L5)</td>
</tr>
<tr>
<td>20</td>
<td>Left L5 nerve root</td>
<td>Sensory</td>
</tr>
<tr>
<td>30</td>
<td>Left L4 nerve root</td>
<td>Sensory and radiated pain</td>
</tr>
<tr>
<td>31</td>
<td>Left L5 nerve root</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>33</td>
<td>Left L5 nerve root (postoperative)*</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>35</td>
<td>Right sciatic nerve</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>36</td>
<td>Bilateral lumbosacral plexus</td>
<td>Sensory and motor</td>
</tr>
<tr>
<td>40</td>
<td>Left S1 nerve root</td>
<td>Sensory</td>
</tr>
<tr>
<td>43</td>
<td>Right lateral cutaneous nerve</td>
<td>Sensory</td>
</tr>
<tr>
<td>56</td>
<td>Right lateral cutaneous nerve (post-EF)†</td>
<td>Sensory</td>
</tr>
</tbody>
</table>

* Occurred after operation.
† Occurred after external fixation.

Fig. 1. SF-36 scores for pelvic fracture versus those of the Japanese population. All patients (shaded bars), patients with neurologic injury (dotted bars), Japanese population (open bars).

Fig. 2. A 19-year-old woman after conservative treatment of type B2 pelvic fracture. The Majeed radiographic score was excellent. The Iowa Pelvic Score was 88 points (excellent).
porra et al. described that the degree of residual vertical displacement did not affect functional outcome.\(^2\) Pohlmann et al. showed that only 27% of the patients with type C were rated good or excellent, although 80% of them healed with less than 5 mm residual posterior displacement.\(^2\) Rommens and Hessmann reported that functional outcome was worse for patients with type C fractures because of not only unsta-bleness and asymmetry but also severity and amount of dam-age to the soft tissue.\(^2\) Miranda et al. showed that there were no differences in functional outcome across fracture types or treatment methods, and questioned whether reduction of pel vic ring injuries could alter patient long-term functional outcome.\(^8\) Korovessis et al. showed that the functional outcomes were superior in patients without associated injuries.\(^13\)

As mentioned above, controversy still remains regarding the factors that affect the functional outcome in the treatment of unstable pelvic ring fractures. One of the reasons is that developing a functional outcome score that exclusively reflects the impairment caused by pelvic fractures is difficult because dysfunction of the pelvis may cause disability to perform nonspecific daily activities, such as walking, sitting, standing, and so on. To date, each investigator has used various outcome scores,\(^1–3,6,9,10\) whereas the Majeed score, the IPS, and the SF-36 have become used most frequently as reviewed in the literature.\(^5,7–15\) In the present study, we have shown that the Majeed score, the IPS, and the PCS of the SF-36 correlate to the same functional impairment. Although the Majeed score and the IPS have not been validated, these scores could combine both the functional score and special local findings using objective findings. Although the SF-36 does not include specific findings that can be limited after pelvic fractures, it is effective in eliciting the patient’s perception of general disability, pain, and emotional state. The SF-36 is also useful to compare with the age- and gender-matched set of normal values.\(^5,9,12\) The results of the present study support the suggestion that using both generic and injury-specific health-related quality-of-life factors correlate to assess patient outcome more comprehensively.\(^5,7,12\)

It is also important to consider that most patients with an unstable pelvic ring fracture sustain multiple injuries,\(^1–3\) and there can often be difficulties in interpretation because the other concomitant injuries may affect the functional outcome.\(^1,9\) Thus, the statistical analysis composed by comparison of the average of each variable should always have the risk biased by the concomitant injuries. To exclude these confounding factors, we chose multiple regression analysis to determine the factors that affect the outcomes. In the present study, we discovered that the long-term functional outcome after unstable pelvic ring fracture was not associated with ISS, fracture location or fracture type, but the presence of neurologic injuries has a detrimental effect on the functional outcome.\(^8\) Korovessis et al. showed that the functional outcomes were superior in patients without associated injuries.\(^13\)

As mentioned above, controversy still remains regarding the factors that affect the functional outcome in the treatment of unstable pelvic ring fractures. One of the reasons is that developing a functional outcome score that exclusively reflects the impairment caused by pelvic fractures is difficult because dysfunction of the pelvis may cause disability to perform nonspecific daily activities, such as walking, sitting, standing, and so on. To date, each investigator has used various outcome scores,\(^1–3,6,9,10\) whereas the Majeed score, the IPS, and the SF-36 have become used most frequently as reviewed in the literature.\(^5,7–15\) In the present study, we have shown that the Majeed score, the IPS, and the PCS of the SF-36 correlate to the same functional impairment. Although the Majeed score and the IPS have not been validated, these scores could combine both the functional score and special local findings using objective findings. Although the SF-36 does not include specific findings that can be limited after pelvic fractures, it is effective in eliciting the patient’s perception of general disability, pain, and emotional state. The SF-36 is also useful to compare with the age- and gender-matched set of normal values.\(^5,9,12\) The results of the present study support the suggestion that using both generic and injury-specific health-related quality-of-life factors correlate to assess patient outcome more comprehensively.\(^5,7,12\)

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It also remains unclear whether the recovery from neurologic injuries may be enhanced by reduction of posterior fractures. Rommens and Hessmann reported that in patients with type C fracture, the neurologic recovery rate was worse than that in type B cases because neurologic structures in type C cases were more severely injured at the time of injury.\(^3\) Other authors have reported that the course of the neurologic injury was not affected by a satisfactory reduction.\(^1,11,25\)

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**Table 2 p Values of the Multiple Regression Analysis Applied to the Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Majeed</th>
<th>IPS</th>
<th>PCS of SF-36*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.066</td>
<td>0.098</td>
<td>0.647</td>
</tr>
<tr>
<td>ISS</td>
<td>0.469</td>
<td>0.545</td>
<td>0.140</td>
</tr>
<tr>
<td>Type of fracture†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td>0.663</td>
<td>0.816</td>
<td>0.495</td>
</tr>
<tr>
<td>Force vectors‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type APC</td>
<td>0.980</td>
<td>0.504</td>
<td>0.096</td>
</tr>
<tr>
<td>Type VS</td>
<td>0.656</td>
<td>0.208</td>
<td>0.472</td>
</tr>
<tr>
<td>Posterior displacement</td>
<td>0.189</td>
<td>0.005§</td>
<td>0.122</td>
</tr>
<tr>
<td>TAE</td>
<td>0.813</td>
<td>0.783</td>
<td>0.936</td>
</tr>
<tr>
<td>Fracture location§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SI fracture dislocation</td>
<td>0.395</td>
<td>0.814</td>
<td>0.865</td>
</tr>
<tr>
<td>Sacroiliac dislocation</td>
<td>0.579</td>
<td>0.547</td>
<td>0.862</td>
</tr>
<tr>
<td>Sacral fracture</td>
<td>0.534</td>
<td>0.088</td>
<td>0.422</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>0.103</td>
<td>0.013§</td>
<td>0.124</td>
</tr>
<tr>
<td>L/E fracture</td>
<td>0.623</td>
<td>0.318</td>
<td>0.067</td>
</tr>
<tr>
<td>Neurologic injury</td>
<td>0.049§</td>
<td>0.028§</td>
<td>0.007§</td>
</tr>
</tbody>
</table>

* Physical component summary of SF-36.
† Type B was excluded to avoid multicollinearity.
‡ Types lateral compression and combined mechanism were excluded to avoid multicollinearity.
§ Significant differences (p < 0.05).
† Iliac fracture was excluded to avoid multicollinearity.

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**Fig. 3.** A 23-year-old woman after internal fixation of type C1 pelvic fracture. The Majeed radiographic score was good. The Iowa Pelvic Score was 96 points (excellent).
the other hand, Reilly et al. reported that anatomic reduction and rigid fixation might provide the best local environment for the injured nerve to recover.26 Other authors have suggested that decompression of involved nerve roots in combination with anatomic reduction might reduce the rate of neurologic damage.4,15 In the present study, the true prevalence of neurologic injuries was uncertain, because most of the patients sustained associated head, chest, or lower extremity injuries and were unable to cooperate with a thorough follow-up examination. Moreover, our study was retrospective and had a relatively small population. Further prospective studies are needed to clarify whether neurologic recovery is promoted by anatomic reduction.

In the present study, we identified specific factors contributing to the functional outcomes of unstable pelvic ring fractures and have shown that, related to outcome, previously reported factors, such as ISS, type of fracture, force vector of fracture, and presence of lower extremity fracture, were not significant. Concomitant neurologic injury was shown to account for poor functional outcome.

REFERENCES

Multiple-Region Scapular Fractures had More Severe Chest Injury Than Single-Region Fractures: A Prospective Study of 107 Blunt Trauma Patients

Ayman M. A. Tadros, FRCSI, FRCS (Glasg), Karl Lunsjo, MD, PhD, Janusz Czechowski, MD, PhD, and Fikri M. Abu-Zidan, MD, FRCS, PhD

**Background:** We aimed to study the relationship between the number of fractured scapular regions, and the severity and distribution of associated injuries in blunt trauma patients.

**Methods:** One hundred seven consecutive patients with fractured scapulae (100 men) with a mean age of 35 (8–65) years were prospectively studied between January 2003 and December 2005. Mechanism of injury, associated injuries, Injury Severity Score (ISS), and the number of anatomic scapular regions involved in each fracture were studied. Patients were divided into single-region fracture (SRF), two-region fracture, and more than two-region fracture groups. Computer tomography was used for fracture classification in 99 patients and plain radiographs were used for the remaining 8.

**Results:** Road traffic collisions were the most common cause of scapular fracture. Ninety-five patients (89%) sustained associated injuries. The most frequent was chest injury (68 [64%]). The median ISS was 9 (4–57) for the SRF group (n = 55), 20 (4–59) for the two-region fracture group (n = 30), and 22.5 (4–54) for the more than two-region fracture group (n = 22) (p = 0.02, Kruskal-Wallis test). The median values of the Abbreviated Injury Scale for chest injuries for the three groups were 1 (0–4), 3 (0–5), and 3 (0–5), respectively (p = 0.001, Kruskal-Wallis test). The SRF group had significantly less posterior structure injury (9 of 55) compared with the multiple-region fracture group (46 of 52) (p < 0.001, Fisher’s exact test).

**Conclusions:** Associated injuries are common in patients with scapular fractures. ISS and Abbreviated Injury Scale score for chest injuries are higher and posterior structure injuries are more frequent in patients with fractures involving multiple scapular regions.

**Key Words:** Scapular fracture, Associated injuries, Single-region, Multiple-region, Posterior structure injury.

*S*capular fractures are uncommon because the scapula is mobile, well protected by thick muscle layers, and located in the posterolateral corner of the upper body.1 Usually, high energy is required to fracture a scapula, hence these fractures are often associated with other major injuries.2–4 However, scapular fractures have received little attention in the medical literature.5 Many authors divide scapular fractures into groups depending on their anatomic site.2,5–10 These authors did not find statistically significant differences among these groups regarding the associated injuries, the Injury Severity Score (ISS), or the nature of trauma. However, Wilber and Evans6 and Ada and Miller9 found difference in the clinical outcome. Because trauma does not respect borders it can involve more than one region of the scapula. Multiple fractures in the same scapula were previously analyzed as separate fractures.7 This is not accurate as these fractures are related to each other. It may be more logical to quantify the severity of scapular fractures by the number of anatomic regions involved. We aimed to study the relationship between the number of fractured regions of the scapula, and the severity and distribution of associated injuries in blunt trauma patients.

**PATIENTS AND METHODS**

This prospective study includes 107 blunt trauma patients with scapular fractures treated in Al-Ain Hospital, United Arab Emirates, between January 2003 and December 2005. Data regarding age, sex, mechanism of injury, side involved, associated injuries, and ISS were collected. Scapular fractures were diagnosed by clinical examination, assisted by either plain radiographs (chest or scapular views) in 8 patients and computed tomography (CT) scans (chest CT or scapula CT) in 99 patients. Fractures were defined in each of the six anatomic scapular regions (acromion, body, coracoid, glenoid, neck, and spine). Accordingly, patients were divided into groups depending on the number of anatomic scapular regions involved, regardless of the amount of displacement, angulation, or comminution of each fracture. In two patients with bilateral fractures, the scapula with maximum fracture severity was used for grouping. The patients were divided into three groups for comparison of ISS and Abbreviated Injury Scale (AIS) score of the different body areas. These groups were single-region fracture (SRF) group (n = 55)
(Fig 1), two-region fracture group (n = 30) (Fig 2), and more than two-region fracture group (n = 22) (Fig 3). Because of the small numbers of some of the associated injuries, the latter two groups were merged as one group (multiple-region fracture [MRF] group) when comparing categorical data. For assessing the association between scapular fractures and posterior structure injury, we have defined the posterior structure as the posterior part of the ribs medial to the lateral border of the scapula, dorsal spine, and soft tissues of the back of the chest. The Local Ethics Committee of Al-Ain Health District Area has approved this study.

**Statistical Analysis**

Kruskall-Wallis test was used for comparison between three independent groups. In case of overall significance, Mann-Whitney U test was used to compare two independent groups. Fisher’s exact test was used to compare categorical data. Spearman’s rank correlation was used to analyze the correlation between the number of regions involved in scapular fractures.
ular fracture and ISS or AIS score. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 13 for Windows, SPSS, Chicago, IL). Difference was considered statistically significant at \( p < 0.05 \).

**RESULTS**

Of the 107 patients studied, 100 were men. Fifty-five had fractures on the left side and 50 on the right side, and 2 had bilateral fractures. The average age (range) of patients was 35 (8–65) years. Road traffic collisions were the most common mechanism of injury (72%), followed by falls from height (18%), falls from the same levels (5%), heavy objects trauma (4%), and other causes (1%). Ninety-five patients (89%) sustained associated injuries, of which chest injuries were the most frequent (64%) (Table 1). Many patients had more than one substantial chest injury. Other common associated injuries were upper limb, head, and facial injuries. Twelve patients (11%) had isolated scapular fractures. The only body area that significantly differs in its AIS score between the three groups was the chest, \( (p = 0.01, \text{Kruskall-Wallis test}) \) (Table 2). The SRF group had significantly lower AIS scores for the chest when compared with the two-region fracture group \( (p < 0.01, \text{Mann-Whitney } U \text{ test}) \) and, with the more than two-region fracture group \( (p = 0.02) \). Similarly, the ISS was significantly different between the three groups \( (p = 0.02, \text{Kruskall-Wallis test}) \). The SRF group had significantly lower ISSs than the two-region fracture group had \( (p = 0.01, \text{Mann-Whitney } U \text{ test}) \). There was also a trend for lower ISS in the SRF group when compared with the more than two-region fracture group \( (p = 0.06) \).

### Table 1 Number of Patients and Percentage of Associated Injuries

<table>
<thead>
<tr>
<th>Associated Injuries</th>
<th>No. Patients (n = 107)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>Rib fractures</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>First rib fracture</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Flail chest</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Major vascular injury</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Upper limb injuries</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Clavicle</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Humerus</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Forearm</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Head and facial injuries</td>
<td>51</td>
<td>48</td>
</tr>
<tr>
<td>Lower limb injuries</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Femur</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Lower leg</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Spinal injuries</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Cervical</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Thoracic</td>
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</tr>
<tr>
<td>Lumbar</td>
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</tr>
<tr>
<td>Pelvic fractures</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal injuries</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Brachial plexus injuries</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as median (range).

### Table 2 Univariate Analysis of ISSs and AIS Scores of Different Body Areas Comparing Patients Who Had Single-Region, Two-Region, and More Than Two-Region Scapular Fractures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single-Region (n = 55)</th>
<th>Two-Regions (n = 30)</th>
<th>&gt;Two-Regions (n = 22)</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>0 (0–5)</td>
<td>1 (0–5)</td>
<td>1.5 (0–5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Face</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
<td>0 (0–2)</td>
<td>0.82</td>
</tr>
<tr>
<td>Chest</td>
<td>1 (0–4)</td>
<td>3 (0–5)</td>
<td>3 (0–5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0 (0–4)</td>
<td>0 (0–3)</td>
<td>0 (0–3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Extremities</td>
<td>2 (2–4)</td>
<td>2 (2–3)</td>
<td>2 (2–3)</td>
<td>0.95</td>
</tr>
<tr>
<td>External</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–1)</td>
<td>0.16</td>
</tr>
<tr>
<td>ISS</td>
<td>9 (4–57)</td>
<td>20 (4–59)</td>
<td>22.5 (4–54)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Data are presented as median (range).

* Kruskal-Wallis test.
DISCUSSION

Our study has shown that the majority of patients with scapular fractures are severely injured. Eighty-nine percent of our patients had associated injuries with 45% having an ISS of more than 15. The frequency of associated injuries varies in different studies. Our results support others who found that chest injuries are the most frequent injury associated with scapular fractures. Lung contusion, hemothorax, and pneumothorax were even more frequent in our series. We think that the prospective nature of our study and our liberal use of trauma CT scanning are the reasons for detecting more chest injuries.

The AIS scores for the chest and ISSs for patients of the MRF group were significantly higher than those of the SRF group were. This may be because the amount of energy needed to cause MRF is greater than that causing SRF. We think that the AIS score of the chest is an accurate parameter for assessing chest injury in both groups because the scapula is considered as part of extremity AIS. Because a scapular fracture is always given a fixed score of 2 in the extremity AIS irrespective of its severity, it would not affect the ISS of patients for which it was part. Consequently, ISS could be used to compare the severity of overall body injury. Body parts injured in the MRF group are mostly concentrated around the scapula. This may imply direct trauma to the scapular area. Structures in the back (posterior parts of the ribs, dorsal spine, and soft tissues of the back of the chest) and structures in the neighborhood of the scapula (chest, cervical spine, and clavicle) are significantly more injured in

Table 3 Associated Injuries in the Single-Region and Multiple-Region Fracture Groups

<table>
<thead>
<tr>
<th>Associated Injuries</th>
<th>Single-Region Fracture Group (n = 55)</th>
<th>Multiple-Region Fracture Group (n = 52)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest</td>
<td>27</td>
<td>41</td>
<td>0.002</td>
</tr>
<tr>
<td>Rib fractures</td>
<td>17</td>
<td>31</td>
<td>0.004</td>
</tr>
<tr>
<td>First rib fracture</td>
<td>3</td>
<td>10</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>14</td>
<td>22</td>
<td>0.07</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>10</td>
<td>19</td>
<td>0.049</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6</td>
<td>14</td>
<td>0.046</td>
</tr>
<tr>
<td>Flail chest</td>
<td>5</td>
<td>11</td>
<td>0.1</td>
</tr>
<tr>
<td>Major vascular injury</td>
<td>0</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Ventilation</td>
<td>3</td>
<td>9</td>
<td>0.07</td>
</tr>
<tr>
<td>Chest complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4</td>
<td>16</td>
<td>0.002</td>
</tr>
<tr>
<td>ARDS</td>
<td>1</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Upper limb injuries</td>
<td>24</td>
<td>30</td>
<td>0.17</td>
</tr>
<tr>
<td>Clavicle</td>
<td>7</td>
<td>16</td>
<td>0.03</td>
</tr>
<tr>
<td>Humerus</td>
<td>4</td>
<td>9</td>
<td>0.14</td>
</tr>
<tr>
<td>Forearm</td>
<td>7</td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>Head and facial injuries</td>
<td>24</td>
<td>27</td>
<td>0.44</td>
</tr>
<tr>
<td>Lower limb injuries</td>
<td>17</td>
<td>12</td>
<td>0.39</td>
</tr>
<tr>
<td>Femur</td>
<td>6</td>
<td>2</td>
<td>0.27</td>
</tr>
<tr>
<td>Lower leg</td>
<td>8</td>
<td>4</td>
<td>0.36</td>
</tr>
<tr>
<td>Spinal injuries</td>
<td>8</td>
<td>20</td>
<td>0.008</td>
</tr>
<tr>
<td>Cervical</td>
<td>0</td>
<td>8</td>
<td>0.002</td>
</tr>
<tr>
<td>Thoracic</td>
<td>2</td>
<td>11</td>
<td>0.007</td>
</tr>
<tr>
<td>Lumbar</td>
<td>7</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Pelvic fractures</td>
<td>15</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Abdominal injuries</td>
<td>8</td>
<td>5</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Fisher’s exact test.
the MRF group. In contrast, pelvic fractures are more common in the SRF group where the impact of trauma seems to be more generally distributed over a wide area of the body. The forces causing MRF seem to be centrifugal and those causing SRF, centripetal assuming the scapula as the center of force.

First rib fractures were more common in the MRF group. First rib fracture indicates high-energy impact because it is protected by the shoulder girdle. This indicates that MRF is a marker of severe chest trauma. Similarly, Collins considered thoracic vascular injury to be an indication of severe chest trauma. However, Armstrong and Spuy have reported multiple thoracic vascular injury to be an indication of severe

First rib fractures were more common in the MRF group. First rib fracture indicates high-energy impact because it is protected by the shoulder girdle. This indicates that MRF is a marker of severe chest trauma. Similarly, Collins considered thoracic vascular injury to be an indication of severe chest trauma. However, Armstrong and Spuy have reported multiple thoracic vascular injury to be an indication of severe chest trauma. However, Armstrong and Spuy have reported it as an unusual association with fracture scapula. Veysi et al. and Brown et al. also supported this finding. We have found only one patient, who was from the MRF group, with possible thoracic vascular injury. He had a periaortic hematoma. CT angiogram showed an intact aorta and the patient was discharged home after 12 days in good condition.

Our approach is different from others who have considered multiple fractures of the same scapula as separate fractures. We have studied the relationship between the number of fractured scapular regions, and the severity and distribution of injury. The lack of association between anatomic regions of scapular fractures and injury severity in previous studies may be explained by their retrospective nature and the small number of subjects in the majority of these studies leading to low power. Our study is a large prospective series of blunt trauma patients; hence, collected data are reliable. Male predominance in our study reflects the nature of the community where the male to female ratio is 2:1 having half of the population as expatriate laborers.

In clinical practice, trauma surgeons must look for serious injuries of the chest and spine (cervical and dorsal) when they encounter patients with MRF of the scapula. McGinnis and Denton have advised that all patients with even apparently isolated scapular fractures should be admitted to the hospital and have a follow-up chest radiograph within 24 to 72 hours. They thought this is essential to rule out pneumothorax, hemothorax, or pulmonary contusion. Our data indicate that more caution should be taken in patients with multiple-region fractured scapulae. Conversely, in patients with severe chest trauma, a high index of suspicion of a possible scapular fracture should be maintained. Similarly, based on our results, in patients with posterior structure injury, a scapular fracture, and often MRF, should be looked for.

In summary, associated injuries are common in patients with all types of scapular fractures. However, the ISS and AIS score for chest injuries are higher, and posterior structure injuries are more frequent in patients with fractures involving multiple scapular regions. Thorough assessment for chest, dorsal, and cervical spine injuries should take priority in the management of these patients. This may entail hospitalization with follow-up chest radiographs and trauma CT scanning if needed.

REFERENCES

A Novel Clinical Instrument for Predicting Delayed Recovery After Musculoskeletal Injuries

Carin Ottosson, MD, Hans Pettersson, PhD, Sven-Erik Johansson, PhD, Olof Nyren, MD, PhD, and Sari Ponzer, MD, PhD

Background: Early identification of patients at risk for delayed recovery after an injury is important to effectively target rehabilitation. This study presents a new instrument, the Prediction of Prolonged Self-Perceived Recovery After Musculoskeletal Injuries questionnaire (PPS), for prediction of self-perceived nonrecovery after musculoskeletal injuries.

Methods: On the basis of a historic cohort (model building set, n = 557), we constructed the PPS consisting of two demographic variables (educational level and working status), a crude injury classification, and patient-rated physical and mental complaints during the acute phase of the injury. We evaluated the PPS’s ability to predict self-perceived nonrecovery at 6 months in a new group of patients with minor musculoskeletal traffic-related injuries (validation set, n = 279).

Results: Our findings demonstrate that the PPS foresees an unfavorable course with a greater accuracy than prediction based exclusively on information about the injury. The overall percentage of correct predictions in the model building set was 77%. The overall percentage of correct predictions in the validation set was 67%. The sensitivity and specificity in relation to non-recovery at 6 months was 55% and 73%, respectively.

Conclusions: This is the first prospective clinical study in which an instrument is used for prediction purpose. On the basis of our results, we think that the PPS, even if not fully developed, can be used by clinicians as a tool for early identification of patients at risk for delayed recovery after trauma. A nonnegligible proportion of the patients who would benefit from additional rehabilitation are missed by the instrument in its present form. Further research is needed to verify our results.

Key Words: Recovery, Prediction, Trauma, Validation, Logistic regression.

I
njuries, including those related to traffic, are considered to be one of the major public health threats to people in productive ages, and even if most injuries are minor, they generate substantial costs for the individual and for society. Despite the often-trivial character of minor musculoskeletal injuries, clinicians often intuit that some individuals are at increased risk for delayed recovery. Factors such as working conditions before the injury, pre-existing psychopathologic disorders, inadequate pain-coping strategies, and high initial pain have been suggested to be predictive for the outcome, in addition to the injury itself and the medical and surgical treatment given. Therefore, an early identification of patients at risk for delayed recovery after an injury appears intuitively appealing to effectively target the resources for rehabilitation for those in need of extra support. Even though several studies have focused on risk factors, to our knowledge, there is no prediction instrument for delayed recovery after trauma.

On the basis of a historic cohort from our previous studies, we constructed a prediction model and a novel instrument, the Prediction of Prolonged Self-Perceived Recovery After Musculoskeletal Injuries questionnaire (PPS), for prediction of self-perceived recovery after trauma. This study aimed to evaluate the predictive ability of the PPS by applying it to a new group of patients.

MATERIALS AND METHODS

Construction of the Prediction Instrument

Patients in the Model Building Set

We compiled a historic cohort of 557 patients with various musculoskeletal injuries treated at an orthopedic emergency room of a large teaching hospital in a metropolitan region (Stockholm, Sweden). The patients were originally included in previous studies conducted during the years 1993 to 2001. Background and injury data for the patients in this cohort (76% of the originally included patients) are displayed in Table 1. The patients in this cohort were followed up at 4 months to 6 months by mailed questionnaires, phone interviews, or by a face-to-face interview. The outcome, self-perceived recovery, was assessed with the question, “Do you feel recovered after your injury?” (yes or no).

The Prediction Model

We used a logistic regression analysis to determine the predictor variables that were associated with the risk of re-
porting nonrecovery at follow-up. Variables considered for
the analysis were chosen based on published literature.5,10–12
The variables measured at baseline were age (continuous),
gender, marital status (married/cohabiting or single), working
status (working/studying or unemployed/retired), educational
level (university or less), current illness at time of injury (yes
or no),13 type of trauma (fall, traffic-related, sports and
other), type of injury (neck pain after a whiplash type of
injury, contusion, dislocation/distortion, or fracture/multiple
injuries) (Table 2), and the Injury Severity Score (ISS).14
Self-ratings of physical (pain) and mental (depression or
anxiety) complaints during the first days after the injury on
visual analog scales (VASs) were also tested as tentative
predictor variables in the model (Appendix, questions 3 and
4). To identify the essential predictor variables, we first
studied the crude associations of each variable with the odds
of nonrecovery in univariable models, and clearly unimpor-
tant variables were dropped. Second, we entered the remain-
ning variables in a multivariable model and kept those that
were significant. Main effects of included variables and their
interactions were tested with two-sided Wald test and re-
garded significant if $p < 0.05$. The Hosmer and Lemeshow
(H-L) goodness-of-fit test was used to examine if the model
adequately fitted the data.

We constructed a receiver operating characteristics
(ROC) curve to find a cut-point that maximized sensitivity
and specificity when predicting nonrecovery, and determined
the area under the curve to quantify the discriminative power.

Based on the significant variables in the prediction
model, a five-item questionnaire, the PPS, was constructed
(Appendix).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model Building Set</th>
<th>Validation Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 557</td>
<td>Percent</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>326</td>
<td>59</td>
</tr>
<tr>
<td>Male</td>
<td>231</td>
<td>41</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;24$</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>25–65</td>
<td>460</td>
<td>83</td>
</tr>
<tr>
<td>$\geq66$</td>
<td>17</td>
<td>3</td>
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<td>Education</td>
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<tr>
<td>University</td>
<td>163</td>
<td>29</td>
</tr>
<tr>
<td>&lt;University</td>
<td>394</td>
<td>71</td>
</tr>
<tr>
<td>Working</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>149</td>
<td>27</td>
</tr>
<tr>
<td>Yes</td>
<td>408</td>
<td>73</td>
</tr>
<tr>
<td>Type of injury</td>
<td></td>
<td></td>
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<tr>
<td>Contusion*</td>
<td>57</td>
<td>10</td>
</tr>
<tr>
<td>Neck pain†</td>
<td>139</td>
<td>25</td>
</tr>
<tr>
<td>Distortion‡</td>
<td>83</td>
<td>15</td>
</tr>
<tr>
<td>Fracture§</td>
<td>278</td>
<td>50</td>
</tr>
<tr>
<td>ISS</td>
<td></td>
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<td>$&lt;9$</td>
<td>542</td>
<td>97</td>
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<td>$&gt;9$</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Type of trauma</td>
<td></td>
<td></td>
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<tr>
<td>Fall</td>
<td>214</td>
<td>39</td>
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<tr>
<td>Traffic related</td>
<td>262</td>
<td>47</td>
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<tr>
<td>Sport</td>
<td>51</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>VAS Physical (pain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq24$</td>
<td>129</td>
<td>23</td>
</tr>
<tr>
<td>25–65</td>
<td>288</td>
<td>52</td>
</tr>
<tr>
<td>$&gt;65$</td>
<td>138</td>
<td>25</td>
</tr>
<tr>
<td>VAS Mental</td>
<td></td>
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<tr>
<td>$\leq5$</td>
<td>121</td>
<td>22</td>
</tr>
<tr>
<td>5–51</td>
<td>298</td>
<td>53</td>
</tr>
<tr>
<td>$&gt;51$</td>
<td>138</td>
<td>25</td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>313</td>
<td>56</td>
</tr>
<tr>
<td>No</td>
<td>244</td>
<td>44</td>
</tr>
<tr>
<td>Current illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>423</td>
<td>76</td>
</tr>
<tr>
<td>Yes</td>
<td>133</td>
<td>24</td>
</tr>
</tbody>
</table>

Values are presented as number and percent.

* Contusions and minor wounds at any part of the body.
† Neck pain related to whiplash type of injury.
‡ Dislocation or distortion.
§ Fracture or multiple injuries.

Table 1 Characteristics of the Patients in the Model Building Set (n = 557) and the Validation Set (n = 279)

Table 2 Injury Panorama Among Patients in the Model Building Set (n = 557) Coded as Whiplash Associated Disorders (WAD),* Contusion, Dislocation or Distortion of a Joint, or Fracture or Multiple Injuries

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck pain after a whiplash type of injury</td>
<td>139</td>
<td>25</td>
</tr>
<tr>
<td>Contusion of upper or lower extremity</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Contusion of face, spine or thorax</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Contusion combined with a minor wound</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Distortion of knee joint</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>Distortion or dislocation of shoulder joint</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Rupture of Achilles tendon</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sternum or clavicle</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Distal radius or hand</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Humerus</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Ankle or foot</td>
<td>121</td>
<td>22</td>
</tr>
<tr>
<td>Patella</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Tibia</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Femoral neck or femoral shaft</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Pelvis or spine</td>
<td>26</td>
<td>5</td>
</tr>
</tbody>
</table>

* Neck pain after a whiplash type of injury.

Evaluation of the Prediction Instrument

To evaluate the predictive ability of the PPS, we con-
ducted a second study involving new patients (validation set)
with traffic-related minor musculoskeletal injuries.

Inclusion and Follow-up of Patients in the Validation Set

Patients with minor or moderate (ISS $\leq 9$) traffic-related
musculoskeletal injuries sustained in the 24 hours before

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admission, aged 15 years to 65 years, who were intelligible in the Swedish language, and resided within the hospital’s catchment area were eligible for this study. All patients were treated and followed up according to the routines at our department, and those in need of rehabilitation (physiotherapy and other) were offered such depending on their injuries.

As shown in Figure 1, during the 16-month patient recruitment period, our inclusion criteria were met by 937 consecutive patients, 423 of whom were unavailable for contact because of missing addresses or phone numbers or no response to contact letters. Men and younger persons were slightly overrepresented in the latter, compared with the included patients. Another 118 patients declined participation. They did not differ from the included regarding age, gender, or type of injury. Because this validation study was part of a randomized intervention study determining the long-term (12 months) effects of an early psychosocial support program for patients with traffic-related orthopedic injuries, an additional 73 patients were excluded from this study because they had been randomized into the intervention group. Another nine patients did not complete all questionnaires and were therefore not included in this study. A total of 314 patients were enrolled, of whom another eight patients were excluded because of a technical error. All remaining patients completed the PPS during the first week after the injury. Background and injury data, collected at the same time for the final validation set (n = 279), are shown in Table 1. The patients were kept blinded from the PPS predictions.

All included patients were sent a questionnaire and a reminder 6 months after the injury and were asked the same question as the patients in the model building set, namely, “Do you feel recovered after your injury?” (yes or no) (n = 96). Patients not answering via mail were called by the study nurse and asked to report if they felt recovered or not (n = 183). The 279 patients (91%) responding formed the validation set.

Statistics
We used Fisher’s exact test to test the null hypothesis that the proportions of recovered patients were equal in the groups predicted to have a high and a low risk, respectively, for nonrecovery. The criterion for significance was 0.05, two-tailed. The sample size was calculated for the intervention study, of which this evaluation study was a part. For this study, we merely confirmed that the sample size was large enough to yield a significant result with 80% power. Based on the observed proportions in the model building set, the risk for nonrecovery was set to 70% for the high-risk group and 30% for the low-risk group. Thus, a total of 58 patients were required (29 in each group), which was within the limits for the intervention study.

The model’s ability to classify patients correctly was measured by sensitivity (true nonrecovery, i.e., proportion of patients predicted to report nonrecovery among those that did report nonrecovery) and specificity (true recovery, i.e., proportion of patients predicted to report recovery among those that did report recovery). Thus, a high sensitivity implicated that patients with a high risk of nonrecovery were identified, and a high specificity implicated that patients with a high chance of recovery were identified. An ideal model would have both a high sensitivity and a high specificity. We used the efficient-score method (corrected for continuity) to calculate the 95% confidence intervals (CIs) for the sensitivity and specificity. This method is suited for situations where the proportion is large, as is typically the case with measures of sensitivity and specificity.
We calculated the area under the ROC curve (trapezoid rule) to evaluate the models ability to discriminate, i.e., the models ability to correctly classify patients that would report recovery and nonrecovery. An area under the curve equal to 0.5 suggests no discrimination, 0.7 to less than 0.8 is acceptable, 0.8 to less than 0.9 is excellent, and above 0.9 is outstanding discrimination. We used the nonparametric method to calculate the SE for the area under the curve used in the CI and in the comparison of the ROC curves. This gives a conservative estimate of the SE, which implies that the risk of a false difference (type I error) in the comparison of the ROC curves is low. The statistical analysis was performed in SPSS version 13.0 (SPSS, Inc., Chicago, IL).

**Ethical Considerations**

The local Ethics Committee approved the study, and all patients gave their informed consent before inclusion.

**RESULTS**

**Characteristics of the Patients in the Model Building Set and in the Validation Set**

The patients in the model building set and in the validation set had similar distribution in most background variables except regarding the injuries; a fairly large proportion of the model building set patients had major musculoskeletal injuries (50%), whereas the validation set patients tended to have less severe injuries with whiplash-related neck injuries as the dominating type (60%) (Table 1). Female gender was predominant in the model building set compared with the validation set, but there were no differences in the recovery rate between the female patients (71 of 125 [57%]) and the male patients (91 of 154 [59%]) in the validation set at 6 months.

**The Prediction Model in the Model Building Set**

The variables that were independently predictive of self-perceived nonrecovery included type of injury, educational level, and self-ratings of pain (VAS Physical) and mental (VAS Mental) complaints during the first week after the injury (Table 3). Variables that did not have any significant association with nonrecovery were gender, age, family situation, current medical illness, and injury severity measured by injury severity score (ISS). Hosmer and Lemeshow statistics for the final model indicated that the model fit to the data was very good (*p* = 0.94).

ROC analysis (Fig. 2A) showed that the area under the curve was 0.80 (95% CI: 0.76–0.84), and that a cutoff point of 0.56 for the risk of not being recovered maximized the discriminatory ability of the instrument. Accordingly, patients with an estimated risk above this cut-point were classified into a high-risk group, and those with a risk below or equal to 0.56 were classified as having a low risk of nonrecovery. The sensitivity of this prediction was 86% (95% CI: 82–89), and the specificity 55% (95% CI: 48–63), with an overall percentage of correct predictions of 77% (Table 4).

To assess the increment in predictive ability offered by the PPS in comparison to prediction based solely on the injury type we measured the area under the ROC curve for both models (Fig. 2A). The area under the curve increased significantly (*p* < 0.05), from 0.67 (95% CI: 0.64–0.74) to 0.80 (95% CI: 0.76–0.84) when all variables in the model were used.

**Evaluation of the PPS in the Validation Set**

Of the 279 patients in the validation set, 112 patients (40%) were predicted as having a high risk of reporting nonrecovery and 69 of 112 (62%) also reported nonrecovery at 6 months, and of the 167 patients (60%) that were classified by the prediction model as having a low risk of reporting nonrecovery only 48 of 167 (29%) reported nonrecovery, (*p* < 0.001).

The PPS with a cutoff point of 0.56 had a sensitivity for nonrecovery of 59% (95% CI: 49–68) and a specificity of 73% (95% CI: 66–80) among the validation set patients, corresponding to an overall percentage of correct predictions of 67% (Table 4). The area under the ROC curve was 0.70 (95% CI: 0.63–0.76) when all predictor variables were in the model, compared with 0.55 (95% CI: 0.49–0.62) (*p* < 0.05) when the prediction was based exclusively on type of injury (Fig. 2B).

**DISCUSSION**

To our best knowledge, this is the first prospective study where a prediction instrument is used to predict outcome in terms of delayed recovery after musculoskeletal injuries. In contrast to previous studies focusing on predicting outcome after trauma, we have taken an additional step by constructing a clinically applicable prediction ruler, the PPS, and evaluated its predictive value in a new, independent set of patients. Our findings demonstrate that the PPS, consisting of simple demographic variables, a crude injury type classification, and self-rated pain and mental complaints during the acute phase of the injury, foresees an unfavorable course with a greater accuracy than prediction based exclusively on information about the injury. Among patients in the validation set predicted as having a high risk of reporting nonrecovery, 62% actually also reported nonrecovery at 6 months, whereas among patients predicted as having a low risk of nonrecovery, 29% in fact reported being nonrecovered at the 6 month follow-up.

The outcome measure chosen for this study was self-perceived recovery as reported by the patient. One might ask if a more objective measure, for example a test of musculoskeletal function, should have been used. However, we postulated that the transition out of the sick role and resumption of normal life involves an element of active decision and does not necessarily coincide with objective medical healing. Hence, the patient is the best judge of if he or she has recovered or not (independently of if the injury has medically healed). In support of this assumption, we have previously
demonstrated that self-perceived recovery is associated with functional health status as measured by the 36-item short form health survey (SF-36), albeit complete restoration of the SF-36 ratings seemed not to be necessary for feeling recovered.

The PPS was easy to use for both the staff and the patients and was completed in a couple of minutes. None of the patients had difficulties in filling in the questionnaire also evidenced by absence of missing PPS data. It should also be kept in mind that most of the injured patients, or their physicians, regardless of the severity of the injury, do not recognize the need of extra support before it is obvious that the rehabilitation does not progress as expected. Therefore, the main benefit of the simple PPS is to make the physician and their patients aware, in the early phase of the rehabilitation, of the individuals with a higher risk of delayed recovery. By using PPS, a ruler, and basically comparable with other algorithms for patient treatment, the risk of being regarded as a “psychiatric” case might be less, and the willingness to take part in an appropriate support program in an early phase of the rehabilitation might be of greater interest.

There are some limitations in the study. First, the outcome probability revision that follows from the use of the instrument derives mainly from its positive and negative predictive values, which are in turn highly dependent on the relative proportions of patients with good and poor prognosis among those who are tested. This potentially limits the applicability of the instrument in different patient populations.

### Table 3: Association Among the Predictor Variables and Self-Reported Nonrecovery at 4–6 mo After the Injury for Patients in the Model Building Set (n = 557)

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Nonrecovered/ Total (n/n)</th>
<th>Odds Ratio (CI)</th>
<th>Univariate</th>
<th>Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>225/326</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>159/231</td>
<td>1.0 (0.7–1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24</td>
<td>55/80</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–65</td>
<td>316/460</td>
<td>1.0 (0.6–1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥66</td>
<td>13/17</td>
<td>1.4 (0.4–5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>95/163</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;University</td>
<td>289/394</td>
<td>2.0 (1.3–2.9)</td>
<td>2.0 (1.3–3.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Working</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>255/408</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>129/149</td>
<td>3.9 (2.3–6.5)</td>
<td>2.5 (1.5–4.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Married</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>213/313</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>171/244</td>
<td>1.1 (0.8–1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current illness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>292/423</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not affecting rehab</td>
<td>71/103</td>
<td>1.0 (0.6–1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affecting rehab</td>
<td>20/30</td>
<td>0.9 (0.4–2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of injury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion*</td>
<td>23/57</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain†</td>
<td>71/139</td>
<td>1.5 (0.8–2.9)</td>
<td>1.8 (0.9–3.8)</td>
<td></td>
</tr>
<tr>
<td>Distortion‡</td>
<td>70/83</td>
<td>8.0 (3.6–17.6)</td>
<td>8.9 (3.7–21.4)</td>
<td></td>
</tr>
<tr>
<td>Fracture§</td>
<td>220/278</td>
<td>5.6 (3.1–10.2)</td>
<td>4.6 (2.4–9.0)</td>
<td></td>
</tr>
<tr>
<td><strong>ISS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>372/542</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥9</td>
<td>12/15</td>
<td>1.3 (1.2–1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VAS Physical/pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24</td>
<td>60/129</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–65</td>
<td>208/288</td>
<td>3.0 (1.9–4.6)</td>
<td>2.0 (1.2–3.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>116/140</td>
<td>5.6 (3.2–9.7)</td>
<td>2.8 (1.5–5.5)</td>
<td></td>
</tr>
<tr>
<td><strong>VAS Mental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>55/121</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–51</td>
<td>210/298</td>
<td>2.8 (1.8–4.4)</td>
<td>2.3 (1.4–3.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;51</td>
<td>119/138</td>
<td>7.5 (4.1–13.7)</td>
<td>4.2 (2.1–8.2)</td>
<td></td>
</tr>
</tbody>
</table>

All predictor variables are measured at baseline.

* Contusions and minor wounds at any part of the body.

† Neck pain related to whiplash type of injury.

‡ Dislocation or distortion.

§ Fractures and multiple injuries.
and underlines that it is critical that the validation-set patient population is representative of the patient populations for which this instrument is intended (in this case, working-age patients with musculoskeletal injuries and therefore, no older patients were included in the study).

Second, although the goal was to include all consecutive patients meeting our predefined criteria, we were able to include only one-third of the eligible patients. Bias would be introduced if the relative proportions with good and poor prognosis would deviate among nonparticipants compared with participants. Men and young persons were overrepresented among our nonparticipants, but our data suggest that neither gender nor age was linked to prognosis. Moreover, it is reasonable to assume that fewer than all lightly injured patients in everyday orthopedic practice would be interested in rehabilitation measures. We think that many of the patients who did not participate in our study would also have declined both PPS evaluation and targeted rehabilitation, had this been offered in routine practice. Therefore, our studied patients may be fairly representative of the patients who would be tested in real life.

Third, the poorer performance of our instrument in the validation set and the seemingly paradoxical shift from a sensitive to a specific test may to some extent be caused by differences in patient mix in the model building and validation sets. As judged from the area under the ROC curve, the overlap of the predictor distributions among patients predisposed to recover and those who were not was greater in the validation set. Clearly, the prognosis was, on average, worse in the model building set, as evidenced by an observed nonrecovery rate of 69%, compared with 42% in the validation set. Because the proportion with major injuries (mostly fractures) was much greater in the model building set, and patients with such injuries were at higher risk of nonrecovery at 4 months to 6 months, the prediction instrument assigned considerable weight to the presence of major injuries. In the model validation set, fractures accounted for 4% and contusions and neck pain for 90%. Hence, other predictors of nonrecovery may have played a greater role. It is conceivable that further development of the instrument may lead to separate sets of predictors for different injury spectra. Still, the admittedly imperfect prediction was sufficiently robust to increase the proportion with genuinely poorer prognosis more than twofold in the group predicted to have high risk, despite

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**Table 4** Sensitivity and Specificity for Nonrecovery Among Patients in the Model Building Set (n = 557) and in the Validation Set (n = 279)

<table>
<thead>
<tr>
<th>Predicted</th>
<th>Observed</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonrecovery</td>
<td>Recovery</td>
<td></td>
</tr>
<tr>
<td><strong>Model building set (n = 557)</strong></td>
<td>331</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Nonrecovery</td>
<td>53</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td><strong>Validation set (n = 279)</strong></td>
<td>69</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Nonrecovery</td>
<td>48</td>
<td>119</td>
<td></td>
</tr>
</tbody>
</table>

* Sensitivity = 331/384 = 86%; specificity = 96/173 = 55%; total correct 77%.
† Sensitivity = 69/117 = 59%; specificity 119/162 = 73%; total correct 67%.

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Fig. 2. ROC curves for the model building set (n = 557) (A) and for the validation set (n = 279) (B). The solid line represents prediction when all variables in the model are used and the dotted line when only the type of injury is used as a single predictive variable. True nonrecovered (Sensitivity) and false nonrecovered (1-Specificity).
the differences in patient mix, and the instrument performed significantly better than predictions based on the injury type alone (which was just as good as chance), both in the model building set and in the validation set.

Fourth, there could be other unrecorded factors related to self-perceived nonrecovery such as general complications, involvement in litigation, or pre-existing psychiatric health problems that were not fully considered. Fifth, the patients in the model building set were included about 10 years before the validation set patients. It is unlikely that the different time periods would have any substantial impact on the recovery rate because the care and rehabilitation services for less seriously injured have unfortunately not changed much during the years even if trauma care has improved generally. Finally, the sixth limitation of our study was that the former were evaluated at 4 months to 6 months after the injury, whereas the latter were evaluated at 6 months postinjury. However, this slight difference in the follow-up time is probably not of clinical importance on group level.

When constructing our prediction model, a large range of variables were considered. Age or current illness did not show any significant association with nonrecovery in our model probably because of the fact that the age distribution in our population was homogenous (only patients of working age were included), and the population was rather healthy. Somewhat more surprising was the fact that gender did not affect the prediction model because previous studies have suggested that women are at risk of worse outcome after musculoskeletal injuries. As the model building and validation sets differed with regard to gender, a separate analysis was performed, but no difference in recovery rate between women and men in the validation set was noted. This is in line with recently published data, which showed no gender differences regarding outcome among patients with musculoskeletal injuries.

The main variables in our prediction model, i.e., initial pain and mental distress, educational level, working status, and the injury itself have also been shown by others to be predictive for delayed recovery. Physical pain during the acute phase of the injury was a strong predictor in our model, which is in accordance with a systematic review by Cote et al., showing that initial pain has a predictive value in cases of whiplash injuries. This finding was confirmed by Hendriks et al., who also recognized work-related activities as being predictive for outcome. Educational level has also been previously shown to be a factor affecting the outcome among injured patients and is probably also related to working status. Depression and anxiety during the acute phase of the injury has been recognized as a predictor of less good outcome and was therefore included in our model. Because there was no doubt that the injury itself affects the outcome, it was clear that the injury severity had to be included in the model. ISS is an often used injury severity measure for predicting survival, but it had no predictive value in our model focusing on minor, seldom life-threatening, musculoskeletal injuries. Therefore, we chose a clinically based simple four-category injury severity “scoring” for our prediction instrument, easily calculated by the regular staff at emergency department or on a ward. The patients with fractures and requiring inpatient treatment were classified as having the worst injuries, distortions, and dislocations treated in an outpatient setting as the second worst category. Because whiplash-related injuries are frequent at any emergency department and might have a different prognosis compared with other minor musculoskeletal injuries (often needing no specific medical treatment), they were arranged to a separate category.

A better accuracy of the prediction could probably have been yielded by adding some other aspects such as the patient’s coping strategies and family situation in the questionnaire. However, because the PPS was designed to be used by the regular staff during the first days after the injury, the number of questions had to be limited. By choosing VAS ratings as a measure of pain and mental complaints instead of adding more sophisticated questionnaires for pain, depression, or anxiety allowed us to keep the questionnaire short, but still get overall information about the patients’ current physical and mental status of the acute postinjury situation, a very important predictive aspect of recovery as previously shown by others. Our choice of VAS was supported by previous studies that have shown that VAS correlates well with other more sophisticated measures, for example, clinically used depression scales and mood swings in patients with anxiety disorders.

Although perfect prediction is probably unattainable, the realistic goal is to improve the selection of patients who are likely to benefit from special rehabilitation efforts. Given the limited resources available for targeted rehabilitation, and because unnecessary treatment might augment patients’ feelings of not being well and result in unmotivated costs, it is more important that patients who are selected for rehabilitation really have the needs, rather than making sure that every single patient with these needs are identified. Hence, in routine care, it is more important to “rule in” patients with such needs than to rule them out among those whose predictions indicate a quick recovery. To “rule in”, specificity is more important than sensitivity. In our validation set, with minor traffic-related musculoskeletal injuries, the specificity was considerably higher than the sensitivity, suggesting the PPS having a better ability to “rule in” than to “rule out”.

Identifying and successfully treating patients at risk for delayed recovery would most likely reduce the personal suffering and the long-term costs for the society. On the basis of our results, we think that the PPS Questionnaire, even though not fully developed, can be used by clinicians as a tool for early identification of patients at risk for delayed recovery after trauma. Admittedly a nonnegligible proportion of the patients who would benefit from additional rehabilitation are missed by the instrument in its present form, but it provides a better prediction than one based exclusively on injury char-
acteristics. Further research is needed to verify the usefulness of the PPS in a clinical setting.

APPENDIX

The PPS-Risk Questionnaire

Please, answer the questions below by marking with an X in the box (☑)

1. What is the highest level of your education?
   - Secondary School/upper secondary school
   - University/college of higher education

2. What is your current employment status?
   - Working
   - Retired
   - On sick-leave
   - Other

3. Please, rate the level of your injury-related physical discomfort/pain during the last 2-3 days my making a mark (X) on the line below.

   0 no discomfort
   10 maximum discomfort

4. Please, rate the level of your psychological discomfort (feelings of depression or anxiety) during the last 2-3 days my making a mark (X) on the line below.

   0 no discomfort
   10 maximum discomfort

5. To be filled in by the staff
   - Whiplash related injury (rear end collision)
   - Minor contusion or sprain (not requiring any specific medical treatment)
   - Distortion/Minor fracture (out-patient treatment)
   - Multi-trauma or major fracture (all hospitalized patients)

Fig. 3.

REFERENCES


Factors Influencing Discharge Location After Hospitalization Resulting From a Traumatic Fall Among Older Persons

Hyun J. Lim, PhD, Raymond Hoffmann, PhD, and Karen Brasel, MD

Objective: To identify significant demographic, clinical, and nonclinical factors among elderly persons influencing the discharge location after hospitalization resulting from a traumatic fall.

Methods: Population-based case-only study with use of data from the 2003 National Trauma Data Bank. The study analysis included 47,234 subjects admitted to 1 of 405 hospitals in the United States between 1989 and 2003, and aged between 65 and 89 years. Demographic characteristics, clinical factors, and discharge location were obtained from the database.

Results: Eighty-three percent were discharged to home, 7% to a nursing home, and 10% to a rehabilitation facility. Female patients and white patients were more likely discharged to a nursing home or a rehabilitation facility than to home. Compared with commercial insurance, a patients who had Medicare was more likely discharged to a nursing home (odds ratio = 20.9; 95% confidence interval: 18.2–23.9) or a rehabilitation facility (odds ratio = 5.39; 95% confidence interval: 4.86–5.96) than to home. A patient who was injured in the face or neck, thorax, or abdomen was less likely discharged to a nursing home or a rehabilitation facility than to home when compared with a patient injured in an upper and lower extremity. A patient with an injury to the spine was more likely discharged to a rehabilitation facility than to home when compared with a patient injured in any other body region.

Conclusion: Gender, race, payment type, body region injured, Injury Severity Score, physiologically based Emergency Department Revised Trauma Score, and need for intensive care unit care were significant predictors of discharge location. Understanding and addressing the factors found in this study can improve the discharge planning process and posttreatment management.

Key Words: Elderly, Falls, Injury, Discharge location.


Falls are the leading cause of injury deaths and are the most common cause of nonfatal injuries and hospital admission for trauma among people more than 65 years old. More than one-third of adults aged 65 years or older fall each year. Of those who fall, 20% to 30% suffer moderate to severe injuries that reduce mobility and independence, and increase the risk of premature death. In 2003, more than 1.8 million people aged 65 and older were treated in emergency departments for fall-related injuries, and more than 421,000 were hospitalized. Falls are also a leading cause of traumatic brain injuries, and among older adults, the majority of fractures are caused by falls. The risk of falling increases with age, and the rates of fall-related death for older adults increase sharply with advanced age. Studies also show that older adults who have fallen previously or who stumble frequently are two to three times more likely to fall within the next year. Among people aged 65 years and older, those who fall are four to five times more likely to be admitted to a long-term care facility for a year or longer.

Because residential environment affects the risk of falling in the elderly population and patients who have fallen previously are more likely to have multiple falls, the patient’s discharge location is important for planning post-discharge patient care as well as a subsequent fall prevention. Little is known about discharge location and the factors that affect it. This analysis was undertaken to identify significant demographic, clinical, and nonclinical factors influencing discharge location after hospitalization resulting from a traumatic fall among elderly persons. Understanding and formally incorporating these factors into discharge planning will enhance subsequent management of geriatric patients injured in falls.

PATIENTS AND METHODS

The National Trauma Data Bank (NTDB) was created by the American College of Surgeons in 1989. A total of 405 hospitals in 43 states contributed some standard demographic and clinical information from hospital-based trauma registries into the NTDB 2003 database, which has accumulated approximately 732,000 records to date. The 2003 NTDB, which is a national database of injured subjects, reported that falls account for 16.7% of cases and fall injury case fatality is 3.9%. It also reported that the incidence of falls peaks around age 82 and deaths after falls gradually increase up to the 80 to 89 years old range. For our study, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to identify fall injury patients in the database.
The NTDB. The inclusion criteria were age between 65 and 89, original injury occurred inside the United States, and discharged alive. Demographic and clinical information was also obtained from the NTDB 2003 database.

The primary outcome of this study was the discharge location of patients after hospitalization from a traumatic fall. This discharge location outcome was grouped into five categories: home (home, home with home health, jail, or psychiatric facility), nursing home, rehabilitation facility, hospital (transferred to another hospital), and other. However, the data for the analysis was restricted only to home, nursing home, and rehabilitation facility. Transferring to another hospital and other were excluded from the analysis because they were an intermediate step for discharge and had a small sample size, respectively. Payment type was categorized into five categories: commercial, Medicaid, Medicare, other, and uninsured. The body region injured was categorized into six categories: head, face and neck, thorax, abdomen, spine, and upper and lower extremity. Injury severity was assessed using the anatomically based Injury Severity Score (ISS) and the physiologically based Emergency Department Revised Trauma Score (EDRTS) at admission. Location of injury was categorized into six categories: home, other residential institution (including nursing home), nonresidential inside (industrial, public building), nonresidential outside (highway, recreation, sport), and unspecified. The American College of Surgeons gave us permission to use this data set, and the Institutional Review Board at the Medical College of Wisconsin also approved this study (286-05).

Descriptive statistics were used to summarize data. A student’s t test or analysis of variance was used for continuous variables and a \( \chi^2 \) test was used to compare categorical variables. Correlation analysis was conducted between covariates. A random effects mixed model was used in this study to include the uncertainty induced by estimating the between-hospital variance. A random effects mixed model takes account of the extra variation in the covariates between hospitals by treating hospital as a random effect. This approach provides and increases the accuracy of the covariate estimate in the model.18,19 To identify potential predictors for the final model, the variables were first looked at individually using univariate analysis of that discharge versus home. Variables were identified as significant using a 0.05 \( \alpha \) level, and only these were included in a stepwise method to determine a final model. For each effect from the models the odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Univariate and multivariable random effect mixed models were implemented by the SAS macro GLIMMIX procedure using SAS Version 9 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 47,234 subjects were eligible for the study analysis. Study selection criterion and the profile of the discharges are shown in Figure 1. Sixty-five percent (n = 30,675) were men and 68% were white (Table 1). The mean age was 78.3 years (±6.5 SD). The majority (46%) used commercial insurance as their primary payment type and 20% were uninsured. The most common primary body region injured was upper or lower extremity (38%) and 28% were injured in the head, face, or neck. The mean ISS was 9.1
(±8.1 SD; quartiles = 4–11) and mean length of hospital stay (LOS) was 6 days (±11 SD; quartiles = 1–7).

Approximately 83% were discharged to home, 7% to a nursing home, and 10% to a rehabilitation facility. Similar discharge proportions were observed through a year, which indicates no specific trend over time. Details of the distribution of the place of injury by discharge location are given in Table 2. Clearly, Table 2 illustrates that the location of injury did not relate to discharge location.

The analysis showed that seven factors were associated with discharge location in the univariate logit models (Table 3): gender, race, payment type, body region injured, ISS, EDRTS, and need for intensive care unit (ICU) care. Of the seven factors, the body region injured was not considered in the multivariate models because of substantial missing cases (44.6%). However, in the univariate analysis, a patient who was injured in the face or neck, thorax, or abdomen was less likely discharged to a nursing home or a rehabilitation facility than to home when compared with a patient injured in the upper or lower extremity. A patient who was injured in the face or neck was less likely discharged to a rehabilitation facility than to home when compared with a patient injured in an upper and lower extremity (OR = 0.48; 95% CI: 0.41–0.56). A patient with a spine injury was more likely to be discharged to a rehabilitation facility than to home compared with a patient injured in any other body region.

The multivariable random effect mixed model (Table 4) showed that gender, race, insurance, ICU care, ISS, and EDRTS were all associated with discharge location. Women

### Table 2 Distribution of Discharge Location by Place of Injury (N = 47,234)

<table>
<thead>
<tr>
<th>Place of Injury</th>
<th>Discharge to Home</th>
<th>Discharge to Nursing Home</th>
<th>Discharge to Rehabilitation Facility</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home (%)</td>
<td>23,578 (83)</td>
<td>2,065 (7)</td>
<td>2,779 (10)</td>
<td>28,422</td>
</tr>
<tr>
<td>Residential Institute (%)</td>
<td>4,875 (83)</td>
<td>430 (7)</td>
<td>584 (10)</td>
<td>5,889</td>
</tr>
<tr>
<td>Nonresidential inside* (%)</td>
<td>2,211 (83)</td>
<td>182 (7)</td>
<td>270 (10)</td>
<td>2,663</td>
</tr>
<tr>
<td>Nonresidential outside† (%)</td>
<td>1,425 (83)</td>
<td>127 (7)</td>
<td>173 (10)</td>
<td>1,725</td>
</tr>
<tr>
<td>Unspecified (%)</td>
<td>5,812 (82)</td>
<td>549 (8)</td>
<td>707 (10)</td>
<td>7,068</td>
</tr>
<tr>
<td>Total</td>
<td>37,901</td>
<td>3,353</td>
<td>4,513</td>
<td>45,767</td>
</tr>
</tbody>
</table>

* Industrial, public.
† Street, highway, recreation, sport.

Missing injury place = 1,467.

### Table 3 Univariate Analysis of Nursing Home Versus Home, and Rehabilitation Versus Home With Odds Ratio and 95% Confidence Interval

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Nursing Home vs. Home*</th>
<th>Rehabilitation vs. Home*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>3.49 (2.23–3.77)</td>
<td>1.72 (1.62–1.83)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>0.44 (0.39–0.51)</td>
<td>0.56 (0.51–0.61)</td>
</tr>
<tr>
<td>Other</td>
<td>0.28 (0.23–0.35)</td>
<td>0.46 (0.4–0.52)</td>
</tr>
<tr>
<td>Payment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1.63 (1.35–1.96)</td>
<td>0.9 (0.8–1.02)</td>
</tr>
<tr>
<td>Medicare</td>
<td>21.9 (19.5–24.6)</td>
<td>3.92 (3.61–4.26)</td>
</tr>
<tr>
<td>Other</td>
<td>1.93 (1.52–2.47)</td>
<td>0.78 (0.66–0.94)</td>
</tr>
<tr>
<td>Uninsured</td>
<td>0.53 (0.42–0.66)</td>
<td>0.45 (0.40–0.51)</td>
</tr>
<tr>
<td>Body region injured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper or lower extremity</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Head</td>
<td>1.14 (0.95–1.36)</td>
<td>0.89 (0.78–1.02)</td>
</tr>
<tr>
<td>Face or neck</td>
<td>0.53 (0.43–0.66)</td>
<td>0.48 (0.41–0.56)</td>
</tr>
<tr>
<td>Thorax</td>
<td>0.73 (0.58–0.9)</td>
<td>0.75 (0.65–0.87)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.41 (0.33–0.5)</td>
<td>0.64 (0.55–0.75)</td>
</tr>
<tr>
<td>Spine</td>
<td>0.92 (0.75–1.2)</td>
<td>2.24 (2.01–2.5)</td>
</tr>
<tr>
<td>ISS</td>
<td>1.06 (1.05–1.06)</td>
<td>1.12 (1.11–1.12)</td>
</tr>
<tr>
<td>EDRTS</td>
<td>0.85 (0.83–0.87)</td>
<td>0.72 (0.7–0.73)</td>
</tr>
<tr>
<td>ICU care</td>
<td>Not needed</td>
<td>1.0</td>
</tr>
<tr>
<td>Needed</td>
<td>1.5 (1.38–1.64)</td>
<td>5.32 (4.99–5.68)</td>
</tr>
</tbody>
</table>

* Discharge to home is the reference group.

### Table 4 Multivariable Analysis of Nursing Home Versus Home, and Rehabilitation Versus Home With Odds Ratio and 95% Confidence Interval

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Nursing Home vs. Home†</th>
<th>Rehabilitation vs. Home†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>2.58 (2.31–2.88)</td>
<td>1.68 (1.55–1.83)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>0.64 (0.54–0.77)</td>
<td>0.73 (0.65–0.82)</td>
</tr>
<tr>
<td>Other</td>
<td>0.63 (0.48–0.83)</td>
<td>0.6 (0.51–0.79)</td>
</tr>
<tr>
<td>Payment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1.35 (1.07–1.69)</td>
<td>0.8 (0.69–0.92)</td>
</tr>
<tr>
<td>Medicare</td>
<td>20.9 (18.2–23.9)</td>
<td>5.39 (4.86–5.96)</td>
</tr>
<tr>
<td>Other</td>
<td>1.94 (1.46–2.57)</td>
<td>0.74 (0.6–0.92)</td>
</tr>
<tr>
<td>Uninsured</td>
<td>0.54 (0.41–0.71)</td>
<td>0.50 (0.43–0.58)</td>
</tr>
<tr>
<td>ISS</td>
<td>1.07 (1.06–1.08)</td>
<td>1.09 (1.09–1.1)</td>
</tr>
<tr>
<td>EDRTS</td>
<td>0.86 (0.83–0.87)</td>
<td>0.85 (0.83–0.87)</td>
</tr>
<tr>
<td>ICU care</td>
<td>Not needed</td>
<td>NS</td>
</tr>
<tr>
<td>Needed</td>
<td>2.48 (2.24–2.74)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

† Discharge to home is the reference group.
Factors of Discharge Location After Geriatric Fall

This study identified significant demographic, clinical, and nonclinical factors that influenced whether an older person was discharged to a nursing home, a rehabilitation facility, or to home after a traumatic fall. Although it is recognized that the elderly who fall are likely to become more dependent and have a higher likelihood of requiring long-term residential care, individual factors associated with discharge location in this population are incompletely understood. This information is becoming more important in the current system of healthcare, where patients are hospitalized only for acute need. Hospital LOS is decreasing, with economic pressure to meet increasingly stringent LOS benchmarks. With shorter LOS comes greater postdischarge needs as patients continue recovery. The ability to identify factors available early in a patient’s hospital course that might predict discharge location could allow discharge planning to begin earlier, making the process both smoother and more patient-friendly. Postdischarge fall prevention efforts, necessary because of the high rate of fall recidivism, may require time to implement; earlier information about discharge location might lead to increased effectiveness.

Two factors found to be significantly associated with discharge location related to individual characteristics. There are several possibilities explaining the gender difference. Women have a longer life expectancy than men do, and currently make up a larger percentage of nursing home residents. As marital status is not available in the NTDB, the influence of marital status on discharge location is unclear. Elderly married women tend to be in poorer health and are most vulnerable to stress than unmarried women, perhaps increasing the likelihood that they be discharged to a location other than home. The increased stress is not mitigated by social support, suggesting that the social contexts affecting the health of elderly women, and likely discharge location after acute hospitalization, are complex. Nonwhites were more likely to be discharged home, which is consistent with previous studies documenting lower numbers of nonwhites in nursing homes and longer time to nursing home placement for nonwhites in a variety of disease states. Given the lack of home health services in these same populations, it has been suggested that this may reflect cultural differences in expectations of family support when a family member is ill or in need. Patients with more severe injuries, measured anatomically by ISS, physiologically by EDRTS, and need for ICU care were less likely to be discharged home. Type of injury has differing effects on mobility and self care and thus affects discharge disposition; patients with extremity and spine injuries are much less able to care for themselves and may be on bed rest for care of their injuries, necessitating nursing home care or some degree of rehabilitation. Reflecting clinical practice, patients with head injury were less likely to be discharged to a rehabilitation facility than to home compared with patients with extremity injury, possibly reflecting that patients with severe head injury are often not candidates for rehabilitation if they are unable to participate in rehabilitation activities. They were equally likely to be discharged to a nursing home or home. Those with minimal head injury may be discharged home, whereas those with significant head injury likely go to a nursing home. With only an anatomic description of head injury available, and not a functional description, it is difficult to analyze this group further.

This study showed that payment type was the most significant independent factor associated with discharge location, implying that discharge location is strongly influenced by economic status. This reflects the differing admission requirements among trauma centers, nursing homes, and rehabilitation facilities. Hospitals are required to care for injured patients regardless of insurance status. However,
nursing homes and rehabilitation centers, because they do not provide treatment for immediate life-threatening conditions, are able to base admission on ability to pay (primarily with insurance). Rehabilitation facilities also require that patients are able to participate in a defined rehabilitation program. Patients with similar injuries and functional status are discharged to a rehabilitation facility if it is in their insurance plan, to a nursing home if no rehabilitation facility is available, or home if they have no nursing home benefits in their insurance coverage.26–28

Our study had several limitations. Because this was an observational study, we were unable to collect sufficient data on several factors that we thought might be of interest, because of the limited amount of information. These included residential place of abode, type of injury, type of procedure, and other socioeconomic variables that have been shown by others to influence discharge status.29 Missing values in the database were also a concern. After the exclusions and missing observations, a total of 47,234 patients were used in the complete analysis. Patterns of missing values were investigated, and all were random.30,31 Another limitation was that the NTDB-contributing hospitals are known to more heavily represent large, academic trauma centers, of which 70% of Level I and 53% of Level II hospitals are submitting data to the NTDB. These hospitals are known to be more resource-intensive and may have nonrepresentative discharge patterns. Because data contribution to the NTDB is voluntary and nonrepresentative, it cannot be used for population estimates. Hospitals that care for an elderly population that is significantly different from the one described with respect to race, insurance status, or injury severity may find differences in discharge location than those reported here. In addition, hospitals in areas where there is availability of rehabilitation and skilled nursing facilities may differ from areas supporting large Level I or Level II trauma centers may also find different results.

Our analysis indicated that gender, race, payment type, body region injured, ISS, EDRTS, and need for ICU care were significant predictors of discharge location. These variables are known at hospital admission or shortly thereafter. This combination of clinical and nonclinical factors presented by each patient should be formally incorporated early into the discharge planning process. Further research is necessary to determine whether these patients ultimately return home, if there is a way to further identify these patients, and how this information might help in implementing fall prevention efforts.

REFERENCES


Base Deficit-Based Predictive Modeling of Outcome in Trauma Patients Admitted to Intensive Care Units in Dutch Trauma Centers

Frank Kroesen, MD, Taco S. Bijlsma, MD, PhD, Mike S. L. Liem, MD, PhD, J. Dik Meeuwis, MD, PhD, FACS, and Luke P. H. Leenen, MD, PhD, FACS

Background: Worldwide, the base deficit is available as an objective indicator of acid base status. We used the base deficit as a measure of physiologic derangement in a Trauma and Injury Severity Score (TRISS)-like model as a predictor for outcome in trauma patients.

Methods: We prospectively recorded data of 349 consecutive trauma patients admitted to the intensive care unit and calculated Revised Trauma Score, Injury Severity Score and Abbreviated Injury Scale, and TRISS and correlated them with the simultaneously determined base deficit value. The delta base deficit is introduced, which is the absolute difference of the base deficit from its normal range (−2 to 2). A statistical model analogous to the TRISS model was designed in which the physiologic disturbance reflected by the Revised Trauma Score was replaced by the delta base deficit [Base Excess Injury Severity Scale (BISS) model]. Calculating the area under the curve (AUC) of the respective receiver operating characteristic curve compared these two models. Finally, the BISS model was validated in a patient group from another tertiary referral hospital in which similar data were recorded prospectively.

Results: We demonstrated a significant correlation between the delta base deficit and the calculated trauma scoring systems. Moreover, the delta base deficit is significantly correlated with mortality. The BISS performed better than the TRISS did when evaluated by the AUC of the receiver operating characteristic curves (AUC 0.806 vs. 0.803, respectively). Validation in an independent prospectively compiled dataset from another referral center showed comparable and even better results (AUC 0.891 vs. 0.885, respectively).

Conclusions: The performance of our proposed BISS model was superior to that of the TRISS model in the populations under investigation. Nevertheless, given the ease of assessment and the objective value of the base deficit, it may be considered as a good method to predict outcome and evaluate care of trauma patients. Whether this can be translated to trauma patients in general needs further investigation.

Scoring systems are required as a basis for quality assessment and improvement. They have to be easily obtained and unequivocal in their use. In trauma over the years, the Trauma and Injury Severity Score (TRISS) methodology has been the mainstay as a basis for assessment of performance and evaluation. Despite critique it has been, until now, evaluated as the most reliable tool for this purpose.

Combining the Revised Trauma Score (RTS)\(^1,2\) and the Injury Severity Score (ISS)\(^3–6\) into the TRISS\(^7\) methodology, addresses both physiologic derangement as well as anatomic injury into the equation for calculating survival probability.

Nevertheless, there are some pitfalls in the use of the anatomic part, which has been addressed in literature manifold, as well as in the physiologic part, the RTS. Obtaining the values that compose the RTS is partly subjective, but can also be hampered when the patient has consumed alcohol or drugs. Moreover, prehospital care improves and highly trained healthcare professionals treat patients on the street, adding advanced life-support techniques such as intubation and the use of medication to the treatment, making an adequate assessment of the Glasgow Coma Score (GCS) at the time of hospital arrival hampered even more. Because the Glasgow coma scale is the major constituent in the coded RTS, this value has major impact on the calculated survival probability (Fig. 1).

Because the base deficit was demonstrated to have a good correlation with the outcome of trauma patients and was a predictor for transfusion requirements and risk of complications,\(^8,9\) we postulate that the physiologic disturbances in trauma patients could be very well assessed by use of the base deficit. It has the advantage that it is a simple objective measure, available in every hospital and part of the diagnostic armamentarium already used in most major trauma patients.

We hypothesized that replacing the RTS in the TRISS equation with the base deficit would perform as good as the original equation, with the possible advantage of unequivocal assessment of physiologic disturbance in obtunded and intubated patients.

DOI: 10.1097/TA.0b013e318151ff22
METHODS

We used a stepwise approach based on a modeling trauma database (the Tilburg dataset) and tested the performance of the newly developed model in a separate trauma database (the Utrecht dataset).

The Tilburg Dataset

We prospectively evaluated all patients presented to the emergency department in the St. Elisabeth Hospital sustaining trauma between January 1994 and April 1997. The St. Elisabeth Hospital is a 650-bed teaching hospital with all the facilities required for a Level I trauma center.

Requirements to enter the study in the Tilburg dataset was an injury sufficiently severe to warrant admission to the intensive care unit (ICU) after evaluation in the emergency department.

We assessed the GCS, respiratory rate, blood pressure, and the calculated RTS. In addition, the Abbreviated Injury Score (AIS) and ISS was determined. Next, the TRISS methodology was used. This methodology combines four elements (RTS, ISS, age, and injury type [blunt or penetrating]) to predict outcome (mortality). Finally, in 312 patients an arterial blood gas sample was taken during trauma screening in the emergency department to measure the base deficit. The remaining patients had their blood sample taken in the operating room or at the time the patient arrived in the ICU. All the samples were taken within the first hour after admission to the hospital. The base deficit was considered normal in a range between −2 and 2.

The Utrecht Dataset

From the University Medical Center at Utrecht (UMC Utrecht) another dataset was independently scored. Between January 1995 and December 1997, patients were prospectively studied, resulting in a validation dataset. The UMC Utrecht is a tertiary referral center of 850 beds and is a Level I trauma center in another region in the Netherlands. Doctors taking trauma call in both institutions were fully ATLS (advanced trauma life support) trained and backed up by trauma surgeons.

Procedure

The base deficit can be negative or positive depending on the metabolic disturbances in the patient, and both the negative and positive base deficits are the result of pathologic processes. Therefore we introduced the delta base deficit. This is the absolute difference of the base deficit from its normal range, which in both hospitals is −2 to 2. For example, −8 is −6 of the normal range so the delta base deficit becomes 6; but +8 will also become 6.

The delta base deficit was compared for survivors and nonsurvivors. The correlation was calculated between delta base deficit on one hand and the ISS, RTS scores, and TRISS survival probability on the other hand.

Step 1

To make it possible to compare the old and new strategy, we used logistic regression to calculate new coefficients from the data of the St. Elisabeth Hospital. The coefficients from the Major Trauma Outcome Study (MTOS) database were used for comparison.

Step 2

Then, by replacing the RTS with the base deficit in the TRISS equation, the new model (BISS) was calculated. Also, by logistic regression, the new coefficients were calculated for this new model.

Step 3

To test the newly developed model we used the independently gathered data from the UMC Utrecht.

Age

To further improve the models, we used age as a continuous variable because Steyerberg et al.,10 elucidated that dichotomization can cause a substantial loss of information in smaller groups when building new regression models.

Statistical Analysis

Medians used as continuous data were not normally distributed and a Mann-Whitney U test was applied to compare these data. Correlations were calculated with the Spearman rank correlation coefficient. The new weight estimates (coefficients) and the BISS model were calculated with stepwise (forward) logistic regression analysis. The Hosmer and Lemeshow test was used to test the calibration performance of the models. Receiver operating characteristic (ROC) curves were used to compare the original TRISS model and the TRISS model with our coefficients, with the BISS model both with and without continuous data for age. The areas

Fig. 1. ROC curve of the Tilburg dataset using the TRISS model with MTOS coefficients. Area under the curve is 0.806.
under the curves (AUCs) of these ROC curves were calculated and compared. SPSS (version 9.0, SPSS Inc., Chicago, IL) was used to perform all calculations.

RESULTS
The First (Tilburg) Dataset

From January 1994 through April 1997, 349 consecutive trauma patients were brought to our emergency department who met inclusion criteria. The majority, 341 patients, sustained blunt trauma, 8 sustained penetrating trauma, and none had burns. Median age was 36 years and 66% of the patients were male. The median time between initial prehospital trauma call and the collection of the blood gas sample at our emergency department was 70 minutes. Median time between arrival in hospital and retrieval of the blood gas sample was 15 minutes. Results of the blood sampling were reported in 8 minutes.

The median RTS was significantly higher for survivors (7.84) versus that of nonsurvivors (5.97) (Mann-Whitney U, p < 0.01). The median AIS or ISS was significantly lower for survivors (16 versus 25) (p < 0.01). The survival probability according to TRISS was also significantly higher (0.98 versus 0.89) (p < 0.01). A blood gas sample taken at admission into the emergency department was collected for 312 of the 349 patients. The other 37 patients had blood gas samples taken in the operating room or ICU. For these samples, the delta base deficit was significantly higher in the survivors (2.07) versus that in the nonsurvivors (3.77) (p = 0.006). There were no differences detected in the pH of these blood gas samples; it was 7.35 in both groups. Correction for the respiratory component showed no significant difference either (7.36 versus 7.33).

The delta base deficit is significantly correlated with mortality (Spearmann rank correlation, ρ = −0.156 and p < 0.01). Correlation with the trauma scores was significant (Table 1). A higher delta base deficit correlates with a lower RTS, a higher ISS, and a lower probability of survival according to TRISS scored with the weight estimates of the MTOS study.

Patient mortality was 14% (48 of 349 patients). Causes of death were brain death in 25, multiorgan failure in 4, cardiac tamponade in 2, and in 1 case the exact cause of death could not be determined. In 2 of 25 cases in which the cause of death stemmed from brain trauma, further treatment was withheld because of poor prognosis. Of those who died, 33 patients had metabolic acidosis, 11 patients were in the normal range, and 4 had a metabolic alkalosis. Mortality is 11% (11 of 103) in the group with a metabolic acidosis. Mortality is 18% (33 of 187) in the group with a metabolic acidosis. The mortality rate in the group with a metabolic alkalosis was also high (20%; 4 of 20).

Logistic regression for the Tilburg population gives the following weight estimates: −0.070 for the AIS, −1.80 for age, 0.38 for the RTS, a constant of 1.39, and the Hosmer and Lemeshow statistic is 0.53. The new weight estimates for the BISS model are −0.082 for the AIS, −0.046 for age, −0.096 for the delta base deficit, a constant of 5.78, and the Hosmer and Lemeshow statistic is 0.33.

Using TRISS with the weight estimates of the MTOS database, the AUC is 0.806 (Fig. 1). When using the weight estimates recalculated for the population from Tilburg, the AUC is 0.811 (Fig. 2). The BISS model scores 0.793 with age as a dichotomous parameter and 0.803 with age as a continuous parameter (Fig. 3).

The Second (Utrecht) Dataset

The UMC Utrecht population consisted of 179 patients with a median age of 40 years and 65% were male. All patients had complete data. There were 40 inhospital deaths.

The median RTS was significantly higher for survivors (10.9) versus that for nonsurvivors (8.25) (Mann-Whitney U, p < 0.01). The median AIS or ISS was significantly lower in survivors (20 versus 30) (p < 0.01). The predicted survival according to TRISS was also significantly higher (0.46 versus 0.46) (p < 0.01). A blood gas sample taken at admission was collected for all 179 patients. For these samples, the delta base deficit was significantly lower in the survivors (2.03

<table>
<thead>
<tr>
<th>Table 1 Results Stratified for Mortality in the Tilburg Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>RTS</td>
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<tr>
<td>ISS/AIS</td>
</tr>
<tr>
<td>TRISS</td>
</tr>
<tr>
<td>Delta base deficit</td>
</tr>
<tr>
<td>pH</td>
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<td>CpH</td>
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</tbody>
</table>

Fig. 2. ROC curve of the TRISS model in the Tilburg dataset with the coefficients recalculated for the Tilburg situation using logistic regression. Area under the curve is 0.811.
versus that in the nonsurvivors (6.10) \((p < 0.01)\). The delta base deficit is significantly correlated with mortality and with all the scoring systems (Spearman rank correlation test, \(p = -0.115\) and \(p < 0.005\)). The recalculated weight estimates are reproduced in Table 2.

The ROC curve for the TRISS and BISS models resulted in an AUC of 0.891 and 0.885, respectively, in this test group (Figs. 4 and 5).

**DISCUSSION**

The newly proposed BISS model, based on base deficit as a measure for physiologic disturbance, replacing the RTS, predicts mortality in our populations as well as the TRISS model does. The main advantage, however, is that it obviates measures such as the Glasgow coma score, which can be easily influenced by drugs, alcohol, or intubation. Moreover, one of the most forgotten items in our own experience in obtaining the RTS is the respiratory rate, leading to missing data in the calculation of the TRISS values. Because a blood gas sample is taken in virtually every seriously injured patient, no extra effort is needed to obtain a more objective measure.

In many studies, attempts have been made to improve outcome estimates in trauma patients.\(^{11-16}\) Initially, scoring systems that are either anatomically or physiologically based have been used to predict outcome in trauma patients. TRISS combines both of these scoring systems and was considered revolutionary. With BISS, the most important drawback of the TRISS, the subjectivity with which the GCS is assessed, may be overcome. The estimation of essential elements of the RTS, such as the GCS, can be severely hampered. The eyes might be shut because of edema, the extremities might be fractured, and the jaw broken. Moreover, when scoop and run was the most performed tactic in prehospital trauma care, adequate estimation of the trauma victim at presentation in the hospital was possible. However, prehospital care has evolved. In its ultimate form, prehospital medical personnel perform full-blown anesthesia and intubation of the patient, thereby making an adequate estimation of the GCS at hospital admission a difficult task. This has serious consequences because the GCS has the highest weight factor in the calculation of the survival probability in the TRISS model.

In this study, we show that the delta base deficit has a good correlation with the outcome of trauma patients. Previ-

---

**Table 2 Weight Estimates of the Different Datasets Recalculated Using Logistic Regression**

<table>
<thead>
<tr>
<th>Weight Estimates</th>
<th>RTS</th>
<th>Delta Base Deficit</th>
<th>ISS</th>
<th>Age</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTOS dataset</td>
<td>0.95</td>
<td>—</td>
<td>-0.077</td>
<td>-1.91</td>
<td>-1.25</td>
</tr>
<tr>
<td>Tilburg dataset</td>
<td>0.38</td>
<td>—</td>
<td>-0.070</td>
<td>-1.80</td>
<td>1.39</td>
</tr>
<tr>
<td>BISS model</td>
<td>—</td>
<td>-0.096</td>
<td>-0.082</td>
<td>-0.046</td>
<td>5.78</td>
</tr>
</tbody>
</table>

---

**Fig. 3.** ROC curve of the BISS model in the Tilburg dataset with age as a continuous parameter. Area under the curve is 0.803.

**Fig. 4.** ROC curve of the TRISS model in the Utrecht dataset with the MTOS coefficients. Area under the curve is 0.891.

**Fig. 5.** ROC curve of the BISS model in the Utrecht dataset with age as a continuous parameter. Area under the curve is 0.885.
ously, Davis and Rutherford et al.\textsuperscript{17,18} have suggested that the base deficit might be used as a prognostic indicator for mortality. Tremblay et al. confirmed this.\textsuperscript{19} Others suggested that the admission base deficit is a good predictor for transfusion requirements and risk of complications.\textsuperscript{20} The use of the base deficit in evaluating trauma outcome is also advocated by other authors.\textsuperscript{21} Our study confirms these indications, but takes one step further in bringing it within the TRISS concept, predicting outcome of trauma patients.

As in this study, several studies have shown an association between metabolic acidosis and mortality. The base deficit reflects the disturbances in the physiologic status of the patient. An imbalance between oxygen delivery and consumption results in an anaerobic metabolism resulting in metabolic acidosis. The base deficit represents the net result of the oxygen demand and delivery to the cells, thus representing the respiratory combined with the hemodynamic pathophysiologic findings of the patient. A highly negative base deficit indicates a patient in whom one or both systems are failing to deliver, with consequences for morbidity and mortality. Interestingly, severe alkalosis is also correlated with mortality, thus a positive base deficit is pathologic too. These patients mostly have chronic metabolic alkalosis because of comorbidity, e.g., lung condition or medication such as diuretics etc. This relates to the higher mortality rate in this group.

The TRISS model is criticized in contemporary literature. Although it is objective, there is a growing demand for a model that can be calculated to an acceptable degree of accuracy within the first hour. The Physiologic Trauma Score\textsuperscript{22} is developed with these goals in mind. It takes physiologic parameters into account and almost totally rules out the anatomic part of the injury. One of the main arguments to do so is the variability and revisions of the AIS. Nevertheless, the anatomic part represented by the ISS improves the model’s fit significantly, as it does in our study. This is probably explained by the relative early time point when we see the trauma victim in our emergency department. The more severe the physiologic disturbances caused by a prolonged prehospital time, the more influence these disturbances will have in predicting outcome as a patient is delivered in our emergency room on average 47 minutes after the injury when the anatomic part of the injury weighs relatively heavily.

Elaborating on this, we developed the BISS, which is a combination of the pathophysiologic findings and the severity of the anatomic injury. The BISS is available within the hour and could be an aid in making bedside decisions. It was, however, primarily developed to evaluate quality of care. In our study, we could not confirm that a model that solely uses the base deficit can achieve the same fit for the population (AUC) as the TRISS or BISS. Nevertheless, possibly further attenuating the anatomic part with the 2005 edition of the AIS or the use of the new ISS, could lead to further improvement of the prediction model.

The last important part of the TRISS model is age. Evaluating the use of logistic regression in developing models for patient outcome, Steyerberg et al.\textsuperscript{10} produced a series of articles using the Gusto database. They propose a strategy in which they conclude that using continuous variables improves the performance of the models under development. In our study, this proves correct because the BISS performed better with the age as a continuous variable.

The base excess as a measure of physiologic derangement has been criticized because it is influenced by alcohol ingestion and the use of various drugs. Dunham et al.\textsuperscript{23} evaluated base deficit in trauma patients intoxicated with alcohol and noted an increase of base deficit. Nevertheless, Dunne et al.\textsuperscript{24} evaluated the predictive value of base deficit and lactate in trauma patients intoxicated with alcohol or drugs. They concluded that lactate and base deficit remained independent predictors for trauma outcome. Davis et al. concluded in a retrospective study that even in the presence of alcohol, a base deficit of \(-6\) remained a powerful indicator of major injury and subsequent morbidity and resources use. Also Cohn et al.\textsuperscript{25} researched the value of base deficit for prediction purposes and compared these with tissue saturation. For their respective ROC curves relating to mortality, they reached AUC values of 0.673 for maximum base deficit and 0.724 for minimum tissue oxygen saturation. Smith et al.\textsuperscript{26} evaluated the use of both predictive parameters after the admission to the ICU and concluded that both parameters were good predictors for outcome; however, their ROC curves reached only 0.73 and 0.78.

Based on these observations and our own results we conclude that the performance of a combined model with both anatomic and physiologic data, represented by base deficit, was superior to base deficit alone.

CONCLUSION

The BISS model predicts outcome in trauma patients as well as the accepted TRISS model and it is more objective and less complicated to score. Because of this, it deserves a role in the evaluation of quality of care in trauma patients. Further studies need to be performed to evaluate its power in different trauma populations.

ACKNOWLEDGMENTS

We thank Prof. Dr. Jolanda van der Graaf, Utrecht, The Netherlands and Prof. Dr. Rolf Lefering, Cologne, Germany for their criticism and support with the statistical analysis.

REFERENCES

Effect of Emergency Medical Technician Certification for All Prehospital Personnel in a Latin American City

Carlos Arreola-Risa, MD, Jorge Vargas, EMT-I, Ismael Contreras, EMT-A, and Charles Mock, MD, PhD

Background: In Mexico and most other Latin American countries, many emergency medical services (EMS) systems rely on employees and volunteers with only on-the-job training and without formal Emergency Medical Technician (EMT) certification. This study sought to evaluate the costs and effectiveness of providing EMT certification to all personnel working in an EMS service in a Mexican city.

Methods: At baseline, only 20% of theprehospital personnel (medics) working for the EMS service in Santa Catarina, Nuevo Leon, Mexico had EMT certification. During a 14-month period, all such medics obtained EMT certification. The process and outcome of trauma care were assessed before and after this training.

Results: Mortality among persons treated by this EMS service decreased from 1.8% Before to 0.5% after the training. The injury severity, as reflected by the prehospital index (PHI), was different between the two periods. Hence, adjustment for PHI by logistic regression was performed. The PHI-adjusted odds ratio for death in the after period was 0.55 compared with the before period, representing a 45% reduction in risk of death after EMT training.

Conclusions: These data support the promotion of policies that require and enable EMT certification for allprehospital care providers in Mexico and potentially also in other Latin American and other middle-income developing countries.

Key Words: Injury, Trauma, Prehospital care, Emergency medical services, Developing country, Less-developed country, Ambulance, Mexico, Latin America.

Trauma has become a leading health problem globally, including in most developing countries. This is especially true in Mexico and other Latin American countries, where increased motorization has led to significant increases in rates of road traffic crashes.1–3 The solution to this problem involves injury prevention and efforts to strengthen trauma care. In terms of trauma care, a preponderance of trauma deaths occurs in the field in most countries. However, the percentage of such prehospital deaths is higher in developing countries than in industrialized countries. For example, it has been shown that nearly three-fourths of all trauma deaths in Mexico occur in the field.4,5 Thus, in Mexico, efforts to lower trauma mortality need to address the prehospital environment.

Any efforts to improve health care in the developing world must address the existing resource limitations. For example, Mexico has a gross national income of $6,770 (in comparison with $40,000 for the United States) and health care expenditures of $380 per capita per year (in comparison with $5,000 for the United States).6 Thus, any improvements in care must be cost-effective within these resource restrictions.

Working within such restrictions, several prior studies have demonstrated improvements in prehospital care through low-cost measures, including improved training using short courses such as the Prehospital Trauma Life Support Course (PHTLS).7–12 Although such short courses are definitely of benefit, we also need to consider more fundamental changes, such as assuring the foundation of basic education for prehospital personnel. Currently, many prehospital services in Mexico and elsewhere in Latin America have very few personnel with formal training such as Emergency Medical Technician (EMT) certification. Many utilize volunteers or employ persons with only on-the-job training and no formal certification.13

We sought to determine the potential benefit of assuring uniform EMT training for all prehospital personnel in an Emergency Medical Service (EMS) system in the context of a Latin American city. We sought to determine the potential benefits in comparison with the costs of this training.

Methods

Setting

The study site was the Monterrey metropolitan area, with a population of 3,000,000 people. The EMS system studied was that of one of the communities in the metropolitan area, Santa Catarina (population 230,000).

In Santa Catarina, several different groups provide EMS. These include the Green Cross and Red Cross, both of which have sites of dispatch in the adjacent city, San Pedro. EMS is...
also provided by a municipally administered service, the Jaguars (Jaguerres). Ideally, the Jaguars provide first response, with transport provided by the Green or Red Cross ambulances from neighboring San Pedro. However, there is considerable overlap between the functions of all three services. The Jaguars are often called upon to transport patients when the Green or Red Cross ambulances are tied up. Likewise, the Green or Red Cross ambulances often provide both first response and transport.

At baseline, the majority of the ambulance service personnel (medics) had only on-the-job training consisting of skills and knowledge they picked up from colleagues in their daily work, with no formal training courses. Only 20% of the medics had EMT certification. At baseline, virtually none of the personnel had any type of trauma-related in-service training, such as PHTLS or Basic Trauma Life Support (BTLS). The staff of the Jaguars consisted of half paid staff and half volunteers, with the full-time staff having slightly more formal EMT certification than the volunteers did.

**Interventions**

Basic EMT certification training was provided to virtually all medics working in the Santa Catarina ambulance service. This consisted of 3-month programs provided by the Cruz Verde (Green Cross) and 11-month programs provided by the Cruz Roja (Red Cross). For both programs, students attended classes for 2 to 3 hours per day. Medical procedures taught were slightly more advanced for the EMT certification awarded by the Cruz Roja. However, the extra training provided by the Cruz Roja certification principally provided greater skills in nonmedical aspects of prehospital care, such as rescue and extrication.

**Data Collection**

Improved record keeping was implemented first. A supplemental data sheet was introduced for use by the medics. This expanded the information collected during the ambulance runs beyond what had been routinely collected previously. It included the type of event, prehospital treatment, vital signs, Glasgow Coma Scale score, prehospital index (PHI), and results of treatment, including survival. These forms became standards in the ambulance service record keeping after the study was completed.

The time periods involved in the study consisted of the following: before any intervention (January 1, 2000 to March 31, 2002); during Cruz Verde EMT courses (20 medics) (April 1, 2002 to June 30, 2002); during Cruz Roja EMT courses (15 medics) (July 1, 2002 to May 31, 2003); and after completion of all training (June 1, 2003 to December 31, 2004).

For the subsequent display of data, the following periods are used: before (January 1, 2000 to March 31, 2002); during (April 1, 2002 to May 31, 2003); and after (June 1, 2003 to December 31, 2004). For statistical analysis, comparisons were made between before versus after data.

### Table 1: Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>807</td>
<td>1,063</td>
<td>1,856</td>
</tr>
<tr>
<td>Mean age, yr (SD)</td>
<td>29 (16)</td>
<td>28 (16)</td>
<td>29 (17)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Blunt (%)</td>
<td>88</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>Mean PHI (SD)</td>
<td>3.9 (4.7)</td>
<td>2.6 (3.5)</td>
<td>2.5 (3.7)*</td>
</tr>
</tbody>
</table>

All statistical comparisons are for Before versus After. Before, January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

*p < 0.001.

In all sites, deaths were recorded if they occurred at the scene without any treatment, at the scene with some type of treatment attempted, dead en route, or dead in the emergency department at the receiving hospital. The latter principally consisted of patients whose deaths occurred while the medics were present.

The costs of the various training courses were converted from Mexican Pesos to US Dollars based on the exchange rates prevalent at the times concerned. Statistical analysis was performed with use of the unpaired Student’s t test for continuous data and χ² or Fisher’s exact test for categorical data. The Mayor’s office of Santa Catarina approved the study.

**RESULTS**

**Study Population**

The total number of trauma patients in the study was 3,726, with 807 in the before group, 1,063 in the during group, and 1,856 in the after group. The groups were fairly well matched demographically (Table 1), and primarily included young male patients with blunt trauma. However, the severity of the injuries, as assessed by the PHI, was somewhat higher in the before phase (mean, 3.8 ± 4.6 [SD]) than in the during phase (mean, 2.6 ± 3.5) or the after phase (mean, 2.5 ± 3.6; p < 0.001 for before vs. after).

**Effects of Training on Process of Prehospital Care**

There was no change in the rates of either cervical or thoracic spinal immobilization. Rates of usage remained intermediate, whether all patients or blunt trauma patients only were considered (Table 2). Blunt trauma patients who did not receive spinal immobilization were less severely injured (mean PHI, 1.7 ± 2.4) than were those who did receive spinal immobilization (mean PHI, 2.6 ± 2.8; p < 0.001). This difference in severity applied to all phases of the study.

Considering all patients, there were no changes in the use of any airway maneuvers in the before versus after groups. Use of oxygen fell in the after period (Table 3). The medics categorized patients according to whether their respirations were normal, labored, or depressed. The labored and depressed categories were considered as respiratory distress. Among such patients and among comatose patients, use of...
and Breathing

During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

October 2007

Table 2: Use of Spinal Immobilization

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>770</td>
<td>1,045</td>
<td>1,819</td>
<td></td>
</tr>
<tr>
<td>Cervical (%)</td>
<td>61</td>
<td>71</td>
<td>61</td>
<td>NS</td>
</tr>
<tr>
<td>Thoracic (%)</td>
<td>60</td>
<td>71</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Blunt trauma patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>650</td>
<td>959</td>
<td>1,586</td>
<td></td>
</tr>
<tr>
<td>Cervical (%)</td>
<td>67</td>
<td>75</td>
<td>64</td>
<td>0.14</td>
</tr>
<tr>
<td>Thoracic (%)</td>
<td>65</td>
<td>75</td>
<td>63</td>
<td>NS</td>
</tr>
</tbody>
</table>

All statistical comparisons are for Before versus After. Before, January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

* Excluding dead at scene with no treatment rendered.
NS, not significant.

Table 3: Use of Procedures for Resuscitation of Airway and Breathing

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>770</td>
<td>1,045</td>
<td>1,819</td>
<td></td>
</tr>
<tr>
<td>Oral pharyngeal airway (%)</td>
<td>0.6</td>
<td>0.8</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Suction (%)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen (%)</td>
<td>5.5</td>
<td>5.2</td>
<td>2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Endotracheal intubation (%)</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Patients in respiratory distress*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>93</td>
<td>66</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Oral pharyngeal airway (%)</td>
<td>2.2</td>
<td>9.2</td>
<td>5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Suction (%)</td>
<td>2.2</td>
<td>7.7</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen (%)</td>
<td>26</td>
<td>52</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Endotracheal intubation (%)</td>
<td>4.4</td>
<td>4.7</td>
<td>2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Unconscious patients (GCS score ≤8)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>54</td>
<td>31</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Oral pharyngeal airway (%)</td>
<td>7.4</td>
<td>25.8</td>
<td>15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Suction (%)</td>
<td>7.4</td>
<td>16.1</td>
<td>7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen (%)</td>
<td>28</td>
<td>68</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Endotracheal intubation (%)</td>
<td>7.4</td>
<td>9.7</td>
<td>7.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Patients in respiratory distress were those with labored or depressed (<10 breaths/min) respirations.

All statistical comparisons are for Before versus After. Before, January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

* Excluding dead at scene with no treatment rendered.
NS, not significant; GCS, Glasgow Coma Scale.

Table 4: Use of Intravenous Fluid Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>770</td>
<td>1,045</td>
<td>1,819</td>
<td></td>
</tr>
<tr>
<td>Any use of i.v. fluids (%)</td>
<td>4.7</td>
<td>6.8</td>
<td>3.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Use of two i.v. lines (%)</td>
<td>0.5</td>
<td>1.2</td>
<td>0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Use of large bore i.v. (%)</td>
<td>1.7</td>
<td>2.7</td>
<td>0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Adults (age ≥15) with SBP &lt;100*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>209</td>
<td>703</td>
<td>656</td>
<td></td>
</tr>
<tr>
<td>Any use of i.v. fluids (%)</td>
<td>9.6</td>
<td>6.8</td>
<td>5.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Use of two i.v. lines (%)</td>
<td>1.4</td>
<td>1.5</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Use of large bore† i.v. (%)</td>
<td>3.8</td>
<td>2.9</td>
<td>1.7</td>
<td>0.06</td>
</tr>
</tbody>
</table>

All statistical comparisons are for Before versus After. Before, January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

* Excluding dead at scene with no treatment rendered.
† Large bore indicates 14 or 16 gauge.
NS, not significant.

Table 5: Mortality

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>807</td>
<td>1,063</td>
<td>1,856</td>
<td></td>
</tr>
<tr>
<td>Dead at scene with no treatment (%)</td>
<td>4.6</td>
<td>1.7</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Dead at scene after treatment (%)</td>
<td>0.7</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Dead enroute or in emergency department (%)</td>
<td>1.0</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Total dead (%)</td>
<td>6.3</td>
<td>2.0</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Before, January 1, 2000 to March 31, 2002 (before any EMT certification); During, April 1, 2002 to May 31, 2003; After, June 1, 2003 to December 31, 2004 (after completion of all training).

* p < 0.001 (Before vs. After).

oral airways, suction, and oxygen increased transiently in the during period. However, there was no consistent change in the use of these modalities for the before after groups.

Considering all patients, the use of any intravenous (i.v.) fluid declined slightly (Table 4), from 4.7% to 3.0%. The use of two i.v. lines remained uncommon, as did the use of large bore i.v. lines (14 or 16 gauge). Considering the subgroup of hypotensive (systolic blood pressure <100 mm Hg) adults (age ≥15 years), similar patterns were observed. Baseline rates of i.v. use were higher (9.6%) and declined to 5.0% (p = 0.02). There were no changes in the use of two i.v. lines. Use of large bore i.v. lines decreased slightly.

The median scene time (the time taken by prehospital providers from arrival at the scene until transporting the patient from the scene) remained the same (10 minutes) in all phases of the study.

Effects of Training on Mortality

The overall mortality rate declined from 6.3% in the before period to 2.5% in the after period (p < 0.001) (Table 5). This group included a high proportion of people whom the medics evaluated and deemed as dead at the scene and for whom no treatment was rendered. Considering only patients who were viable enough to receive some treatment, whether at the scene or en route to the hospital, the mortality rate declined from 1.8% in the before period to 0.5% in the after period (p = 0.002). Such deaths included those who died at the scene after receiving treatment, those who died during transport, and those who died on arrival to the emergency department while the prehospital personnel were still present to note the death.
The severity of injury, as measured by the PHI, was lower in the after period (Table 1). There was thus the possibility that this difference might have accounted for the observed decrease in mortality. Therefore, a multivariate logistic regression analysis was undertaken. Risk of death in the before versus after period of the study was adjusted for PHI. The decreased risk of death in the after period remained significant. This was the case for both all deaths and deaths after treatment. For all deaths, the PHI-adjusted odds ratio for death in the after period was 0.61 (95% confidence interval, 0.37–1.01; p = 0.056) compared with the before period. For deaths after treatment, the PHI-adjusted odds ratio for death in the after period was 0.55 (95% confidence interval, 0.30–0.99; p = 0.046) compared with the before period. The latter represents a 45% reduction in severity-adjusted risk of death after the intervention.

Costs

The 3-month EMT program provided by the Green Cross cost US$200 per medic. The year-long EMT programs provided by the Red Cross cost $600 per medic. In comparison, the costs of short (2–3 days) standardized courses, such as PHTLS and BTLS, are approximately $150. Hence, the 3-month EMT programs are only slightly more expensive than these brief refresher courses. All of these costs must be put in the context of the local economy, in which the pay for a full-time medic is approximately $300 per month and the per capita health care expenditures for the entire country are $380 per year.

DISCUSSION

In the study, we sought to determine the potential benefits in comparison with the costs of providing EMT certification to all prehospital personnel in the setting of an EMS service in a Mexican city. Before drawing conclusions from the data, the limitations of the study methods must be addressed. First, the study encompassed a 5-year period. There may have been general improvements in care occurring throughout Mexico during that time and, hence, the improvement noted in the study may not have been specifically related to the EMT training. That is, the paramedics may have been better trained and mortality may have indeed gone down, but they are not necessarily related. However, a previous analysis of the early and late components of the 2-year period showed no change in the process or outcome of care delivered. Furthermore, in terms of establishing a causal link between the training and the decreased mortality, it is important to note that the EMT certification for almost all medics in the Jaguars was, in fact, the major change performed during the study period.

Second, inhospital deaths were not recorded. It is possible that the improved process of care might only have shifted deaths from the prehospital to the hospital location without changing the overall mortality rate. However, the large number of hospitals involved and the inadequacies of record keeping precluded follow-up of all transported patients.

Third, the costs considered in this study involve only those associated with training. It is possible that the training increased resource utilization and, hence, cost of care delivered, which was not detected by the study.

Fourth, the improvements associated with training would likely wane over time. Thus, the improvements noted in the first 2 years after training may not be sustainable without increased inputs of in-service training, which would add additional costs. The likelihood of this is demonstrated by the fact that the period during the training was accompanied by a transient increase in the performance of several procedures, such as use of spinal immobilization, airway maneuvers, and i.v. insertion (Tables 2–4). Nonetheless, it is interesting to note that the mortality rate decreased from before to during and then remained low in the after phase.

Despite these limitations, we think that the data allow us to make reasonable conclusions regarding the potential benefits of promoting EMT training for all prehospital personnel in the setting of a Mexican city. There was a definite decrease in mortality associated with this training, even after adjustment for the differing injury severities, as measured by the PHI. Interestingly, there were only minimal changes in the process of care associated with this decreased mortality. The only increase in process of care that approached statistical significance was use of oral airways in patients with respiratory distress or who were comatose. Use of i.v. fluids decreased slightly after training.

All other studies that have shown a decrease in mortality from use of short training courses have also shown notable increases of use of prehospital treatments, such as basic airway maneuvers, endotracheal intubation, and use of i.v. fluids. Perhaps there were other aspects of care that were not recorded, such as improved triage and diagnosis of life-threatening injuries, which were responsible for the decreased mortality. It might also be that basic airway maneuvers are one of the most essential components of prehospital care and that better performance of them was most crucial in improving outcome. The potential importance of such basic life support measures is reinforced by several other studies, which demonstrate that advanced life support measures applied in the field, including endotracheal intubation and use of i.v. fluids, add little and may even be detrimental in some circumstances.

It is also notable that many patients in respiratory distress or who were comatose did not receive even basic airway maneuvers or oxygen. Discussion with the medics indicated that oftentimes lack of equipment and supplies prohibited them performing therapies that were indicated. This indicates the need to consider other aspects of prehospital care in addition to training. In particular there is a need to link improvements in training with measures to assure minimum of levels of equipment. The importance of approaching such improvements in an organized system has been emphasized...
It is debatable whether the time has come to require EMT certification of all who wish to be prehospital care providers in Mexico. This might have the unintended negative consequence of driving away many experienced, capable medics who just have not had the opportunity and funding to obtain certification. If there is not a sufficient number of capable persons with EMT certification to replace them, such a requirement might lower the availability and quality of prehospital care. However, obtaining such certification should be strongly encouraged. If sponsorship and subsidies can be enacted and the financial barrier to obtaining EMT certification diminished, eventually requiring EMT certification for all prehospital providers may be a reasonable policy to promote.

In conclusion, EMT training for all prehospital personnel has been shown to lower mortality in a Mexican EMS system. These data suggest the need to promote policies that decrease the cost and increase availability of such training.

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Intrathoracic fracture-dislocation of the proximal humerus is exceedingly rare.\textsuperscript{1} Variations of these injuries have been reported in elderly patients after falls onto the outstretched extremity\textsuperscript{2,3} and in younger patients after high energy trauma.\textsuperscript{4,5} We report the case of a 27-year-old man who suffered an intrathoracic fracture-dislocation of the proximal humerus after a motorbike crash. The head fragment was retrieved from the chest cavity through an extended deltopectoral approach, along the path of displacement at the time of injury. The surgical technique and the outcome of open reduction and internal fixation of this particular variant of injury have not been previously reported. We think this surgical approach allows preservation of any remaining soft tissue attachments to the head fragment, potentially maintaining tenuous blood supply and minimizing the risk of osteonecrosis.

**CASE REPORT**

We report the case of a 27-year-old right-hand dominant man who suffered an injury during an off-road motorcycle competition. He was thrown approximately 20 feet from his vehicle at a speed of 30 mph, landing upon his left side. There was no loss of consciousness, but the patient had obvious left upper extremity injury and was transferred to our facility for emergent evaluation and management. There was no history of prior chest wall or left upper extremity injury. The patient was clinically stable on arrival with obvious tenderness, swelling, and ecchymosis of the upper left arm and left chest wall. Peripheral pulses were palpable; sensation was intact in the radial, median and ulnar nerve distributions. Sensory examination of the axillary nerve was inconclusive. Motor function revealed voluntary firing of all muscles distal to the elbow; examination of those proximal to the elbow was complicated by pain, although the patient had palpable voluntary contraction of the biceps and triceps.

Imaging studies revealed an anterior glenoid rim fracture, comminuted proximal humerus fracture, left rib fractures, and intrathoracic dislocation of the humeral head fragment (Fig. 1). Secondary survey and radiographic imaging failed to reveal other injuries. Angiography demonstrated intact axillary artery perfusion. Computerized tomography and three-dimensional reconstruction demonstrated the intrathoracic position of the humeral head fragment as well as a hemopneumothorax (Figs. 2 and 3). A thoracostomy tube was placed in the emergency room. The patient was brought to the operating room and positioned in the beach chair position. An extended deltopectoral approach was performed. The pectoralis minor and coracobrachialis tendons were released from the coracoid allowing identification of the infraclavicular brachial plexus. No anatomic brachial plexus lesions were noted and all muscle groups contracted appropriately to intraoperative stimulation. The chest wall cavity was accessed after identifying and protecting the branches of the brachial plexus and axillary artery, through dissection along the path of displacement of the humeral head fragment. The fragment was delivered out of the chest without complications (Fig. 4). The middle and lower portion of the subscapularis tendon remained attached to the lesser tuberosity that remained attached to the head fragment. There was an associated rotator cuff tear involving the anterior portion of the supraspinatus, and upper portion of the subscapularis. The infraspinatus and teres minor remained attached to a displaced greater tuberosity fragment that remained in the vicinity of the shaft.

Great care was taken to preserve the remaining subscapularis attachment to the humeral head fragment. The glenoid rim fracture and labrum were repaired using suture anchors. The humeral head fragment was repaired anatomically to the humeral shaft using a locking proximal humerus plate (Synthes LCP plate) with tension band suture fixation of the tuberosity fragments. The rotator cuff tear was also repaired (Figs. 5 and 6). Postoperatively the patient was treated in an abduction sling with passive motion exercises. Active assisted motion was begun at five weeks postoperatively. Active motion was begun at ten weeks postoperatively and gentle strengthening was initiated at 14 weeks postoperatively. The patient achieved clinical and radiographic union.

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of his fracture with no evidence of loss of reduction or avascular necrosis at 1 year follow-up (Fig. 7). Range of motion at final follow-up was to 140 degrees of elevation, 35 degrees of external rotation, and internal rotation to the T-12 level. The patient had full strength of all upper extremity muscle groups and no sensory deficits.

**DISCUSSION**

Intrathoracic fracture-dislocations of the proximal humerus are rare injuries with potentially devastating consequences, particularly with respect to the young, active patient. This injury pattern was originally described by West in 1949.4 West reported a case in a young patient after a high energy injury in which the humeral head remained in continuity with the shaft and was reduced with traction. A displaced fracture of the greater tuberosity was treated nonoperatively which resulted in limited shoulder abduction. In a similar case report by Simpson5 reduction of the humeral head was facilitated by digital manipulation through the thoracostomy wound followed by internal fixation of the greater tuberosity and repair of a tear of the rotator cuff. The patient had complete return of function after extended physical therapy. In both of these cases, the only osseous disruption was the fracture of the...
greater tuberosity. We are aware of only four other cases of intrathoracic fracture-dislocation in which the large head fragment remained detached from the shaft within the thoracic cavity, the youngest of which was a 56-year-old woman. In the case reported by Glessner, the detached humeral head was surgically removed from the chest wall and discarded. The remaining rotator cuff was attached to the shaft of the humerus and resulted in satisfactory function for this low-demand patient. Eberson reported a case of a 64-year-old man who fell 15 feet and suffered a contralateral intrathoracic fracture-dislocation. The humeral head was removed from the chest through a thoracoscopic assisted approach, however, humeral head replacement was performed. The patient had a satisfactory postoperative course despite a partial brachial plexopathy.6 Harman recently reported a case of a 56-year-old woman involved in a high speed motor vehicle crash who sustained an intrathoracic humeral head fracture dislocation, which was also treated with hemiarthroplasty through a deltopectoral approach and subsequent humeral head excision by a thoracotomy.7 We are unaware of any case report of a four-part fracture dislocation where retrieval of the humeral head fragment and open reduction and internal fixation were performed. The arterial supply to the humeral head is known to be tenuous in high-energy multi-part fractures such as the case we report here. The primary arterial supply to the proximal humerus is derived from a branch of the anterior humeral circumflex artery.8 Lesser vascular contributions arise from the posterior humeral circumflex artery and vessels that enter through the soft tissue attachments of the rotator cuff. It has been proposed that during open reduction and internal fixation, protection of soft tissue attachments may preserve some flow to the humeral head, thus decreasing the risk of avascular necrosis.9 In a case such as ours, retrieval of the humeral head fragment via an inferior thoracotomy approach such as that performed by Glessner and others, requires transection of any remaining soft tissue attachments to the head in addition to the need for a separate incision. The extended deltopectoral approach we describe is somewhat technically demanding. However, this approach may allow for preservation of remnants of the rotator cuff that may be maintained on the humeral head fragment at the time of injury. In our case, had the head fragment been retrieved by an alternate surgical approach, these soft tissue attachments...
would have been sacrificed. In addition, this approach allows for direct inspection and repair of any neurovascular injury which might occur at the time of the intrathoracic dislocation. Our patient demonstrated clinical and radiographic union of the fracture with no obvious evidence of avascular necrosis of the humeral head at 1 year follow-up. It is our thought that critical perfusion to the humeral head was likely maintained through the preserved soft tissue attachments of the subscapularis until reconstitution of interosseous perfusion could occur in the postoperative period. We are cautiously optimistic with regards to the future clinical outcome of our patient. This is the first reported case which demonstrates that retrieval of the humeral head fragment in intrathoracic fracture dislocation of the proximal humerus can be performed safely and with satisfactory outcome through an extended deltopectoral approach. We recommend consideration of this surgical technique for the management of similar injuries, particularly in the young, active patient.

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SUBJECTIVE EMphysema resulting from facial fractures is one of the frequently observed findings in maxillofacial surgeons' daily practice, especially when the trauma affects the paranasal cavities. It is usually confined to the cervicocephalic region, although rarely the air, discharged into the facial soft tissues, descends along the deep fascial planes into the thoracic region and the mediastinal space, producing subcutaneous emphysema, pneumothorax and/or pneumomediastinum.

The authors report a case of pneumomediastinum secondary to angular and symphyseal mandibular fractures, discussing the onset modalities and management of pneumomediastinum in the patient with maxillofacial trauma.

CASE REPORT

A 24-year-old male was seen in the emergency room of the San Giovanni Battista Hospital in Turin for facial trauma caused by a blow to the mandible. The neurologic examination was negative, whereas the clinical examination evidenced a painful swelling at the left mandibular angle associated with trismus and posttraumatic malocclusion. Swelling was observed in the laterocervical and supraclavicular regions with soft-tissue crepitation due to subcutaneous emphysema. The intraoral examination showed a mucosal laceration at the level of the left third molar on the lingual and vestibular sides, also affecting the attached gingiva. Radiographs revealed a moderately displaced fracture of the left mandibular angle and a compound symphyseal fracture of the mandible. Radiographs on lateral view excluded injury of the cervical spine, but showed emphysema in the retropharyngeal space. A computed tomography (CT) scan of the mandible, neck and chest was performed, confirming the double mandibular fracture (Fig. 1) and showing emphysema extending from the submandibular space into the perypharyngeal, subclavicular (Fig. 2), and mediastinal spaces (Fig. 3) in an asymptomatic patient. The patient was placed on prophylactic antibiotics, and panendoscopy findings revealed no evidence of perforation of the upper digestive tract. On admission to the Maxillofacial Surgery Division, a facial and chest CT was repeated after 48 hours, with no worsening of the mediastinal emphysema. Subsequently, the patient was taken to the operating room for open reduction and internal fixation of the mandibular fractures. The postoperative course proceeded without complications and the patient was discharged four days after the operation. Thirty days after the traumatic event, a facial and chest CT was performed, showing correct alignment of the mandibular segments and complete resolution of the perimandibular, cervical, and mediastinal emphysema.

DISCUSSION

Pneumomediastinum, or mediastinal emphysema, is the presence of air in the mediastinal space. Pneumomediastinum resulting from severe thoracic-abdominal injury with perforation of the trachea, bronchus, lung, esophagus, or a hollow abdominal viscus is a frequent, well-documented event. This can also produce subcutaneous emphysema in the cervical region due to the ascending air via the deep fascial planes and subcutaneous space.1

Air descending into the mediastinum from the maxillofacial region is less common. Several authors have reported the onset of cervical and mediastinal emphysema following iatrogenic causes, such as orthognatic surgery,2 endodontic procedures,3–6 and third molar surgery,4,7–11 especially in the mandibular region. Multiple case reports in the literature have documented the formation of pneumomediastinum after facial fractures.12–21 Vigorous blowing of the nose appears to be a precipitating factor in the formation of pneumomediastinum. The air is forced into the surrounding tissues through mucoperiosteal tears resulting from the fractures of the paranasal sinuses and takes the path of least resistance between the loose connective tissues situated along the cervicocephalic fascial planes.

A review of the literature found only four cases of pneumomediastinum secondary to mandibular fracture22–25 and a fifth case associated with a Le Fort fracture.26 As described in these four articles and in the present case, pneumomediastinum almost always occurs in young patients with a mandibular

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angular fracture that has resulted in a tear of the oral mucosa. At the moment of the trauma, the patient might have inadvertently performed the Valsalva maneuver, forcing air through the lacerated oral mucosa and into the sublingual space. This area communicates with the mandible in the area of the first, second, and third molars and is situated between the mylohyoid muscle and the floor of the mouth. The submandibular, pterygopharyngeal, parapharyngeal, and retropharyngeal spaces are continuous with sublingual space. The major communication from the mouth to the mediastinum is via the retropharyngeal space; thus, air entering the sublingual space from an angular mandibular fracture can extend to the retropharyngeal space and eventually involve the mediastinum.

The diagnosis of pneumomediastinum can be made through the etiology of the traumatic event and clinical examination. The predominant symptom of mediastinal emphysema is substernal chest pain (in 80% to 90% of cases) radiating to the back, neck, and shoulder that may be exacerbated by swallowing, coughing, deep inspiration, and clinostatism. The pain can be decreased on sitting up, breathing lightly, or bending forward. During hospitalization, our patient had no pain in the chest region. Less common symptoms are dysphagia, dyspnea, dyslalia, and neck pain.

The pathognomonic sign of pneumomediastinum is Hamman’s sign, a “crunch” sound that can be detected over the retrosternal area, sometimes audible without a stethoscope. It can be confused with the friction rib produced by pericarditis; however, it is synchronous with systole, emphasized by expiration, in the left lateral decubitus position, and reduced when the patient is in orthostatism. This sign, present in 50% to 80% of cases of mediastinal emphysema, was not detectable in our patient. Other signs included subcutaneous emphysema and evident signs of increased mediastinal pressure, such as cyanosis, distended neck veins, pneumothorax and cardiovascular collapse. Also reported are electrocardiographic changes, with S-T segment elevation and T-wave inversion, decreased voltage, and shifts in the electrical axis.

The presence of free air in the mediastinum is confirmed by chest radiography, showing a distinct line parallel to the left hilus and also a thin radiolucent border outlining the cardiac silhouette on posteroanterior projection. On lateral projection, the posterior mediastinal structures, especially the aorta, are clearly defined by the presence of air.

Pneumomediastinum secondary to maxillofacial fracture is usually self-contained, as air is quickly reabsorbed in the mediastinum. In the literature, cases of pneumomediastinum associated with facial trauma have resolved spontaneously without treatment of the mediastinal pathology, except for adequate antibiotic therapy. The risk of upper airway obstruction is probably low because air dissection preferentially takes place along loose, low-resistance structures and not along the relatively tight submucosa of the glottis and trachea. In the only case reported in literature in which trache-
ostomy was performed, the retropharyngeal emphysema was substantial enough to cause respiratory distress. In this situation, panendoscopy of the upper airway is recommended to exclude pharyngeal-laryngeal injuries.

As in the case reported here, close follow-up and a check-up involving chest radiography or CT 30 days after the trauma to confirm resolution of the pneumomediastinum are the only precautions to be taken in the patient with no maxillofacial surgical indications.

Whenever it is necessary to intervene surgically, the anesthetic precautions for patients with pneumothorax and pneumomediastinum include administering general anesthesia without nitrous oxide. These precautions prevent worsening of the pneumomediastinum and avoid the risk of causing a pneumothorax, requiring unilateral or bilateral tube thoracostomy to evacuate the air. Such a procedure is necessitated by the fact that the air in the mediastinum of a patient may increase the central venous pressure because closed chest trauma or peripheral alveoli tears cannot be ruled out. Any increase in vascular resistance to venous flow at the upper cava vein, especially during maxillofacial or neurosurgical intervention, should be avoided due to its negative effect on intracranial pressure, with the consequent risk of serious intraoperative bleeding, onset of edema, or worsening of a cerebral contusion.

REFERENCES


Penetrating Injury to the Intra-abdominal Esophagus From a Stab Wound to the Left Flank

Lana Bijelic, MD, and Enrique Daza, MD, FACS

Esophageal injuries are rarely encountered even in busy trauma centers. Gunshot wounds are the most common cause but they can also occur from stab wounds and rarely from blunt trauma. Although early recognition and treatment play a critical role in determining outcome, they often represent a diagnostic challenge. Here we present a case of a through-and-through injury to the abdominal esophagus from a single stab wound to the left flank.

CASE REPORT

A 38-year-old man was admitted to our trauma center after sustaining a stab wound to his left flank. At arrival he was awake, diaphoretic, and in some respiratory distress. His primary survey revealed diminished breath sounds on the left but good oxygenation of 96%, blood pressure of 125/80, and a heart rate of 118 bpm. His examination also revealed a single deep stab wound to the left of the paraspinous muscle in the flank area, at the level of L1. His abdomen was soft and nontender and he had no other injuries.

A chest radiograph was performed and revealed a left hemopneumothorax. A left chest tube was then placed, which relieved the pneumothorax and drained about 400 mL of blood. His trauma bay evaluation also included a focused abdominal ultrasound for trauma, which showed no free fluid in the abdomen. Considering the location of the stab wound a diaphragmatic injury was suspected. He was further evaluated with a computerized tomography of the abdomen. This showed the path of the stab wound along the diaphragm as well as a small amount of fluid in the pelvis (Fig. 1). These findings further consolidated the suspicion for a diaphragmatic injury.

The patient was therefore transferred to the operating room and underwent a diagnostic laparoscopy. This revealed penetration of the peritoneum with blood above the spleen and minimal amount of blood in the pelvis as well as a hematoma close to the gastroesophageal (GE) junction while the diaphragm appeared completely intact. Based on these findings, a laparotomy was then performed and a through-and-through perforation of the esophagus at the GE junction was found after full mobilization of the stomach and distal esophagus. There was no clinical or radiologic suggestion of aortic injury on preoperative evaluation; therefore, proximal control of the aorta was not performed before the beginning of dissection. The esophagus was repaired with a single layer of polydioxanone suture (PDS) over a no. 50 Bougie and then buttressed with a Nissen fundoplication. The patient had no other abdominal injuries. The pleura were penetrated close to the hiatus at the left crus, which explained the hemopneumothorax.

The patient’s postoperative course was uneventful and he was discharged on postoperative day 6. Before discharge he underwent a gastrograffin esophagogram, which showed an intact repair.

DISCUSSION

Esophageal injuries are rare and require a high index of suspicion for early diagnosis. They are most often caused by gunshot wounds, accounting for 75% of esophageal injuries, followed by stab wounds causing 18%.1–3 The cervical esophagus is most commonly involved with decreased incidence in the more distal portions. Injuries to the abdominal esophagus represented 17% of all esophageal injuries in one series.1 These are typically caused by gunshot wounds traversing the midline and are usually associated with multiple injuries to the surrounding structures including the trachea and the great vessels.4–6 The case we describe here is an unusual case of isolated injury to the esophagus from a stab wound distant from the anterior midline.

An injury to the esophagus is suspected in patients with symptoms of dysphagia, crepitus in the neck, or in gunshot wounds with the missile tract traversing the midline.5 In all cases of penetrating trauma close to the midline along the length of the esophagus, the possibility of an injury should be considered. Esophagography or esophagoscopy are recommended for the evaluation of the esophagus if the patient does not have another indication for surgical exploration.7

In our case, the lateral location of the stab wound in the thoracoabdominal region raised the possibility of a diaphrag-
matic injury, which prompted laparoscopy. Preoperative computed tomography scan in this case did not suggest the possibility of an esophageal injury and did not show an obvious diaphragmatic injury. It did, however, demonstrate the likely trajectory of the penetrating instrument.

Laparoscopy has proven to be an excellent tool for evaluation of diaphragmatic injuries but is not sensitive enough for a thorough evaluation of the entire abdomen. Once penetration of the peritoneum was confirmed along with the findings of blood in the pelvis and a hematoma at the GE junction, we chose to perform a laparotomy. This approach allowed us to diagnose and repair early a very unlikely injury and played an important role in the excellent outcome.

The management of penetrating esophageal trauma depends on the extent of tissue damage and the time from injury to operative repair. The optimal time frame for repair has not been established. Primary repair should probably be attempted if viable tissue is present and the extent of surrounding inflammation is not excessive, even later than 24 hours from the time of injury. Buttressing the repair with autologous tissue is advocated by many authors, especially in cases of associated tracheobronchial injuries. Pleural flaps, intercostal muscle flaps, the Thal fundal patch, and fundoplication are some examples of commonly employed techniques.

This is an interesting case of penetrating injury to the esophagus that stresses the importance of a high index of suspicion for intra-abdominal injury in penetrating injuries to the back or the flank. A similar case has not previously been reported in the literature. It also indicates that high resolution helical computed tomography is helpful in the evaluation of these injuries by delineating the path of the penetrating agent.

REFERENCES

Whenever digestive tract perforations, because of either local or general causes are considered to be high-risk, the dehiscence of sutures performed on such perforations keeps an object of concern to surgeons. It has been estimated that this complication involves up to 30% of cases, with a mortality about 40%. The possibility of using biomaterials such as expanded polytetrafluoroethylene (ePTFE) to repair those lesions on the basis of encouraging results achieved in research1–3 and its use in a case report4 have prompted us to present the following cases.

MATERIALS AND METHODS

Two cases are presented with digestive tract perforations in the stomach (case 1) and in the small bowel (case 2). Owing to both local and general adverse conditions, it was considered that, besides suturing lesions with separate, extramucous stitches with 3-0 polypropylene (Prolene, by Ethicon, Edinburgh, UK), a reinforcement would be appropriate. Therefore, it was decided to use an ePTFE patch, dual mesh type, 1-mm thickness, 20 μ porosity (Gore-Tex, by W.L. Gore & Associates, Flagstaff, Ariz.), to cover the suture line all over and up to 0.5 cm more with the patch smooth surface. The patch is grafted to the surrounding seromuscular tissue by means of a continuous suture done with 4-0 Polypropylene (Prolene, by Ethicon). An endoscopic follow-up was performed in the gastric reparation case (case 1 hereinbelow), and autopsy studies were performed in the small bowel case (case 2 hereinbelow). Thus, we have been able to follow the interaction of the biomaterial with the tissue involved in sutures.

RESULTS

Case 1

An 82-year-old woman complaining of abdominal pain and vomiting for 24 hours. She had a history of chronic arthropathy in both knees, for which she had been given Diclofenac 75 mg/d for 6 months. Peritoneal signs were observed during the physical examination. Because a chest radiograph showed a pneumoperitoneum, surgery was immediately decided. During surgery, 1.5 L of bilipurulent fluid was found and a perforated, giant, gastric ulcer of approximately 6 cm diameter was discovered. It was located next to the lesser stomach curvature and extended to both stomach faces. While the patient was being operated on, she suffered an important hemodynamic impairment with a drop of blood pressure that could only be reverted by means of high doses of inotropic drug infusion; therefore, it was decided to shorten the surgery. A local resection of the ulcer, with a longitudinal suture on the edges of stomach was performed, and an ePTFE patch was grafted as it has been described in Materials and Methods. The patient was taken to the Intensive Care Unit (ICU) with a severe sepsis and an acute respiratory distress syndrome. However, she progressively improved and could be transferred to general ward 14 days later. She was discharged 20 days after the postoperative period. The anatomicopathological study on the resected lesion showed a benign chronic ulcer.

Follow-Up

Seven months after surgery, the patient underwent a control videogastroscopy that showed that at the ulcer resection area on the gastric wall the ePTFE patch was almost covered by a tissue identical to the surrounding gastric mucosa with the exception of its central area (Fig. 1). The rest of the endoscopic examination was normal.

Case 2

A 64-year-old woman complained of vomiting and lack of intestinal gases elimination for 72-hours. Four years before she had undergone an enterolysis as well as a 60-cm resection of the small bowel because of an intestinal occlusion caused by bridles. During the physical examination it could be ob-
erved that she was both dehydrated and undernourished. Her abdomen was distended and painless. Admission studies showed anemia with a 7 g/L concentration of hemoglobin, and an hypoalbuminemia of 2 g/L. Radiograph showed gastric dilatation, and air fluid levels.

The patient was given an intestinal occlusion diagnosis, was admitted, and medical treatment was established. On hospital day 4 she showed no clinical or radiologic improvement, so then surgery was decided. Peritonitis caused by small bowel firm adhesions was observed, involving all the small intestine, the wall of which was friable as well as edematous. An enterolysis was performed. During the surgery, two 4 cm-long perforations on the antimesenteric edge, at 60 and 120 cm from the angle of Treitz, respectively occurred. Both perforations were sutured and covered with two ePTFE patches employing the technique above mentioned. The patient evolved favorably and 3 days after surgery oral intake was installed and well tolerated. Seven days after surgery, however, intestinal fluid draining from the surgical wound was observed and a new operation was decided. During surgery, approximately 1 L of enteric fluid was found and a 0.5 cm-diameter perforation was discovered on the antimesenteric edge of the small bowel. This perforation was located on an area lacking of serosa, at 30 cm from the angle of Treitz. Nevertheless, the two sutures that had been performed during the first operation were undamaged: neither the ePTFE patches had been displaced nor any enteric fluid was draining. The new lesion was sutured, and an ePTFE patch was grafted upon, according the above mentioned technique.

The patient was taken to the ICU where a severe sepsis was diagnosed and treated. Thereafter, a multiorgan failure occurred, resulting in eventual death (postoperative day 16).

Autopsy Findings

Patient’s family authorized the autopsy, and studies were performed on the three small bowel areas where the patches had been grafted. A macroscopic observation demonstrated no evidence of either displacement or suture dehiscence in the first two patches (16 days after they had been placed, Fig. 2A,B), as well as in the last patch (9-day’s after it had been placed, Fig. 2C). Moreover, when the three intestine portions were observed on their endoluminal face, the mucosa was complete on the whole suture surface with no continuity defects (Fig. 3A–C).

A microscopic observation showed that the mucosa was well preserved in the suture areas. Meanwhile, granulation tissue, constituted by inflammatory infiltrate with predominance of monocytes, fibroblasts and neoformation vessels, could be observed at the muscular, submucosa, and serosa. Concerning the ePTFE patch, its structure had been infiltrated by inflammatory tissue, fibrin, and neoformation vessels, a process that had started on the patches edge, thereafter covering their external surface, and penetrating through the pores (Fig. 4A,B). Infiltration was deeper in the patches that had been grafted 16 days before, compared with infiltration in the patch that had been grafted 9 days before (Fig. 5A,B).
DISCUSSION

Repairing perforations of the gastrointestinal tract could be performed by means of a simple suture with very good outcomes whenever conditions are favorable. Instead, when reparation is performed under adverse conditions; either local such as contamination and tissue edema (or general such as hypoalbuminemia or sepsis) the possibilities for complications, such as suture dehiscence increased. In these cases, different surgical techniques are proposed, such as the small bowel serosal or pediculate patching, or either the de-functioning or the exteriorizing of the sutured area. However, these techniques yield not quite convincing results.

The use of biomaterials such as the ePTFE to repair hollow viscera lesions begun in the urological practice for bladder widening, and, in the gynecological practice for uterine ruptures. By late 1990s initial research works dealing with perforations of the digestive tract, in particular stomach, duodenum, and small bowel were reported. However, most recent reports give a better understanding about the interaction between the material and the tissue to which it is incorporated. The experimental research by Ohs et al. compares the ePTFE performance in its three presentations, namely cardiovascular, dual mesh, and dura mater covering in laboratory animals. In that work, perforation was not sutured but it was covered with a patch fixed to the healthy portion of the organ involved. According to this research, the dual mesh evidenced the best interaction with tissues because it caused lesser number of displacements and dehiscence.

This is why we have chosen this type of ePTFE to be used in our above mentioned cases but unlike the work of Ohs et al., the patch was used as a reinforcement of the primary suture rather than a replacement of the perforated wall.

Based on the findings of the endoscopic follow-up procedure and on the autopsy studies, we assume that: (1) This material allows proliferation of mucus tissue over the inner surface material, which is, apparently, similar to the tissue of the viscera involved. (2) The ePTFE patch allows that cell elements forming the matrix of the connective tissue be

Fig. 3. Endoluminal face of the three small bowel portions covered with the patch. There is not a break in the mucosa (A,B, seen on postoperative day 16; and C, seen on grafting day 9).

Fig. 4. Microscopic image of a patch being infiltrated by inflammatory tissue and neoformation vessels on edges (A) (magnification ×10) and in-depth (B) (magnification ×4). Hematoxylin and eosin stain. ES, external surface; IS, internal surface.

Fig. 5. In-depth microscopic image of the patch infiltration after different grafting periods. (A) On postoperative day 16 and (B) on postoperative day 9. Hematoxylin-eosin stain (magnification ×10).
included within its structure. This process starts on the ex-
ternal patch surface and is facilitated by porosity. Such char-
acteristic secures the fixation to serosa tissue as well as
maintains the impermeability of the patch, thus hindering any
patch displacement as well as any possible draining processes
from the suture involved. (3) The ePTFE patch does not
interfere with normal cicatrization of tissues involved in the
suture to which the ePTFE patch protects. (4) Neither local
nor general adverse conditions affect the interaction between
the ePTFE patch and the tissue involved. However, the
ePTFE patch preserved its protective function all over the
suture.

CONCLUSIONS

The foregoing encourages us to consider that the ePTFE
patch, in particular its dual mesh form, can be successfully
used as a reinforcement of sutures on gastrointestinal perfo-
rations performed under unfavorable conditions. However,
the use of other efficient and rapid techniques, like greater
omental pedicled flap, should not be discarded, although their
results in multiple or extensive lesions must be compared
with the ePTFE patch. It should be considered those situa-
tions in which greater omental cannot be employed because
of its shortening as a consequence of previous surgical pro-
cedures, ischemia, or generalized peritonitis. Nevertheless,
more research needs to be developed on the performance of
ePTFE patches, and its interaction with tissues of other di-
gestive tract organs such as colon and esophagus, so as to
investigate the possibility of adhesions formation between the
external surface of the patch and the peritoneal serosa. In that
case, it could be avoided by modifications of the porosity and
texture of the biomaterial to make the surface smoother and
with more little pores. We also suggest that there is an
interesting possibility of studying the ePTFE patches grafting
for repairing traumatic perforations to be used as either de-
finitive or temporary treatment for severe lesions where dam-
age control is performed.

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Life-Threatening Bleeding of Bilateral Maxillary Arteries in Maxillofacial Trauma: Report of Two Cases

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Key Words: Maxillofacial injuries, Maxillary artery, Angiography, Massive bleeding, Shock.

The incidence of maxillofacial injuries is around 10% in most major trauma centers. The injury is usually associated with a variety of problems including airway compromise, intracerebral hemorrhage, cervical spine injury, and oronasal bleeding.

Unless airway obstruction exists, isolated maxillofacial trauma is rarely life-threatening. In addition, although oronasal bleeding after facial fracture is common, life-threatening bleeding is considered relatively rare with a reported incidence between 1.25% and 11%. The main vessel responsible for intractable bleeding is the internal maxillary artery (IMA) as well as its branches, and in most cases injury to the IMA is unilateral. If a patient sustains bleeding from a bilateral IMA injury, there is greater potential for blood loss resulting in a more life-threatening situation and greater urgency for resuscitation.

Here we report two cases who sustained life-threatening hemorrhage of bilateral maxillary arteries in maxillofacial injury and suffered mortality and morbidity.

CASE REPORT 1

A 45-year-old man sustained a fall from three meters height on February 7, 2003. He was transferred to our emergency room with a presentation of facial deformity, active bleeding and left patella fracture. On examination an emergency room admission and revealed severe brain swelling as well as a small intracerebral hemorrhage over the left frontal and brain stem areas. Persistent hypotension with systolic blood pressures around 80 mm Hg was noted even with fluid replacement in 3/4 kg/min. With a suspected diagnosis of disseminated intravascular coagulation (DIC) and brain stem failure, the patient’s family decided against any further resuscitation and he was discharged.
challenged against advice on February 9, 2003 and died on the same day.

CASE REPORT 2

A 22-year-old man sustained a complex LeFort-II midface fracture with multiple facial laceration wounds, right rib, and femoral shaft fractures in a traffic crash on April 16, 2004. After endotracheal intubation, he was transferred from a local clinic to our emergency room with a GCS score of E1 VtM1. He was in hypovolemic shock and had active oronasal bleeding on arrival. Nasal packing for the active nasal bleeding was performed in addition to fluid replacement and transfusion of 4000 mL of blood (12 units packed red blood cells, 2 units whole blood, and 24 units platelets). Brain CT showed fractures of midfacial bones but no intracranial hemorrhage.

Because of failure of oronasal packing to control the bleeding, emergent angiography was performed with trans arterial catheter embolization 4 hours postarrival despite unstable vital signs and a systolic blood pressure around 50 to 60 mm Hg. Active contrast medium extravasations were noted from the bilateral internal maxillary arteries (Figs. 5 and 6), with the largest one being supplied by the left IMA (Fig. 6).

Selective catheterization into the bilateral ECAs was performed with the tips remaining closed to the origins of the bilateral IMAs and gelform cubes were slowly infused to stop the blood flow. After embolization, almost complete obliteration of the bilateral distal ECAs, distal to the origins of the facial arteries, was noted in the common carotid artery injections (Figs. 7 and 8), and the patient’s systolic blood pressure improved to around 90 mm Hg. An exploratory laparotomy

Fig. 1. (Case 1) Multiple contrast medium extravasations were noted over right internal maxillary artery on the lateral view angiograph.

Fig. 2. (Case 1) The largest bleeder was supplied by the posterior superior alveolar branch of the left IMA. Insufficient blood flow of the left internal carotid artery to the cerebral hemispheres was noted (arrowhead).

Fig. 3. (Case 1) Insufficient blood flow of the right internal carotid artery to the cerebral hemispheres was still found (arrowhead) in the beginning of venous phase perfusion through the right common carotid artery.

Fig. 4. (Case 1) Embolization was successfully carried out in the largest bleeder of the left internal maxillary artery.
was performed 2 hours later because of suspected blunt abdominal trauma and intra-abdominal bleeding following physical examination and abdominal sonography; however, no intra-abdominal organ injury or internal bleeding was found. In addition, bloody oozing from the posterior pharyngeal wall was noted during the operation and was controlled with the inflated balloon of Fr 16. Foley catheter passed through the oral cavity.

After resuscitation, the patient’s level of consciousness improved to El VtM5. Brain CT performed 5 days later showed multiple infarctions of the brain with compression of bilateral lateral ventricles (Fig. 9). Bilateral complete blindness because of traumatic optic neuropathy was diagnosed by an ophthalmologist and the patient was in a drowsy and agitated conscious status. He received open reduction and internal fixation for the right femoral shaft fracture 2 weeks later and was transferred to a general ward 1 month later. One episode of status epilepticus was noted during hospitalization and controlled with antiepileptic medication. Progressive improvement of consciousness and orientation was noted and he was discharged 7 weeks after admission. The patient’s cognitive state became clearer and he was able to follow commands during follow-up, despite his family complaining of an altered temperament manifested as a low threshold for becoming agitated. His blindness did not resolve.

**DISCUSSION**

When post-traumatic intractable oronasal bleeding occurs, adequate airway protection should be considered first as...
massive hemorrhage and blood pooling in the oronasal cavity can cause immediate life-threatening problems including aspiration and airway obstruction. Nasal packing or tamponade with balloon catheter are thought to be effective procedures, especially in the mild to moderate hemorrhage. These can be performed quickly and easily in expert hands, however complications such as local palate edema, alar necrosis, aspiration and hypoxia can occur. In most mild to moderate bleeding, this procedure may be enough to eliminate the bleeding; however, with reported failure rates ranging from 21 to 53%, its efficacy in stopping severe oronasal bleeding is questionable. One reason for failure is that the bleeding may originate from the oral cavity, not the nasal cavity. In addition, in severe midfacial fractures there is only soft tissue but no solid wall for the packing to buttress against. In addition, when the injury is located at or proximal to the second part of the maxillary artery, which is defined as lateral to the lateral pterygoid muscle, the packing method cannot be expected to be able to compress the bleeder and stop the bleeding. However, disadvantages as risky general anesthesia for the critical patient as well as difficult to perform reduction in a patient with massive bleeding and severe tissue swelling preclude the feasibility of early fracture reduction. Angiographic intervention is useful for diagnosing and locating the injured vessel and providing a therapeutic method to embolize the bleeder. TAE is considered the better choice for stopping intractable oronasal bleeding. No general anesthesia is necessary, which is particularly of benefit for multiple trauma patients with a compromised hemodynamic status. There are possible the complications of embolization including soft tissue necrosis, blindness, facial nerve palsy, and hypoperfusion during the initial hypovolemic shock. Ischemic stroke resulting from traumatic hemorrhagic shock is uncommonly reported in the literature. Bladin et al. reported that only 9.6% of 300 consecutive patients with acute ischemic stroke had documented or presumed hypotension at stroke onset, and most presentations were related to underlying medical compromise including myocardial ischemia, cardiac arrhythmias, and orthostatic hypotension that was because of diabetic dyautonomia or antihypertensive therapy. In this patient, angiography was very useful in detecting and stopping the bleeders and the complication may be reduced by more aggressive fluid replacement to correct the hypovolemic status.

In conclusion, we have reported two cases that sustained bilateral maxillary arterial injuries in maxillofacial trauma.
Although massive fluid replacement was initiated, one patient died because of the intracranial hemorrhage and another patient sustained the rare but severe complication of brain ischemic stroke because of massive bleeding. When dealing with such illnesses, angiography is recommended for diagnosis and treatment intervention.

REFERENCES

Dislocation of All Metatarsophalangeal Joints Caused by Horse Injury

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The metatarsophalangeal articulation is a complex structure. Dislocation of all metatarsophalangeal (MTP) joints is rare. The mechanism of this injury is hyperextension stress placed upon the joint from the volar aspect of the proximal phalanx directed dorsally in a foot that is plantar flexed and the metatarsophalangeal joints are dorsiflexed. The injury in this case was caused by a major trauma involving a horse and it was impossible to reduce the dislocation closely. The first to fourth toes were reduced using the plantar approach, and pinning could be performed. However, the fifth MTP joint, which did not appear to be dislocated on the initial radiographs, was found to be dislocated after pinning. Then a dorsal approach was selected and the dislocation was fixed with a C-wire. Here, we describe the dislocation of all MTP joints by a horse and discuss the presentation of this injury.

CASE REPORT

In 2002, a 23-year-old male stock farm worker was injured on the dorsal side of the right foot by a horse. He presented with severe pain, swelling, and deformation of the foot, and could not walk. He could not move the toes of the injured foot and showed sensory disturbances on both the dorsal and plantar side of the foot. The skin color of the foot was pale, and circulatory disturbance was suspected although the dorsal pedis artery was palpable. Radiography showed fracture of the fourth metatarsal head and dorsal dislocation of the first to fourth MTP joints. In addition, lateral dislocation of the sesamoid bone and fracture of medial malleolus and medial one-fourth of the navicular bone complicated the injury (Fig. 1). We selected conservative treatment of all fractures along with reduction and temporary fixation of all dislocated MTP joints. Closed reduction was attempted on the day of injury but was unsuccessful, and open reduction was performed. The joints were reduced after releasing the plantar capsules by a plantar approach. The joints were temporarily fixed with C-wires 1.1 mm in diameter to maintain the reduction. The fifth MTP joint, which did not appear to be dislocated on the initial radiography, was found to be dislocated after pinning (Fig. 2). Because no reduction impairing factor for the fifth toe was observed using the plantar approach, another dorsal incision was added, and the fifth MTP joint was reduced and fixed with a C-wire. The reduction impairing factor for the fifth toe was the capsule caught in the joint on the dorsal side. Postoperatively, the skin color and circulation improved. Ankle range-of-motion exercise was started 3 weeks after surgery for rehabilitation. All pins were removed 6 weeks after surgery, and partial weight-bearing was started. Full weight bearing was permitted 8 weeks after surgery, when radiography showed reduction of all MTP joints (Fig. 3). The patient returned to work after three months. At the final follow-up seven months after surgery, he felt no pain and had no problem at work.

DISCUSSION

There have been some previous reports describing cases of traumatic MTP joint dislocation. Dislocation of MTP joints often occurs in the first, second, or third toes; dislocation of all MTP joints from the first to the fifth toes is rare. Neurovascular injury is occasionally observed in multiple MTP joint dislocations. The MTP joints play an important role in plantar flexion immediately before the toe-off phase of walking as well as in the transverse arch formation of the foot. Therefore, anatomic repair after injury is indispensable. Takashi reported that MTP joints are dislocated when an external force is applied from the plantar to the dorsal side of foot in a slightly tiptoed position of the foot with slight dorsal flexion of the MTP joint. Dislocation of the MTP joints has frequently occurred in traffic crashes, but the injury in this patient was caused by the patient’s foot being struck from the dorsal side by a horse. External force from the ground is considered to have been applied to all metatarsal heads from the plantar side to the dorsal side. Closed reduction of dorsal dislocation of the proximal phalanx is often prevented by several factors interfering with reduction. These have been reported to include the capsule, deep transverse metatarsal ligament, and fibrocartilage plate, necessitating open reduction.

According to anatomic findings, the deep transverse metatarsal ligament is a band that connects the metatarsal heads of the five toes. Therefore, we do not consider that the presence of the
deep transverse ligament alone is a reduction impairing factor. However, we cannot detect a band-like strong tissue that connects the proximal phalanges (Fig. 4). If there were such a bandlike strong tissue, one proximal phalange dislocation might cause simultaneous dislocation of the other MTP joints because of tension on this band. The absence of such a bandlike strong tissue is considered to explain the rarity of simultaneous dislocation of all MTP joints in the foot. In the present case, an external force is considered to have been applied simultaneously to all MTP joints, a situation that appears possible in an injury caused by a horse. Concerning the surgery, a dorsal approach is useful for reduction of MTP dorsal dislocation. After reduction, internal fixation was performed using C-wires, which were removed before full weight bearing was permitted. The interval until resumption of weight-bearing was 4 weeks or less after surgery in many reports, but weight-bearing was resumed after 6 weeks in this case in consideration of the involvement of all MTP joints. Burnet reported that almost all patients with MTP dislocation returned to work, though range of motion in the MTP joint was limited. This patient returned to the same job without suture of the deep transverse metatarsal ligament. It is not necessary to suture the deep transverse metatarsal ligament if alignment of the metatarsal heads in the MTP joints is acceptable.

REFERENCES

We present a case of splenic rupture as a rare cause of massive hematemesis. A previously healthy 23-year-old man presented to the emergency department with massive hematemesis secondary to a ruptured spleen from a motorcycle crash 12 days previously. We describe his injury pattern and treatment. We discuss this unusual presentation of ruptured spleen with hematemesis, which has not been reported in the literature previously.

CASE REPORT

We present a case of splenic rupture as a rare cause of massive hematemesis. A previously healthy 23-year-old man presented to the emergency department after two episodes of massive hematemesis consisting of large volumes of old blood. He also described a 5-day history of melena and left-sided abdominal pain of over a week’s duration. At examination, although conscious, he was hemodynamically compromised with a tachycardia and hypotension. There was a perceptible diffuse fullness in his left abdomen and he was tender in the left iliac fossa. Results of blood investigations were hemoglobin, 4.0 g/L (reference range 13.0–18.0); white blood cell count, 29.6 (3.7–11.7); platelet count, 1,174 (150–400); hematocrit, 0.13 (0.4–0.54); urea, 9.7 (2.5–7.0 mmol/L); and creatinine, 174 (60–120 μmol/L).

Twelve days previously, he had been involved in a motorcycle crash and had sustained fractures of the 9th and 10th ribs on the left side. He had been admitted under a different surgical team for intercostal drainage of a small apical pneumothorax. No other injuries were apparent at that time, he was hemodynamically stable, and his abdomen was soft and nontender. There had been no clinical indication of intra-abdominal injury. Although splenic rupture was considered because of the mechanism of injury, he was not scanned because, regardless of the result, the management of such a stable patient would have been conservative. He was discharged on the third day after injury.

At his second admission, at urgent upper gastrointestinal endoscopy, more than 1 L of fresh blood was aspirated from the stomach. A large fresh clot lay on the posterior gastric body extending up to the cardia and fundus. Fresh blood was welling up almost as quickly as it was being washed off and aspirated. The visible gastric mucosa was entirely normal with no gastritis and the esophagus and both the first and second parts of the duodenum appeared healthy. A provisional diagnosis of an arterioenteric fistula was made and urgent surgical exploration was arranged.

At laparotomy, the spleen was in two completely separate parts (Fig. 1). A macerated portion lay in the splenic bed within a hematoma of variable maturity, extending down and across into the lesser sac, behind the posterior gastric wall, over the posterior peritoneal cavity, reaching across to the midline as far as the left crus of the diaphragm. The other portion of splenic tissue was adherent to the peritoneum of the left anterolateral abdominal wall, and also attached to the splenic flexure of the colon with some organizing fibrous tissue. There was about 100 ml of free thickened old blood in the peritoneal cavity tracking down the left paracolic gutter. There was also a large, contained, tense retroperitoneal hematoma on the left.

We performed a partial splenectomy to remove the bleeding upper portion of the spleen from the splenic bed. The lower splenic portion, attached to the splenic flexure of the colon, was not actively bleeding and so was preserved. Complete hemostasis was achieved.

The stomach was opened through a high anterior gastrostomy. A posterior wall ulcer high on the gastric fundus was a distinctly palpable mucosal thickening 3 to 4 cm across, located just below the cardia. This corresponded to the portion of the posterior stomach wall that was adherent to the splenic remnant and organizing hematoma in the lesser sac. After this was peeled off by finger fracture, a distinct point of contact where the stomach wall was eroded was identified and a punctate full thickness ulcer was confirmed (Fig. 2). This was oversewn and inverted.

The patient made an uneventful recovery and was discharged 9 days after surgery. He was given triple vaccination...
and prophylactic Augmentin according to the protocol for postsplenectomy patients.

Histology of the excised splenic portion showed evidence of extensive coagulative necrosis associated with hemorrhage, consistent with venous infarction. There was organization around the infarcted areas, including the capsule. The changes were compatible with splenic vein thrombosis after the injury.

**DISCUSSION**

A search of the literature has not identified any reports of a similar cause of massive hematemesis. An isolated bleeding ulcer, particularly on the posterior wall, arouses suspicion of an arterioenteric fistula. The ulcer was unlikely to have been a primary abnormality because at endoscopy the remainder of the gastric mucosa was normal with no surrounding inflammation, and the ulcer itself was in a very atypical position (proximal stomach) for an isolated peptic or stress ulcer.

Ruptured splenic artery aneurysms are recognized as a rare cause of hematemesis, with similar fistula formation through posterior stomach wall. These aneurysms may result from trauma or as a complication of chronic pancreatitis, but are most common in pregnant women. At laparotomy, there was no evidence of aneurysm formation in this case.

The confined space of the lesser sac lying behind the posterior wall of the stomach can contain the hemorrhage from splenic injury or from aneurysm rupture, albeit temporarily, leading to a delayed manifestation of signs. Balachandran et al. noted blood in the lesser sac in 9% of computed tomography scans for splenic injury.

The viability of the lower portion of the bisected spleen can be explained by an anatomic variant in this patient’s blood supply. The arterial supply is from the splenic artery, which divides into lobular branches. This branching may occur early, as in this case, to form an inferior polar artery. This was described in 22.5% of spleens by Ignjatovic et al. A similar situation has been described by Baron et al.

This report highlights splenic rupture as a rare cause of massive hematemesis. This may become a more common presentation as more splenic ruptures are treated conservatively.

**REFERENCES**

Ankylosing spondylitis (AS) is a well-known seronegative arthritis characterized by inflammation of the axial spine and sacroiliac joints. In long-standing AS, syndesmophytosis, accompanied by osteoporosis of the entire spine, results in a rigid and brittle bamboo-like spine, which is easily broken in the face of external force.1 The fused cervical spine is especially prone to such an injury.2,3 Chiropractic spinal manipulation (CSM) is a popular physical therapy for nonspecific back and neck ache.4 Although chiropractic is claimed to be harmless, some complications, such as cerebral vascular accidents, myelopathy and radiculopathy, have occurred.5 Rare cases of fracture dislocation of the cervical spine, resulting from CSM, have been reported.6 We encountered such a patient whose bamboo spine was unintentionally fractured during CSM. The associated neurologic deficits and functional impairments improved dramatically after combined anterior and posterior surgical decompression with three-column internal instrumentations.7 After this type of surgical management, a noninvasive external orthosis, such as a four-poster brace, can afford sufficient postoperative cervical support to obviate potential complications and the intolerable confining nature of halo-vest immobilization.

CASE REPORT

Presentations

A 66-year-old man suffered from long term AS, and his spine became fused with a bamboo-like appearance 20 years ago. Although the neck was fixed in a flexion posture with a kyphotic angle of thirty degrees, his horizontal vision could be maintained. Because of subjective neck stiffness, he attended a conventional Chinese medical clinic where CSM was performed. He did not have cervical trauma or neck pain before the CSM. During a passive neck extension exercise, he experienced acute excruciating neck pain associated with a tingling sensation in both hands after a subjective click of the neck. Although he could walk slowly without support after the manipulation, ascending numbness into the trunk and weakness in both legs progressively worsened 2 days after CSM. However, he did not pay attention to the abnormal sensations of trunk until 1 week after the CSM when he became quadriplegic and bedridden. The patient was first brought to a local clinic where incomplete quadriplegia with urinary retention was recorded necessitating placement of a Foley catheter. Plain films of the cervical spine revealed a fracture angulation of stick-like spine at the level of C6 vertebral body (Fig. 1). After an intravenous megadose of methylprednisolone was infused, the patient was transferred to our hospital with his neck fixed in the preinjury flexed posture with a Philadelphia collar.

Examinations

In our emergency room (ER), the patient lay still because of severe neck pain. Examinations of the cranial nerves were unremarkable. Based on the standard classifications of spinal cord injury developed by the American Spinal Injury Association (ASIA), the powers of the key muscles of the upper limbs ranged from two to three grades on the right and three to four on the left.8 Meanwhile, the powers of the key muscles of the lower limbs ranged from 0 to 1 on the right and two to three on the left. He did not experience a deterioration of muscle power during the hospital transfer. Hypoesthesia to pin pricking was noted below the T1 dermatome, but allodynia was experienced at the C6 to C8 dermatomes. Joint position sensations were impaired in the fingers, ankles, and toes. The external sphincter contracted tightly during the digital examination. Based on the ASIA8 and the Nurid grades9 (grade 1, normal walking with possible clinical spinal irradiation; grade 2, slight difficulties in walking with normal domestic and working life; grade 3, functional disability limiting normal work and domestic activities; grade 4, significant weakness making walking impossible without help,
and grade 5, bedridden or wheelchair bound), the patient was coded as ASIA grade C and Nurid grade 5 at the ER.

Magnetic resonance (MR) images of the cervical spine revealed a bursting fracture spanning the inferior portion of the C5 and the superior portion of the C6 vertebrae, and the fracture line extended to the posterior element between C6 and 7 (Fig. 2). Bone fragments compressed the spinal cord both anteriorly and posteriorly. A posterior epidural lesion at the fracture site was suspected to be an epidural hematoma because of the heterogeneous intensity on T2-weighted images. Extreme instability of the fracture was evident, because the alignment was reduced spontaneously when the patient lay in the supine position for MR imaging. Although cranial cervical traction was performed to keep the alignment straight after MR imaging, the neurologic deficits did not improve. In addition to the slowly progressive nature of the neurologic deficits, emergency surgical decompression of the spinal cord was considered to be necessary to prevent further deterioration.

**Operations**

Four hours after performing the MR imaging, the patient was transferred to the operating room. Awakened nasal endotracheal intubation was performed with the patient’s head maintained in preinjury alignment. General anesthesia was induced after neurologic examinations confirmed that no further deterioration of the neurologic deficits had occurred after intubation. The surgical procedures were performed with the head and neck positioned in the pre-anesthetic posture. Anterior corpectomy of the fractured C5 and upper portion of the C6 was initially performed, until the dural sac had expanded fully. Interbody fusion followed by Caspar plating was achieved with an autogenous left iliac graft measuring 2.8 cm. Two more screws were put into the C7 vertebral body, because the residual C6 body might not have been able to hold the screws securely, and one screw had penetrated the ossified C6-7 disc space. The T2-weighted MR image revealed a posterior indentation of the spinal cord because of a fractured bone chip, so the patient underwent laminectomy after the anterior corpectomy was finished. Partial C5 and complete C6 laminectomy was performed with the patient in a sitting position. The impinging ossified yellow ligament and the posterior epidural fusiform lesion, histologically confirmed to be a subacute epidural hematoma, were removed. Fracture lines could be found crossing the ossified C6-7 interspinous ligament and the bilateral corresponding facet joints. Plates and screws (14 × 4 mm) were affixed to the bilateral C6 and 7 lateral masses after laminectomy, and achieved an immediate three-columned rigid fixation (Fig. 3). Posterior bone grafting was not performed.

**Postoperative Course**

Because the combined anterior and posterior internal plates fixation had achieved immediate three-column stability...
in the operation, the patient was able to wear a four-poster cervical brace for postoperative external immobilization. The Foley catheter was removed on the postoperative fourth day, with good self-voiding. The muscle powers of key muscles of the upper and lower limbs rapidly recovered to four to five grades 1 week after operation. Meanwhile, allodynia of the hands and hyposthesia of the trunk had almost disappeared. He was transferred to the rehabilitation department on the 7th postoperative day, with neurologic deficits improved to ASIA grade D and Nurick grade 3. Despite minimally residual numbness in both hands, he completely regained motor function and returned to work as a farmer 3 months after operation (Nurick’s grade 1). Rigid bone fusion was achieved 6 months after operation.

DISCUSSION

AS is a male predominant, HLA-27-associated, and se- ronegative arthritis characterized by inflammation of the sacroiliac, the hips, and the articular joints of the axial spine. Over 50% of patients with AS will suffer from moderate to severe spinal restriction in the late stage of the disease, and they are usually complicated by vertebral osteoporosis because of prolonged immobilization. In long-standing disease, ossification of the ligaments and joints of the involved spine occurs, and leads to universal spinal syndesmophytosis (bamboo spine). Spinal fracture is 3.5 times more common in AS patients than in the normal population. Even in the face of minor external stress, the rigid and brittle fused spine is easily broken because of the altered biomechanics, which leads to the spine behaving much like an osteoporotic long bone rather than an elastic spine. The cervical spine is especially prone to such an injury, because the protecting muscle is weak and the supporting paravertebral soft tissues are ossified. Minor trauma, such as a fall during walking or from a standing height, is the most common cause of cervical spinal fracture in AS patients. In Taiwan, as in the United States, CSM is a popular physical therapy for nonspecific back and neck ache. Although the general population views chiropractic as harmless, some undesired complications have been reported, such as stroke or myelopathy, injury to the vertebral artery, spinal cord injury, aggravation of symp- toms related to herniated intervertebral disc and, rarely, fracture dislocation of the vertebral column. Blaine reported three chiropractic atlanto-axial dislocations in which a patient with odontoid fracture died of progressive quadriplegia because of his removing the cervical collar against medical advice. Rinsky reported a C3-4 fracture with C4 quadriplegia after CSM in an AS patient. Despite surgical decompression and internal fixation, the neurologic deficits did not recover. Schmidley reported an AS patient who developed an incomplete cervical myelopathy below C7 because of C6-7 spondylitic canal stenosis after a minor fall. The myelopa- thy was aggravated after a CSM that also caused a fracture of the left transverse process of the C7. Fortunately, the neuro- logic deficit improved after cervical discectomy and fusion. All these patients, including ours, first presented with sudden excruciating neck pain during CSM followed by progressive neurologic symptoms related to vertebrae and spinal cord injury. Thus, violent spinal manipulation bears a potential danger not only to the cervical vas- culature but also the skeletal system. Physicians caring for patients with rheumatological spinal pathology should warn them of the potential danger of CSM.

Fractures of the cervical spine in AS patients are accom- panied with a high incidence of severe neurologic deficits and mortality. Murray reported a 57% rate of severe neurologic deficits (quadriplegia and paraplegia), and a 35% mortality rate associated with vertebral fracture in AS patients (three times and twice more frequently than the normal population, respectively). The prognosis of severe neurologic deficits (quadriplegia or paraplegia) associated with vertebral fracture in AS patients is generally poor. In a multicentric analysis, Apple pointed out that merely 4 out of 35 nonsurgically treated patients and 2 out of 22 surgically treated patients had neurologic improvement at the last follow-up. Ticó collected 13 AS patients with cervical spinal fracture and spinal cord injury. Among them, 6 of 12 patients who were not operated on died, and only one had neurologic improvement, from ASIA D to E. Whether AS patients with spinal fracture
and spinal cord injury should be treated with surgery followed by external immobilization, or with external immobilization alone, remains controversial. In early reports, because of a relatively high prevalence of respiratory complications and minimal neurologic recovery after surgical fixation, some authors suggested that conservative treatment, such as craniocervical traction followed by Halo-vest immobilization, would be the first choice of treatment for cervical spinal fracture complications in AS patients. Although secure immobilization in a Halo-vest after well close reduction can achieve rapid bone union, it may only be performed in patients without spinal cord compression. Any neurologic deficits resulting from spinal cord compression by epidural hematoma or intervertebral disc herniation, warrant surgical decompression. Surgical intervention is also indicated in the management of fractures that fail to be stabilized with nonoperative devices. After surgical decompression and internal instrumentation, it was generally recommended that postoperative halo-vest immobilization would be required to prevent early instrument failure and facilitate bone union. However, facing ample complications and the intolerably confining nature of halo-vest immobilization, the cervical collar or cervico-thoracic brace have replaced the halo-vest after the internal fixation of cervical fracture in some AS patients. Taggard and Traynelis treated cervical fracture in seven AS patients with three-point posterior instrumentations, followed by a cervical collar as external immobilization. None experienced postoperative neurologic deterioration, and all achieved rigid bone fusion. Taggard and Traynelis also mentioned that combined anterior and posterior instrumentations might be necessary when the structural integrity of the vertebral body is significantly compromised, and overt instability of the fracture is present. Our case provided an opportunity to perform this type of 360 degree internal fixation. Although combined anterior and posterior decompression can thoroughly decompress the spinal cord, they also completely destroy the three-columned stability required for interbody bone fusion. After such management, the postoperative halo-vest can be replaced safely with a four-poster thoracocervical brace.

CONCLUSIONS

Physicians caring for patients with rheumatological spinal pathology should be aware that CSM is dangerous, and should be avoided, if possible. Fractures of the cervical spine in AS patients carry a high incidence of severe neurologic deficits and mortality. This study supports the notion that thorough surgical decompression can rescue spinal cord function, if neurologic deficits develop because of spinal cord compression at the fracture segment. Combined anterior and posterior instrumentations can restore the immediate three-columned stability required for interbody bone fusion.

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Pelvic fractures are uncommon in children, with a prevalence of about 3% in the American National Pediatric Trauma Registry. \(^1\) Their mortality rate varies between 1.4% and 14% \(^1,3,6,8,9\) and is mainly related to associated injuries. \(^1,3,6,7\) Pediatric pelvic fractures are most often classified according to Torode and Zieg,\(^8\) based on degree of instability and the consequent need for open versus closed reduction and for operative stabilization in type III and IV fractures. However, the vast majority of children who sustain pelvic fractures (>90%), \(^3,6,10\) particularly those whose bony immaturity is reflected by open triradiate growth plates, do not require surgical intervention because of the opportunity for extensive remodeling. \(^7,11,12\) Formal open reduction and internal fixation of unstable pediatric pelvic fractures may therefore only be indicated in injuries with gross instability, major deformity or dislocation, as well as in open injuries or in a situation where the patient requires a primary laparotomy. \(^4,10,11,13–15\)

The purpose of this report is to describe an unusual, grossly unstable, open, comminuted, posterior pelvic ring disruption with neurologic injury in a child, caused by a high-velocity gunshot injury, and to recommend operative treatment methods.

**CASE REPORT**

A 10-year-old girl sustained a high-speed rifle wound to the midline buttock region, which resulted in a laceration the size of an average hand and rectoperineal hemorrhage with perforation of the colon. The patient also sustained a pelvic ring fracture in which her right hemipelvis was essentially dissociated from the main axis of the sacrum. She was initially resuscitated at an outside hospital, where she underwent an exploratory laparotomy, diverting colostomy, and partial sigmoid colectomy. Posterior wound care was performed as well, with placement of antibiotic beads. The patient was then transferred to Harborview Medical Center for further treatment.

At admission, the patient was noted to have a 10-cm (diameter) open, clean wound above the rectum and a rectal laceration. Abdominal examination showed a healing abdominal incision and left colostomy. Neurologic examination was consistent with a severe right lumbosacral plexopathy, with mild preservation of hip flexion and the absence of any other voluntary, right lower extremity motor function and severe hyperpathic right leg pain. Bowel and bladder control was absent. The plain pelvic radiographs demonstrated a comminuted fracture of the right posterior ilium and sacral ala with polymethylmethacrylate beads as well as the presence of metallic fragments (Fig. 1). Computerized tomography confirmed the severely comminuted open transalar/tranforaminal Denis zone II sacral fracture with complete dissociation of the comminuted posterior ilium from the sacrum, and destruction of the sacroiliac joint (Fig. 2).

Twelve days after her injury, the patient underwent wound debridement, removal of antibiotic beads, and lumbo pelvic fixation. Through a midline exposure performed between L3 and the sacrum, an extensive debridement of necrotic tissue and multiple bony fragments was performed. Severe instability of the right hemipelvis was confirmed, with extensive associated loss of posterior iliac and sacral alar bone adjacent to the consequently destroyed sacroiliac joint. After debridement, the iliac artery and vein, as well as the sciatic nerve, were exposed through the posterior exposure. The right S1 and S2 nerve roots were noted to be avulsed at their foramina, whereas the S3 nerve root appeared to be intact but contused. The L5 nerve root could not be identified. Stabilization of the pelvic ring was achieved with lumbopelvic fixation using 6- × 40-mm screws in the right L4 and L5 pedicles, connected through a vertical rod to three 7-mm screws up to 100-mm in length placed into the right iliac wing (Fig. 3). These iliac screws were inserted bicortically to improve fixation, but were kept sufficiently short to avoid

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**Unstable Pediatric Sacral Fracture With Bone Loss Caused by a High-Energy Gunshot Injury**

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being palpable through the soft tissues. Antibiotic-impregnated methylmethacrylate beads were applied before partially closing the wound with a right pedicled fascial flap and covering the remainder of the wound with a vacuum-assisted closure dressing.

Three days later, a repeat irrigation and debridement was performed, with exchange of antibiotic beads and vacuum dressing. Because the condition of the soft tissues was found to be satisfactory, the lumbosacral soft tissue defect was covered with a right, inferiorly based, rotational gluteal fasciocutaneous flap on the following day. Four weeks later, the patient was returned to the operating room for a staged bone-grafting procedure. Because the patient had developed a partial, superficial wound dehiscence, locally necrotic skin was excised before elevating the flap. After removal of antibiotic beads and thorough pulsatile lavage, the right posterior ilium, remaining sacral ala, and L5 transverse processes were decorticated before a mixture of morselized autogenous bone

**Fig. 1.** Anteroposterior (A), lateral (B), inlet (C), and outlet (D) pelvic radiographs after initial sacral wound debridement. The polymethylmethacrylate beads and shrapnel can be identified at the right posterior pelvic ring.

**Fig. 2.** The axial computed tomography scans demonstrate the severe comminution of the right posterior ilium and sacral ala, with complete destruction of the sacroiliac joint. Antibiotic beads have been placed within the bony defect.
graft from the left ilium and vancomycin powder, OsteoSet pellets (Wright Medical Technology, Arlington, TN) with tobramycin, and 10 mL of demineralized bone matrix putty (DBX, Synthes, Paoli, PA) were packed into the bony defect, thereby performing a formal arthrodesis between L5 and the posterior ilium. The wound was then closed by advancing the flap.

Postoperatively, the patient was kept on bedrest for 2 weeks and then mobilized on crutches as tolerated. Her right leg was placed in an ankle-foot orthosis because of her lumbosacral plexopathy. During the following weeks, progressive neurologic recovery occurred, with increasing strength and level of alertness. She regained her bladder function and anal sphincter tone, allowing her colostomy to be reversed 6 months after her injury. Sixteen months after injury, the patient’s gait had almost completely normalized, and leg lengths had remained equal. Her only neurologic deficits were mild right hip abductor weakness and mild dysesthesia and numbness along the lateral border of the right foot. Her sacral wound flap had fully healed. The anteroposterior pelvic radiograph demonstrated a consolidated fusion of her right posterior pelvic ring to L5. Two and a half years after injury, the patient’s gait was nonantalgic, hip motion is symmetric bilaterally, and leg lengths are equal. From a functional standpoint, she is able to participate in gym class, run and jump without discomfort, and has normal bowel and bladder function. The only remaining neurologic deficit consists of decreased sensation along the lateral border of the foot and fifth toe in the S1 distribution. The anteroposterior pelvic radiograph demonstrates anatomic alignment of the pelvis without hardware loosening or failure, and Risser IV developmental stage, equivalent to that of the contralateral ilium (Fig. 4).

**DISCUSSION**

Gunshot wounds to the pelvis are often devastating injuries. Their high mortality rate is related to major blood loss, soft tissue injury, pelvic instability, and complications caused by associated visceral, vascular, and neurologic injuries.\textsuperscript{16–19} Life-saving measures are therefore of paramount importance and may include immediate surgical exploration, airway management, fluid resuscitation, pain control, and correction of blood loss and coagulopathy.

Although emergent exploratory laparotomy after gunshot injuries to the pelvis constituted the standard of care in the 1950s and 1960s based on wartime experience, the civilian trauma standard has gravitated to selective operative management. Most authors have cited clinical peritoneal signs, hemodynamic instability, gross hematuria, and rectal bleeding as indications for exploratory laparotomy after gunshot injury to the pelvis.\textsuperscript{17,20,21} They have recommended that stable patients be treated nonoperatively with appropriate diagnostic evaluation such as angiography, rectal examination, and proctoscopy, as well as triple-contrast abdominopelvic CT.\textsuperscript{17,20} However, because of the density of vital structures in the pelvis and logistical difficulties in the procurement, quality, and interpretation of adjunctive diagnostic studies in stable patients, other authors have recommended surgical exploration.
tion in every patient with a transpelvic bullet trajectory.\textsuperscript{22} In our pediatric patient, hemodynamic instability and rectoperineal bleeding indicated the need for emergent abdominal exploration. Perforation of her left colon necessitated partial sigmoid colectomy and diverting colostomy.

Characteristics of high-energy gunshot wounds include comminuted fractures, devitalized soft tissue, and periosteal stripping.\textsuperscript{23} They mandate operative exploration, multiple debridements, delayed closure, and grafting or flap procedures to obtain coverage.\textsuperscript{23} In our patient, extensive wound debridement was initially performed, with antibiotic beads applied as a void filler. Nevertheless, two more irrigation and debridement procedures were necessary before delayed and final wound closure, as well as local muscle coverage, was possible.

Standard stabilization techniques for comminuted posterior pelvic ring fractures involving the iliosacral joint include tension band transiliac plate osteosynthesis\textsuperscript{24,25} and iliosacral screw fixation,\textsuperscript{25–28} alone or in combination with each other. These osteosynthesis techniques, however, are limited in their biomechanical stability and therefore necessitate prolonged restricted weight bearing. Moreover, their effectiveness is unproven in the presence of severe sacral comminution where thread purchase is likely to be compromised, and in open fractures with severe juxta-articular bone loss. Transiliac plating is subject to the same biomechanical challenges, with the additional potential disadvantage of requiring soft tissue stripping in excess of that having already resulted from the gunshot injury.

Stabilization of this unusual comminuted sacral/posterior ilium fracture was therefore performed with lumbopelvic fixation techniques, as previously described for the treatment of posterior pelvic ring disruptions in adults using triangular fixation techniques.\textsuperscript{29–36} Lumbopelvic fixation offers significantly greater posterior pelvic ring stability than standard operative stabilization techniques,\textsuperscript{3,5} a particularly important detail in light of the findings of Woods et al.,\textsuperscript{39} who identified mechanical stability as the only variable with a statistically significant association with infection in open pelvic injuries. They found that a mechanically unstable pelvis, as determined by physical examination, was associated with a 10-fold increased risk of infection. The stability of the lumbopelvic fixation allows for immediate postoperative mobilization and weight bearing as tolerated.

Lumbopelvic fixation with long iliac screws provides vertical stability between the lumbar pedicles within the “cephalad” fracture fragment and the iliac wing within the “caudal” fracture fragment. Bypassing the area of fracture comminution allows the posterior pelvic ring to be stabilized in appropriate alignment and unloads the sacral fracture, allowing for relative fracture stability and healing, by neutralizing the tendency for cephalad migration and sagittal plane rotation of the injured hemipelvis.\textsuperscript{35} Since a two-point vertical fixation would still allow splaying of the fracture, cephalad fixation was anchored in two pedicles (L4 and L5), and sufficient caudal fixation was gained by inserting three divergent iliac screws. The direct relationship of screw diameter and length to screw pull-out strength\textsuperscript{40} served as the impetus for using extra-long modified pedicle screws in the ilium. Extra-long iliac screws guarantee multiple-point cortical fixation within iliac bony constrictions. Conversely, regular length pedicle screws would obtain fixation mainly in the cancellous bone of the posterior ilium, resulting in decreased pull-out strength.\textsuperscript{34}

Although optimal iliac screw direction is along the bony channel between the posterior-superior iliac spine and the anterior-inferior iliac spine,\textsuperscript{34} size restrictions in our pediatric patient allowed the placement of only one screw in the optimal trajectory. The two other iliac screws were therefore directed above the anatomic canal within the thin iliac wing and beyond the iliac cortex to gain solid bony purchase. Despite their bicortical placement, these screws were not palpable and did not cause the patient any discomfort.

The comminuted fracture site and large bony defect of the posterior pelvic ring necessitated the use of extensive graft material, which consisted of a mixture of autologous bone graft, calcium sulfate pellets (OsteoSet, Wright Medical), and demineralized bone matrix (DBX, Synthes) as an osteoinductive biomaterial including growth factors. This mixture of biomaterials resulted in a large consolidated bone mass at the posterior pelvic ring. Bone grafting of the comminuted fracture site, however, required arthrodesis of the right sacroiliac joint, which was not reconstructable because of the degree of injury. Because of the extensive bone loss, pelvic ring deformity and leg length discrepancy, neither of which occurred in our patient, have to be considered as possible consequences of this injury and its treatment in young children.\textsuperscript{31}

Intraoperative nerve root decompression by removal of bony fragments may have had an influence on the favorable outcome on the initially profound right lumbosacral plexopathy and absent bowel and bladder function. However, preservation of even unilateral lower sacral root function has been well documented to be sufficient for voluntary bowel and bladder control.\textsuperscript{42} The function of the avulsed S1 and S2 nerve roots must have been compensated for by the adjacent roots, since the patient presented with no neurologic deficit other than mild, right hip abductor weakness and mild dysesthesia and numbness on the lateral border of the right foot merely 16 months after injury.

In conclusion, open unstable and severely comminuted posterior, pelvic ring fractures can be effectively stabilized with lumbopelvic fixation and long iliac screws, even in pediatric patients. Aggressive early wound debridement, diverting colostomy, nerve root decompression, and stable fracture fixation may result in a favorable outcome with the return of neurologic function as well as early patient mobilization and weight bearing in pediatric, open, comminuted pelvic ring disruptions caused by a high-energy gunshot injury.
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As an air-powered firearm, BB guns are often considered to be toys. They have the potential to cause life-threatening injuries. Air gun injury to the heart presents several diagnostic and therapeutic challenges. When faced with an unstable patient sustaining cardiac injury from an air gun with subsequent pellet embolization, questions arise as to appropriate management. We present such a case, with a review of the literature addressing operative treatment of the wound, the use of cardio-pulmonary bypass (CPB) in the repair, and whether embolectomy should be attempted.

CLINICAL SUMMARY

A 9-year-old, 45-kg boy presented to the trauma bay of the University of Chicago Children’s Hospital after sustaining a close range (1 m) BB gunshot to the left chest. En route, the patient was responsive, but not alert. On arrival to the trauma bay, he was pale and diaphoretic. His vital signs were heart rate 136 bpm, blood pressure 50/palpation, palpable femoral pulses, respiratory rate 33 breaths/min, and oxygen saturation 99% on face mask, with a Glasgow Coma Scale score of 14. During the primary survey, the patient’s level of consciousness deteriorated, necessitating a rapid sequence intubation. Breath sounds were decreased over the left chest and a left tube thoracostomy was performed. No air leak or effusion was noted. Fluid resuscitation was achieved via two large-bore peripheral intravenous cannulae with improvement of the patient’s blood pressure to 108/palpation but without change in his tachycardia. The secondary survey revealed a single penetrating wound to the left chest, 2 cm medial to the nipple. An emergency department (ED) ultrasound examina-
At the 2-month and 16-month follow-ups, both transthoracic echocardiogram and CXR were performed, showing no abnormalities and a stable position of the BB (Fig. 3).

DISCUSSION

Despite improved prehospital and hospital care, overall survival after gunshot wounds to the heart is 16% to 23%.1,2 However, for the population of victims who arrive to the ED with intact vital signs (spontaneous ventilation, heart rate, and blood pressure) survival improves to 70% to 75%.1,3 Among patients with cardiac injuries who do require an emergent thoracotomy, there is a significantly improved survival rate for those patients stable enough to undergo an OR thoracotomy versus an ED thoracotomy (23% vs. 2.8%).2 As can be expected, better physiologic status at presentation to the ED confers a survival advantage.

The problem of firearm-related injury is certainly not specific to adults. In children under the age of 16, there are approximately 4,500 firearm-related deaths per year and in an institutional review spanning 9 years, 1% of these deaths were caused by air gun injury.4 The common perception of air guns as toys is therefore misguided. When examining the kinetics of air guns, the potential for serious injury is readily apparent. Ballistic studies of air gun pellets found that skin penetration occurs at a velocity of 331 feet/s for a 0.177 caliber pellet and at 245 feet/s for a 0.22 caliber pellet.5 Pneumatic rifles are all capable of firing pellets at velocities in excess of 390 feet/s, and some can reach more than 900 feet/s.5 For comparison, the muzzle velocity of a conventional (powder) 0.22 caliber rifle is 800 to 1,000 feet/s, and a 0.38 caliber revolver exceeds 750 feet/s.6 Because of the low mass of the pellet, kinetic energy is lost quickly but at close range (5–10 feet) this loss is minimal. The literature contains numerous reports of air gun fatalities, which generally result from injury to either the head or chest from air guns being fired at close range.4,7–11

Fig. 1. Emergency room ultrasound of the heart. Pericardial effusion (closed arrow).

A problem with nonfatal air gun injuries, especially those to the chest, is the propensity for the missile to embolize because of its low mass and size. Depending on the site of entry into the vascular system, embolization of any missile can be to arterial, pulmonary, or even venous systems.12–15 The presence of a missile embolus in the pulmonary arterial system raises a question of management, namely whether to operatively extract them. Symbas and Harlaftis reported on 10 patients with bullet emboli, 5 of which were to the pulmonary artery.16 Four of the five patients with pulmonary emboli were successfully treated with embolectomy and remained well at follow-up. Stephenson et al. reported on two cases of bullet emboli to the pulmonary artery, and reviewed
In our particular case, it remains to be seen if the pellet will cause any adverse effects, such as migration to the systemic circulation, empyema, or abscess formation. The patient was asymptomatic at the 16-month follow-up.

Operative management of air gun cardiac injuries is reserved for patients who show evidence of clinical instability, such as arrhythmia or tamponade. Missle embolectomy has a reported mortality as high as 9.5% and therefore should not be undertaken lightly. There are, in general, three options for operative exploration: a left thoracotomy in the ED (EDT), a left thoracotomy in the OR, or a median sternotomy in the OR. As mentioned previously, patients who require an EDT represent the most unstable patients and have the poorest prognosis. In their institutional review, Ladd et al. found that in patients sustaining penetrating cardiac injury and requiring an EDT, survival increased to 16.2% if the procedure was performed on patients with measurable blood pressures and pulses. There were no survivors in patients with no signs of life or those with only pulseless electrical activity and no measurable blood pressure or pulse.

For those patients stable enough to be transported to the OR for exploration, the heart can be approached by either a left thoracotomy or a median sternotomy. In a review of their experience with penetrating cardiac injuries, Mitchell et al. describe their experience using both approaches. Left thoracotomy is the traditional choice for exploration because it provides excellent exposure of the lung, thoracic aorta, and left mediastinum. Exposure of the heart can be limited, and transsternal extension with selective right thoracotomy was occasionally required (25% of patients). A median sternotomy provides excellent access to the heart and anterior mediastinum, but more limited access to the thoracic cavities and posterior mediastinum. This approach also more readily accommodates CPB should it be required. Further, patients show better pulmonary function with less need for pain medication after a median sternotomy. Mitchell et al. concluded that in the hemodynamically stable patient, their incision of choice is median sternotomy, saving left thoracotomy for those patients who require immediate interventions such as aortic cross-clamping, pericardial decompression, or open cardiac massage.

For patients requiring a sternotomy for their cardiac injury, subsequent repair can be performed either on CPB or off-pump. Most free wall and coronary injuries can be handled off bypass. CPB is usually reserved for intracardiac injuries and extensive free wall and coronary injuries. Off-pump repair using cardiac stabilization devices have been described for penetrating trauma. Off-pump repair is preferred because one avoids systemic heparinization, which can be deleterious especially in the setting of associated injuries (i.e., head trauma).

In our patient, the RV free wall injury very likely could have been repaired off bypass. However, we were not able to perform a thorough exploration without bypass because of clinically significant hypotension with cardiac manipulation.
TEE has been used in blunt and penetrating cardiac trauma. Penetrating cardiac trauma not only can cause injury to the free wall of the heart and great vessels, but also to the interatrial and interventricular septa, cardiac valves, conduction system, and coronary arteries. The incidence of intracardiac injuries after penetrating injury has been reported to be anywhere between 4% and 56%. Many of the injuries are detected days to weeks posttrauma. Hemodynamically significant septal and leaflet injuries should be dealt with in a timely fashion as delay can cause significant morbidity and mortality. TEE can provide comprehensive intracardiac evaluation of the heart intraoperatively and prevent delay in repair of significant injuries. Mollod et al. reviewed 16 consecutive trauma patients specifically referred for TEE by trauma and cardiothoracic services. Ten of the 16 patients had penetrating trauma. Seven of the 10 penetrating trauma patients had significant intracardiac or aortic injuries requiring surgical repair. The authors state that TEE influenced the treatment of each patient including the timing of the surgical intervention, type of repair, precise location of an intracardiac foreign body, time to extubate, and optimal medical therapy.

In our patient, TEE demonstrated no evidence of intracardiac injury by the missile. Repair of an intracardiac injury, had it been identified, would have depended on the extent of the injury and the hemodynamic status of the patient.

There are an estimated 17,438 children aged 19 years and younger who are treated annually for nonfatal air gun injuries. The persons at highest risk for sustaining an air gun injury are boys, aged 10 to 14 years, with the vast majority of injuries being unintentional. Of further concern is the fact that about 75% of the shootings happen in the home environment, and in up to 21% of the cases the shooter is an immediate family member. Trends in air gun injuries are encouraging, however. An increased injury rate from 1988 to 1992 was followed by a steady decline through 1999. A search of state laws pertaining to air guns, and firearms in general, reveals that from 1994 to 1996 the number of states restricting the use and sale of air guns to minors has increased from 14 to 28. By the year 2000, that number has further increased to 48. Currently, 11 states classify air guns as firearms or dangerous weapons, 19 states hold parents or guardians legally responsible for injuries or deaths resulting from minors using firearms, and 10 states legally require parents or guardians to store firearms safely away from minors. Safe storage practices alone have contributed to a 23% decrease in unintentional firearm-related deaths in children under 15 years of age. Although progress has been made, public awareness, adult supervision, safety training, and appropriate legislation continue to be critical in decreasing the risks of these potentially lethal weapons.

Despite seeming to be harmless toys, air guns have the potential to inflict serious cardiac injury. Proper management requires a high degree of respect for the potential damage caused by an air gun. Patients should be managed in the trauma bay using Advanced Trauma Life Support protocols, just as if they sustained an injury from a conventional firearm. Observation may be appropriate for asymptomatic patients, but operative treatment should follow the established protocols for treating traumatic cardiac injuries, with CPB employed as needed for safe exploration and repair. Further, embolectomy is not required for pulmonary missile emboli as long as certain established criteria are followed.

Although this article is a single case report, it is an important addition to the literature. Few reports of distal pulmonary embolization have been made; our patient had long-term follow-up without adverse consequences, which further supports that embolectomy is not necessary in all cases.

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Brachial Plexus Palsy Secondary to Clavicular Nonunion

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Brenchial plexus injury is a rare complication following clavicular fracture, occurring in less than 1% of cases. The symptoms occur insidiously and usually affect the medial cord. The resulting brachial plexus palsies arise from direct pressure caused by hypertrophic nonunion, and are usually localized to the middle third of the clavicle. Surgical decompression is the treatment of choice. We describe and illustrate a case where a patient developed a brachial plexus palsy following clavicular nonunion, which was treated by surgical decompression.

Neurovascular injury following a fractured clavicle is a rare occurrence. Brachial plexus injuries following shoulder injuries usually occur secondary to glenohumeral dislocation or humeral neck fracture. Traction injuries to the brachial plexus usually arise from high-velocity injuries. Rarely does brachial plexus palsy arise from callus formation following clavicular nonunion.1 We present a brachial plexus palsy following hypertrophic nonunion of a clavicle.

CASE REPORT

A 60-year-old right-handed gentleman sustained a closed midshaft fracture of his right clavicle, measuring 5 cm of displacement and medialization, following a fall (Fig. 1). Initial neurologic assessment revealed no focal neurologic deficit in the upper limb. The clavicular fracture was treated with a broad arm sling. Other than local tenderness at the fracture site, there were no symptoms at 4-week review postinjury. He presented two months later with pins, needles, and numbness in the right hand. He also noticed that there was a reduction in the grip strength of his right hand, preventing him from shaving and brushing his teeth. Clinical examination of the right upper limb revealed a reduction in abduction at the shoulder and reduced power grip. There was no evidence of muscle atrophy. Two-point discrimination revealed a reduction in sensation in the distribution of the ulnar and median nerves. Diminished triceps and supinator reflexes were elicited. Arterial examination of the upper limb was normal. A radiograph of the right clavicle showed non union (Fig. 2). Magnetic resonance imaging performed 2 months after injury revealed fracture components overlapping each other by 5 cm. A large mass of callus existed between the bone ends (Fig. 3), and this can be compared with Fig 4, which demonstrates normal clavicular anatomy. Electromyographic and nerve conduction studies showed evidence of a lower motor neuron disorder affecting the right arm. There were some motor conduction changes and the flexor response to abductor pollicis brevis was absent. Sensory potentials were preserved. The electromyogram (EMG) studies suggested a deficit at either brachial plexus or possibly at root level in the distribution of C7/8, T1 (Table 1). Workup by the neurology team was followed by vascular referral for thoracic outlet syndrome.

The patient underwent decompression of the right clavicle nonunion site. Operative findings confirmed the presence of a large callus mass between the overlapping clavicular ends (5-cm overlap). Osteotomy with partial excision of the lateral portion of the clavicle was performed. This decompressed the underlying soft tissues and brachial plexus. A six-hole dynamic compression plate (DCP) was used to maintain reduction of the clavicle (Fig. 5). The patient noted a moderate improvement in hand strength, sensation and shoulder abduction postoperatively. He was discharged 3 days postoperatively. The patient was reviewed 3 months postoperatively in the outpatient clinic. He had no clinical evidence of neurologic dysfunction, and his functional range of movement returned to normal. Follow up EMG 3 months postoperatively demonstrated complete resolution with no evidence of brachial plexus damage.

DISCUSSION

The majority of clavicular fractures involve the middle third. Clavicular nonunion or malunion is rare in itself, occurring in less than 1% of clavicular fractures.1,2,3 Brachial plexus palsy secondary to clavicular malunion or nonunion is extremely rare, and occurred in two out of 690 patients as reported by Rowe.1 These were late neurovascular complications arising in midshaft clavicular fractures, and were treated by excision of the offending callus, as described by ourselves.
Rowe, however, describes the use of a Kirschner pin to perform intramedullary fixation, whereas we used a six-hole DCP to maintain fixation. It is important to differentiate a secondary brachial plexus injury from a primary injury, as the latter have a less favorable prognosis. Primary injuries of the brachial plexus are often traction injuries following high-velocity accidents. These injuries tend to involve the lateral cord of the brachial plexus. Secondary injuries to the brachial plexus may be associated with manipulation of a fracture, an expanding false aneurysm of the subclavian artery or hypertrophic callus formation. The onset of symptoms of delayed brachial plexus injuries is variable and occurs insidiously.

Delayed pressure palsies of the brachial plexus often affect the medial cord, thereby giving rise to ulnar nerve symptoms. A triad of features describing the delayed brachial plexus palsy has been reported in the literature, and our patient demonstrated all of these features. The mechanism of the delayed neuropraxia has already been suggested in the literature. The typical deformity of a midclavicular fracture...
is downward with posterior displacement of the lateral fragment, due to the weight of the shoulder, bringing it into direct contact with the neurovascular bundle. The medial fragment is elevated due to the upward and backward pull of the sternocleidomastoid muscle. When malunion occurs in this position, the excess callus places pressure on the medial cord of the brachial plexus, as this is where it consistently crosses the first rib.8

Treatment options for decompression of the brachial plexus secondary to hypertrophic callus formation include osteotomy, internal fixation, and bone graft.9,10 Partial clavicular excision or excision of hypertrophic callus alone have been reported.1,9 Vascular surgeons should be aware of the development of neurologic signs in patients with a precocious history of clavicular fracture.

CONCLUSIONS

The patient presented in this report developed a rare complication of neurologic compression secondary to clavicular nonunion. It is vital that the neurologic status of a patient presenting with a clavicular fracture is assessed and documented. The patient should also be warned to return if they develop any neurologic symptoms. Investigations should include nerve conduction and magnetic resonance imaging to define the anatomy. There is no time scale on when to operate but, based on our knowledge of neurobiology, operative procedures to decompress the brachial plexus should be undertaken as early as possible following diagnostic workup. In our patient, diagnosis was confirmed 2 months following injury and surgery was undertaken immediately thereafter. Follow up shows excellent return of function and nerve conduction studies confirm the clinical findings.

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Amputation in Military Trauma Surgery

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Background: Major limb amputations are among the most debilitating wounds sustained by those who survive a combat injury. These very visible injuries also jar public sensibilities, and leave clinicians, themselves frontlines of the battle, haunted by “life or limb” decisions. Since the beginning of the current conflicts in Afghanistan and Iraq, concerns have been raised in the media and by medical personnel that amputation rates were higher than for previous conflicts. In a previous article, we examined current amputation rates and mechanisms of injury of major limb amputations in this conflict and in comparison with what little data are available on amputation rates for the Vietnam War. In this article, we examine the history of major limb amputation in military trauma and some of the surgical and weapons issues underlying that history.

The History of Surgical Amputation

Ancient, medieval, and renaissance surgeons all discuss major limb amputation. For the ancients, to some extent pain control but principally hemorrhage obviated the use of major limb amputations as a life-saving measure in open long-bone fractures, other than to excise already dead tissue. Hippocrates, writing in the fourth century before Christ, and Sushruta, writing 200 years to 400 years before Hippocrates, note that distal limb amputations, that is, below the wrist or ankle, could be tolerated through live tissue without excess blood loss. (Hippocrates was aware of tourniquets for hemorrhage control but also viewed them as one of the causes of distal limb gangrene.) Sushruta is credited with an understanding of ligature for hemorrhage control but does not appear to have incorporated this technique into his consideration of the feasibility of major limb amputation. Hellenic-Roman surgeons, including Celsus and others, describe ligature for hemorrhage control and major limb amputation as the only hope of salvaging the life of one with an open limb fracture. However, after these writers, vessel ligature for hemorrhage control largely disappears from extant European sources through the early medieval period.

Cautery was well known to the ancients and is discussed as an alternative to ligature by Celsus but takes over as “state of the art” in post-Roman Europe. The standard explanation for this is that the technique of ligature was “lost” in the civil, political, and intellectual chaos of the period, but silk suture was known and discussed by major writers, and so the truth may be more complex. Among other things, most medical advances during this period were nurtured by Arab scholars, and, although their medical insight was unparalleled for the time, the proscription of anatomic dissection limited similar advances in surgery. Another possibility for the loss of ligature as a familiar surgical technique relates to the weapons of the time. The wounds produced by early medieval weapons, although extremely lethal at close range (considerably...
more-so than modern personal arms\textsuperscript{13}) when nonfatal, would demand skill in the repair of lacerations and quick cauterization of the small-vessel disruptions of digital and distal limb amputation rather than innovative ways of dealing with major tissue disruption.

The arrival of gunpowder onto the battlefields of Europe in the early mid 14th century produced wounds of unprecedented complexity and forced surgeons of the time to solve the problems of major limb amputation. Ambroise Paré (1510–1590) is conventionally remembered for what he did not do, that is, pour hot oil into open wounds. What is less often appreciated is that the use of hot oil in battle wounds was an attempt to “detoxify” the horrifying tissue devitalization seen in gunshot wounds and thought to be the result of some kind of poison in gunpowder.\textsuperscript{14,15} Paré’s far greater contribution was the promulgation of techniques for major vessel ligation and major limb amputation for open fractures, actually in increasingly wide use through the 16th century.\textsuperscript{16} and for recognition of amputation as a prelude to limb rehabilitation.\textsuperscript{17} (Interestingly, both Paré and, later, the English surgeon Percival Potts survived open tibial fractures from horse-related incidents without undergoing the amputations advocated for them by surgical colleagues. Both recovered.\textsuperscript{15})

The history of amputation as a life-saving military surgical technique is entwined through the 16th to 18th centuries with the development of the tourniquet as an adjunct to hemostasis.\textsuperscript{10,18} However, with the increasing use of amputation for open fractures and for devastating battlefield injuries, the nature and consequences of “inflammation”—what we now recognize as septic contamination—came to dominate postsurgical care and to frame the debate on the optimal utilization of amputation. This debate is most clearly illustrated by the writings and practice of John Hunter, the great London surgeon of the end of the 18th century, and of Dominique Jean Larrey, Napoleon’s chief of surgery, at the beginning of the 19th. Hunter advocated judicious use of amputation after what we would call a stabilization period: casualties who survived the stabilization period and still needed amputation were in far better condition to survive the procedure as well as the injury.\textsuperscript{19} Larrey thought equally strongly (and, like Hunter, cited battlefield casualty statistics to prove) that prompt evacuation from the battlefield and amputation in the most forward surgical areas possible, on shipboard in the midst of battle if necessary, resulted in far better outcomes than waiting on transport to more conventional hospital settings.\textsuperscript{20} It is possible to see the contrasts between the—in general—French vs. English views on the timing and location of surgical care in the current debate on the utility of Forward Surgical Teams and Combat Support Hospitals. Larrey instituted the “flying ambulance” system and immediate transport to adjacent field surgical sites, a model that would dominate practice in the American Civil War, with later transport to conventional established hospitals, what we would now call rehabilitation centers. During the same period, in the Napoleonic Wars, the English tended to set up new hospitals in communities adjacent to the battlefields, which then continued to provide care to the wounded after the armies had moved on.\textsuperscript{21,22}

The surgical techniques for major limb amputation used in the American Civil War were essentially those of Larrey and his colleagues of 50 years before.\textsuperscript{21,24} However, during the century preceding the American Civil War, scientists like Linnaeus, Gray, and Virchow, to name only the best known, worked out novel, comprehensive, logical, objective and, to the extent possible in their times, what we would now call “evidence-based” nomenclatures to describe biologic, anatomic, and pathologic reality. It was this new tool, the words to describe what they were seeing clearly, reproducibly, and in stunning detail, that the medical officers swept up into the carnage of American Civil War battlefields and the terrible aftermaths of the surgical hospitals used to describe the first encounter of both soldiers and surgeons with high-velocity weaponry.

John Hunter, writing in the 1790s, recognized the importance of weapon muzzle velocity in the resulting wound tissue destruction.\textsuperscript{19} Larrey, in his Memoirs, describes an experiment in which a pistol was fired into a lump of wet clay, leaving a track in the clay that we (and the experimenters, with whose interpretation Larrey disagreed) recognize as ballistic cavitation.\textsuperscript{25} Through the American Civil War, the infantry increasingly used weapons with rifled barrels, which hugely increased range and accuracy. These were then loaded with Mine balls, massive 0.58 caliber soft lead projectiles with a muzzle velocity of 950 feet per second that tumbled through tissue and created wounds described by one Confederate surgeon as “. . . the shattering, splintering, and splitting of long bones, both remarkable and frightful”.\textsuperscript{21} The terms of the postwar compendium are perhaps cooler but no less devastating: “The shot fractures . . . furnished every variety of comminution, of extraordinary fissuring, of detachments of large fragments, of cases in which the bone was almost pulverized”.\textsuperscript{26} Statistics from both sides suggest that gunshot wounds to the extremities made up 65\textperthousand to 70\textperthousand of wounds and resulted in roughly 50,000 amputations, about half of which were of a lower extremity and half, upper extremity.\textsuperscript{21} Among the 87,793 upper extremity gunshot wounds recorded by the Office of the Surgeon General, 6.5\textperthousand died and 8,022 (9.1\textperthousand) underwent major limb amputation (that is, excluding hands or fingers), almost a quarter of whom died. Among the 86,413 with lower extremity gunshot wounds, the overall mortality was 13.8\textperthousand and 12,516 underwent major limb amputations (excluding toes or feet), 43.5\textperthousand of whom died.\textsuperscript{24} And, as horrifying as these statistics are, mortality for abdominal wounds approached 90\textperthousand.\textsuperscript{26} Limb injuries were about the only severe battle injury that was potentially survivable under the medical and surgical conditions of the time (and continue to be so in extreme modern situations like the Russian incursion into Afghanistan in the 1970s and 1980s\textsuperscript{27}).
From the American Civil War to the present, the development and need for utilization of amputation as a major surgical technique is characterized by a see-saw history of remarkable medical and surgical advances coupled with the equally astounding augmentation of the destructive power of battlefield weapons. World War I saw roughly 60 million men in arms and 7 million killed. Of roughly 19 million wounded, 8% died of their wounds, considerably better than the 20% died-of-wounds rate for the Crimean War and the 13%, noted above, for the American Civil War. Much of this is because of the scientific elucidation of sepsis and the development of antiseptic techniques before, and of blood transfusion during, World War I, but the numbers are still staggering. Somewhere between 300,000 and 500,000 casualties underwent amputation, the majority from artillery shells, shrapnel, and increasingly high velocity gunshot wounds that “...produced mutilation on a scale never seen before.” Comparison of casualty statistics between wars, even in the modern period, is difficult, usually because of variations in whether the roughly 50% of military casualties who are only slightly wounded (“Carded for Record Only” in the World Wars, Korea and Vietnam; “Returned To Duty within 72 hours” in current military usage) are included or excluded from denominators. As an example, the same official source that records an amputation rate in World War I of 2% of all American Army casualties, cites a rate of 5.3% among American Army personnel in World War II “... which probably reflects the more devastating properties of modern weaponry, or perhaps the higher immediate mortality of World War I”. Unfortunately, the doubling of the rate for the later conflict may just be because of the exclusion of the less injured from the World War II denominator.

Surgical Amputation in Modern Warfare

Published casualty statistics from World War II provide the first data on the pathophysiologic issues surrounding the use of and need for amputation in combat casualty care, that is, a distinction between traumatic amputation, amputation made inevitable by primary tissue loss, and surgical amputation, amputation required after failed surgical attempts at limb salvage. DeBakey and Simone, in their discussion of vascular injuries in that war, note:

... Accurate data are available from the Mediterranean and European Theaters of Operation. Among 3,177 major amputations from the theaters, 2,179 (68.6%) were the result of extensive trauma, 380 (11.9%) were the result of clostridial myositis or other serious infections, and 618 (19.5%) were the result of major arterial injuries. Figures which became available with the capture of a German amputation center showed that among 1,359 major amputations, 64.3% were the result of trauma, which is close to the American incidence. Only 6% were the result of vascular injuries, whereas 29.7% were the result of clostridial myositis. Corresponding figures on the Russian experience have been reported by Kramarov, who observed that trauma was the cause for amputation in 16% of the cases, vascular injury in 5% and gas gangrene and other infections in 79%.

This same article is more usually quoted as the source for the statistic that 50% of lower limb vascular injuries in World War II required amputation because attempts at vascular repair, particularly of the popliteal artery, had no better, and sometimes worse, outcomes than ligation. By the end of World War II, changes in surgical technique, particularly renewed appreciation for the need for adequate debridement of devitalized tissue and the appropriate adjunctive use of antibiotics, had reduced infection as a cause of surgical amputation to near nothing. The elimination of infection as a primary factor in the need for amputation and failure of limb salvage, shifted the focus of surgical thinking during the subsequent 30 years—and, with it, arguably, public perception—from acceptance of amputation, as a catastrophic but important and sometimes unavoidably necessary surgical tool, to limb salvage as the norm of success in combat casualty care. This shift was based on tremendous advances in vascular surgical technique and in speed of evacuation from the battlefield to expert surgical centers.

The Korean War saw deployment of medical units with specific combat casualty care agendas. Among these was vascular repair of popliteal artery injury. By the end of the war, these and other researchers were reporting 75% to 80% reductions in amputation rates after vascular injury, particularly major amputations of the lower extremities. All of these authors discuss the role of rapid evacuation—thus decreasing tissue ischemia time—by helicopter to expert surgical centers in decreasing the need for surgical amputation.

Reports from and immediately after the heaviest periods of fighting in the American engagement in Vietnam (mid 1966 to mid 1968) emphasize the role of rapid evacuation to advanced care in improving surgical outcomes. However, as Dr. Whalen and his colleagues also write, “Evaluated on amputation rates alone, results in two of the Vietnam series are slightly more favorable than those in the Korean War, the rate being 9%. Not included are less favorable results at Clark Air Base Hospital in the Philippines, where 57 amputations were necessary in 171 arterial injuries in 167 patients—a 33% amputation rate”. These authors, like Spencer and Crewe, writing about Marine casualties in the Korean War, are aware of the arrival at advanced surgical centers of casualties with degrees of injury that would have never survived the battlefield in previous conflicts. This presents caregivers with unprecedented clinical challenges and the conundrum of increased died-of-wounds and surgical amputation rates at a time in the evolution of combat casualty care that would have predicted the decrease of these rates.

An unforeseen consequence of the outcome of the Vietnam War has been the lack of a summary of battle casualties for that conflict of the scale, detail, and clinical and public health insight of the Medical and Surgical History of the War.
of the Rebellion, British casualty reports of World War I, the work of DeBakey and his collaborators for World War II, and of Frank Reister for Korea. The only work that approaches these is analyses by Ronald Bellamy and various collaborators of the data on roughly 8,000 US Army and Marine Corps casualties from 1967 to 1969, collected by the Wound Data and Munitions Effectiveness Team of the Army Materiel Command.13,41,42 These data suggest that major amputations represented about 2.6% of serious injuries among ground personnel in Vietnam, a figure uncomfortably close to the proportion for Korea. In World War II, although the true proportion, like the proportion for World War II, may be more than twice that.13

The Wound Data and Munitions Effectiveness Team data also suggest that the proportion of traumatic amputations, that is, amputations made inevitable by the degree of tissue destruction present when the casualty reached surgical care, was about 75%, higher than World War II, at least equivalent to that of the Korean War,44 and possibly as high as 90% (Bellamy, personal communication). The degree of tissue destruction will, obviously, be directly related to the forces, ballistic, and otherwise, associated with the dominant weapons in use in any given conflict situation. “...The tactical situation alters the mix of wounding weapons”.13 In general, in Korea and in Vietnam, rapidly shifting ground force tactical situations were dominated by small arms fire and a greater proportion of gunshot wounds, in the range of 25% (Vietnam) to 50% (Korea). More static situations, in Korea from October 1951, through the end of the war, and in Vietnam after 1970, show increased proportions of wounding by fragments from explosive devices.13,43 The latter mechanism, also known as secondary blast injury, and the blunt and crush injuries subsumed in the term tertiary blast injury,45 dominate modern urban and terrorist-driven conflicts16–48 and can be anticipated to be associated with increasingly profound tissue destruction resulting in limb amputation.

**SUMMARY AND CONCLUSION**

The potential for major limb amputation as a surgical technique has been recognized for at least 3,000 years, but its effective utilization required first the ability to control hemorrhage without further endangering the casualty or the limb and then the ability to avoid sepsis. During the last 60 years, among battle casualties, the proportion of major amputations forced by infection and by vascular injury has decreased from 30% to 40% of all major limb amputations to about 10%. Unfortunately, modern warfare and urban terrorism tend to be dominated by explosive devices of increasing power and destructiveness, suggesting that the incidence and prevalence of injuries that are survived but result in major limb amputation is unlikely to decrease.

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edation and analgesia are important components of the management of intubated, mechanically ventilated patients. Patient comfort is a central goal, but is especially challenging after severe injury. In addition, pain and anxiety may be associated with intubation, invasive bedside procedures performed for monitoring or management, and the intensive care environment. In the trauma patient, these issues are complicated by pain associated with operative incisions, fractures, and soft tissue injury. The prior use of excessive alcohol or illicit drugs in the trauma population adds additional complexity to management. Head injury management often requires a very meticulous balancing of medication to enable patient comfort without clouding neurologic assessment. Patient comfort may be further complicated by delirium. This is a syndrome of fluctuating consciousness, with reduced attention and impaired cognitive function. Its multifactorial origins may include the metabolic and physiologic derangements of critical illness as well as acute brain injury. Delirium is associated with prolongation of hospital stay and increased mortality.

Overuse of medication for sedation and analgesia may have adverse effects, including hemodynamic instability, prolongation of mechanical ventilation, other complications associated with sustained bed rest and immobility, and may facilitate the development of later posttraumatic stress disorder. Thus, appropriate use of drugs for the management of sedation and analgesia has implications that extend beyond patient comfort.

The recognition of pain, anxiety, and delirium as independent contributors to patient distress enables a more appropriately focused management strategy that targets these symptoms individually with appropriate medication. Symptoms should be rapidly controlled, to avoid a cycle of inadequate dosing and escalating need. Pharmacotherapeutic intervention should be directed to minimize adverse effects while accomplishing this goal. It is also important to recognize that sedation and analgesia are closely related; that is, anxiety reduces the pain threshold, and pain control may reduce anxiety. This concept justifies the use of multiple
drugs for symptom management. Narcotics are primarily used for pain management in the intensive care unit (ICU), whereas benzodiazepenes and propofol are used for anxiety control, and antipsychotic medications are used for other agitation and delirium. A regular and systematic assessment of the intubated patient for signs of distress, using a consistent evaluation tool, should minimize the amount of sedation necessary and allow the patient to recover from the sedated state more promptly.

Inflammation and the Host Response to Injury is a large-scale collaborative research project funded in September 2001 by the National Institute of General Medical Sciences, National Institutes of Health. The purpose of this study is fourfold: (1) to develop a large database with baseline patient characteristics and defined outcomes pertaining to the host immunoinflammatory response after injury; (2) to identify gene-expression patterns in circulating leukocytes and tissue samples to classify the response to injury; (3) to determine the relationships among genes and gene clusters, and how they are expressed over time after injury; and (4) to determine the relevance of murine models of injury to human disease through comparison of the immunoinflammatory response. The clinical components of this project are managed through the Patient Oriented Research Core (PORC), whose members comprise the named authors of this article.

Standard operating procedures for clinical care (SOP) were developed by the participating investigators to minimize clinical variation and establish uniform practices to enhance the estimations of the host inflammatory response to injury. The SOPs were developed because of an absence of any such protocols in print to use in this patient population. The PORC meets quarterly, and communicates between meetings electronically. After review of the medical literature, the principle author presents an analysis of the available data to the PORC, this SOP was created after modification.

For the present inquiry, standard search engines (PubMed and MedLine) for comprehensive data acquisition were queried for references to sedation and analgesia in mechanical ventilation, which were used to supplement more immediately accessible literature in this matter. After internal review by the PORC investigators, this SOP was created based on the best available external evidence.

The Inflammation and the Host Response to Injury Investigators will use this SOP, and others prepared by the PORC, to eliminate background variations in clinical interventions. The product also sets a standard for trials directly focused on the SOP criteria. The authors recognize that these are not static documents and will modify SOP as new evidence-based data directs or new approaches to care have demonstrated benefit.

The primary purpose of this guideline is to provide physician and nursing staffs with a strategy for the pharmacologic management of pain, anxiety, and delirium that may affect intubated patients.

The Protocol has as its principal goals the following:

- To ensure that sedation level is evaluated using an objective-scoring tool;
- To provide guidelines for medication use that will lead to prompt and adequate control of pain, agitation, and delirium, without causing oversedation; and
- To provide an algorithm for medication management that enables more timely responsiveness to changes in patients’ medication requirements.

**Protocol Rationale**

**Objective Assessment of Sedation Level**

Ideally patients requiring mechanical ventilation should be pain-free and calm. Pain, agitation, and delirium may be multifactorial, but the recognition of these distinct conditions is central to effective pharmacologic control of symptoms. The management of sedation requires that a clearly defined goal of therapy be established. Precise communication between providers is necessary to maintain consistency in symptom management. The balance of adequate versus inadequate medication depends on an objective serial evaluation of a patient’s response to therapy in the context of the stated goal. Recent clinical practice guidelines for sedation and analgesia recommend the use of a sedation scale for this purpose. Although several scales have been developed, the Richmond Agitation-Sedation Scale (RASS) is used in these guidelines. This simple system assigns a score between 4 (combative) and −5 (unresponsive). A score of zero indicates that the patient is alert and calm. The RASS is notable for ease of use, excellent inter-rater reliability, and greater discriminatory capacity than other commonly used scales.

**Management of Sedation and Analgesia by Algorithm**

The status of critically ill patients changes frequently and so, too, do their requirements for sedation and analgesia. The ability to respond promptly to dynamic changes in medication requirement must be a central component of a program to manage these effectively. Sedation management by algorithm has been studied and is clearly advantageous. In a prospective, randomized, controlled study, sedation management of 321 mechanically ventilated patients according to a nurse-implemented protocol was associated with significantly shorter duration of ventilation, decreased rate of tracheostomy, and improved ICU and hospital length of stay. This study was notable for using a protocol that used physician input to establish a target goal of sedation, and then empowered the nursing staff to adjust analgesia and sedation medication in a more timely fashion to achieve this endpoint.

**Intermittent Versus Continuous Sedation**

Controversy exists over whether continuous or intermittent sedation is best for critically ill patients. In one prospec-
tive observational study, the use of continuous intravenous sedation was associated with significantly longer duration of mechanical ventilation, ICU stay, and hospital stay. The same authors affirmed the relationship of continuous sedation and duration of ventilation in a subsequent randomized, controlled trial, although this was not the primary purpose of the trial. This evidence must be balanced against concerns that intermittent dosing may undermedicate patients in the short term and lead to greater cumulative dosing in the long term. A recent, open-label, randomized trial compared length of mechanical ventilation in patients receiving continuous propofol versus intermittent lorazepam, incorporating a daily sedation interruption. Median ventilator days were significantly reduced in patients receiving continuous propofol, suggesting that the choice of sedating drug may be as important as the mode of delivery. Similar consensus pain management guidelines have not entirely resolved this issue, with recommendations that analgesia should be administered either continuously or on a scheduled intermittent basis, with supplemental bolus doses as needed. Acknowledging the lack of definitive data to direct practice clearly, but with focus on the principle of prompt symptom control, we propose the initial approach to sedation and analgesia management should include an intermittent dose strategy. Continuous infusions should be reserved for those patients in whom the target sedation level cannot be achieved within a timely manner.

**Interruption of Sedation and Analgesia**

Because “adequate” sedation is often equated with unresponsiveness, the possibility that sedation itself contributes to prolonged mechanical ventilation and its attendant complications must be considered. A randomized, controlled trial of daily interruption of continuous sedation has been performed to assess the affect on length of mechanical ventilation. Continuous sedative and analgesic infusions were stopped until the patient was awake or uncomfortable and in need of resumed medication. In the cohort in which sedation was interrupted on a daily basis, the duration of mechanical ventilation was significantly reduced (median duration 2.4 days less than standard care), as were the length of ICU stay and total drug used. The rate of unplanned extubation was not increased. Interrupting medication may be inappropriate for patients who require sustained deep sedation for medical management (e.g., adult respiratory distress syndrome [ARDS], shock, or open chest or abdomen). For other patients, however, the guideline presented here incorporates the concept of the daily sedation interruption by setting the target sedation level to a RASS of 0 to -2, which approximates the criteria for “awake” described in the trial above.

**Protocol Summary**

A. The responsible physician should make an initial determination of the goal level of sedation for each patient, defined by the RASS score. This goal should be reassessed as often as clinically appropriate, but no less than daily.

B. The patient should be assessed regularly for signs or symptoms of pain, anxiety, or delirium. The patient’s RASS score should be assessed every 15 minutes until symptoms are controlled within the target range, and then every 4 hours thereafter.

C. Fentanyl is the drug of choice for pain, chosen for its relative lack of histamine release and greater hemodynamic stability. (Morphine is also widely used for analgesia. Its use has been associated with histamine-related hemodynamic change and impaired clearance in patients with renal failure. Nevertheless, provider familiarity and experience may, in some centers, be grounds for its preferential use.) Propofol may be used for anxiety if the expected duration of sedation is less than 48 hours and if frequent neurologic assessments are necessary. Alternatively, or if the duration of sedation will exceed 48 hours, lorazepam should be used to control anxiety. Lorazepam offers significant cost savings over propofol and avoids potential complications of hyperlipidemia and, rarely, cardiac decompensation. Because of the speed with which propofol is cleared when discontinued, and the potential for faster weaning and extubation, it may be cost effective to use propofol when the anticipated duration of ventilation is short. Haloperidol is used when pharmacologic control of agitation from delirium is required. This guideline does not attempt to prevent, minimize, or diagnose delirium but rather to control the agitation that established delirium may produce. Part of delirium management should be to identify and control the inciting cause, and in some cases, sedation and analgesia may contribute to this problem. Delirium severity scales have been described to help in this assessment. A recent retrospective, observational analysis in patients mechanically ventilated for more than 48 hours found a significant reduction in hospital mortality in those patients who received haloperidol within 2 days of initiation of mechanical ventilation.

The explanation of this finding remains speculative, and these results have not been reassessed in a randomized, prospective, placebo-controlled trial.

D. Initial dosing should be intermittent. If adequate symptom control cannot be achieved with the described regimen of bolus dosing, a continuous infusion may be used for pain and anxiety control, titrated to the lowest dose necessary to achieve the target RASS score.

**Guideline Details**

1. A target level of sedation will be established based on the patient’s condition and expected duration of mechanical ventilation (Fig. 1). Unless medically contraindicated, the optimal level is that at which the patient is alert, not agitated, and able to maintain...
brief contact and follow simple instructions (RASS 0 to −2; Fig. 2).

2. Assess pain and sedation level every 15 minutes until the patient reaches the desired level of sedation. Thereafter, assess every 4 hours unless otherwise indicated.

3. Analgesia for pain: bolus fentanyl, 25 μg to 100 μg intravenously every 5 minutes to achieve the specified goal. If the goal is met, continue bolus dosing every 30 minutes to 60 minutes. If the sedation goal is not met after 3 hours, begin an infusion at 50 μg/hr. If the goal is not met in 1 hour, give a bolus with the amount of current infusion rate and increase infusion by 25 μg/hr.

4. Sedation for anxiety:
   a. Anticipated duration of mechanical ventilation exceeds 48 hours: Lorazepam: bolus 1 mg to 2 mg intravenously every 15 minutes to achieve the specified goal. If the goal is met, continue bolus doses every 2 hours to 4 hours as needed. If the goal is not met within 3 hours, begin scheduled doses of 4 mg intravenously every 6 hours and continue bolus doses. If the goal is not met in 24 hours, begin an infusion at 2 mg/hr and continue bolus doses as needed. If the goal is not met after 1 hour, increase the infusion rate by 1 mg/hr and continue bolus dosing as needed. Consider the possible contribution of pain and delirium to the appearance of agitation.
   b. Anticipated duration of mechanical ventilation less than 48 hours, or need for frequent assessment of neurologic status: Propofol bolus 0.5 mg/kg intravenously, then infuse 20 μg/kg/min (consider use if expected duration of mechanical ventilation will be less than 48 hours, or for patients [e.g., neurosurgical or head-injured] in whom frequent neurologic checks are necessary). If the goal is not met in 15 minutes, bolus with 0.5 mg/kg during a period of 2 minutes and increase

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**Fig. 1.** Sedation or analgesia protocol for mechanical ventilation.
the infusion by 10 μg/kg/min every 15 minutes to a maximum of 100 μg/kg/min. Consider the possible contribution of pain and delirium to the appearance of agitation.

5. Antipsychotic for delirium: Bolus haloperidol, 2 mg to 10 mg intravenously every 1 hour as needed. If the goal is not met in 6 hours, begin scheduled doses of 5 mg intravenously every 6 hours and continue bolus doses.

6. Unless medically contraindicated in patients sedated to a RASS score of −3 to −5, sedation should be interrupted daily until the patient is awake (establishes brief eye contact or follows simple instructions) or until the patient becomes agitated or uncomfortable.

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Displaced Comminuted Midshaft Clavicle Fractures: Use of Mennen Plate Fixation System

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Background: Surgical treatment of displaced comminuted midclavicular fractures includes open reduction and stabilization with wires, pins, or screwed plates. However, it is often difficult stabilizing small fragments, and there are several complications. The aim of this study was to assess an alternative technique using a Mennen plate.

Methods: From 1999 to 2004, we treated a cohort of 43 patients with a displaced three- or four-part midclavicular fracture. All patients were followed up at an average of 1 year after the injury; they had a functional evaluation and were assessed radiographically.

Results: The fractures of 41 patients had healed, with two cases of nonunion and no case of infection or osteomyelitis. All of them presented normal function of the shoulder and shoulder girdle symmetry.

Conclusions: A Mennen plate is a good device for the treatment of displaced midshaft clavicle fractures. The technique is simple and the operation time is shortened; the bone architecture is protected by any damage caused by drill holes; and the endosteal blood supply is preserved as a result of the paraskeletal position of the plate.

Key Words: Clavicular fractures, Fixation systems, Fixation failure, Mennell plate.

Clavicle fractures represent 2.6% of all fractures and 44% of those in the shoulder girdle. In most cases (81%), they involve the middle third of the bone and are displaced to a varying extent (48%).

Treatment options for acute midshaft clavicle fractures include nonoperative treatment, open reduction, and internal fixation with plates, wires, nails, or pins. However, the optimal choice remains controversial, especially for displaced and comminuted fractures; few biomechanical data assist surgical decision and surgical choice.

Most surgeons prefer nonoperative treatment; however, recent studies indicate that long-term results are not as good as previously shown because of frequent pain at rest and during activity, cosmetic defects, reduction in strength, paraesthesia, and nonunion (rate of 5.9% and 15.1% for displaced fractures). Factors associated with long-term sequelae after nonoperative treatment are indicated in fracture displacement, fracture comminution, number of fracture fragments, and old age.

Screwed plates are now considered the gold standard for the treatment of displaced comminuted midshaft clavicle fractures, with a relative risk reduction of 57% for nonunion compared with nonoperative treatment (86% for displaced fractures). However, they have some negative points: it is often difficult to stabilize small fragments, especially when the fracture lines lie on different planes; X-ray examinations are necessary during the operation; and the use of a motorized system can damage the underlying neural and vascular structures and the bony architecture. Complications include deep infection, plate breakage, nonunion, and refracture after plate removal.

The aim of this study is to assess an alternative technique using the Mennen plate, a paraskeletal clamp-on plate, which has been developed to keep the operatively reduced position of a fractured long bone during the healing phase while having a minimal effect on the healing process.

The plate consists of a central ridge with a paired finger-like projection on each side (Figs. 1 and 2); each projection is just more then a semicircle, and they are wedge-shaped and bend at right-angles toward the center.

Patients and Methods
From 1999 to 2004, we treated a cohort of 43 patients (39 men and 4 women) with three- or four-part midshaft clavicle fractures (group I, subgroup c according to the Allman classification). Road traffic crash was the most frequent cause. Two patients had sports injury. Radiographic evaluation of both shoulders was performed for all of them before surgery, and they were assessed radiographically and clinically after operation. The mean follow-up was 12 months after the injury. At review, we obtained a functional evaluation using the Constant score, a radiographic control, and we noted local deformity.

Surgical Technique
The patient is given general anesthesia, and he or she is placed in a beach-chair position. A transverse incision is...
made along the superior surface of the clavicle. The skin and subcutaneous tissue is raised, and the underlying myofascia is identified and it is raised as contiguous flaps. The first step is to identify the fracture site and to evaluate the gap between the lateral and the medial major fragments, preserving with great care the periosteum while cleaning the fracture ends. In some cases, especially in very comminuted ones, we use an intramedullary Kirschner wire to restore the length of the clavicle; next, the fracture fragments are reduced in an anatomic position and held together using, if necessary, a cerclage of nonabsorbable sutures. Then a Mennen plate is applied on the superior face of the clavicle. First, we open the lateral projections before the plate is applied on the bone (Fig. 3). Second, we stabilize the central ridge of the plate perfectly in contact with the bone (Fig. 4) using two or three Kockers, and then, we squeeze the teeth of the plate around or into the bone with a crimping tool (Fig 5), so that all the fragments are kept together. Great care should be taken to avoid the underlying neural and vascular structures while clamping the projections. The arm is placed in a conventional sling postoperatively for 2 weeks to avoid pain and allow healing of soft tissues; the patient begins a specific rehabilitation program, according to the Lyonnaise protocol, immediately postoperatively, and the clinical and functional recovery is obtained in 3 months (Figs. 6 and 7). The plate can be removed after 8 months (Fig. 8).

RESULTS

Most patients had a very good result; the mean Constant score was 96, range from 92 to 100. The mean active anterior elevation was 160 degrees; all of them reached T12 in intrarotation; the mean extrarotation was 30 degrees. No patient had osteomyelitis or infections of soft tissues; 10 patients had hypoesthesia around the skin scar. Two patients had non-union because of a technical mistake, and in one case, we found that one pair of projections had been squeezed into the fracture line, and in the other patient, we found a screwed Kirschner wire (DMO) in the fracture line, under the plate.
Both patients underwent surgical operation, and they were successfully treated with a screwed plate. Two patients had capsulitis treated successfully, in one case with a rehabilitation program and in the other with arthroscopic release. At the last follow-up, all patients had shoulder girdle symmetry, assessed clinically.

During our learning curve, in 10 cases, we used a temporary transfiction with a percutaneous Kirschner wire, which was removed after 30 days. In 11 patients, we removed the Mennen plate after fracture healing because of a specific request of the patient for cosmetic reasons.

**DISCUSSION**

Midclavicular fractures are the most frequent in the shoulder girdle. Their management is controversial. Several studies show that undisplaced midclavicular fractures have favorable outcome with nonoperatively treatment,\textsuperscript{12–15} whereas other studies have reported an increased risk of persistent shoulder disability after conservative treatment of displaced midclavicular fractures in adults.\textsuperscript{12,16–19} So, the authors have recommended surgical treatment for displaced and comminuted midclavicular fracture. Surgical choices include percutaneous intramedullary K wire, Knowles pins, and screwed plates, but each device is not able to stabilize small fragments and has several complications: pins and wires may migrate;\textsuperscript{20–22} and according to Bostman,\textsuperscript{6} screwed plates have a high rate of infections, breakage, nonunions, and refracturing after plate removal: 24 of 103 patients with acute displaced midclavicular fractures (23%) had one of these complications.

The present study shows that the Mennen plate is a good device for surgical treatment of displaced comminuted clavicle fractures. The technique is simple. X-ray examination is not necessary during the operation. The risk of subclavian structural damage is reduced. Minimal soft tissue dissection, especially periosteal, is required for application. Sometimes, patients ask for a second removal operation because of cosmetic reasons, but it is not necessary. There is no sign of bone reabsorption around the plate at radiographical control.

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**Fig. 5.** Final result.

**Fig. 6.** Fracture preoperatively.

**Fig. 7.** Fracture postoperatively.

**Fig. 8.** Fracture after plate removal.
REFERENCES

Trauma Intubations: Can a Protocol-Driven Approach be Successful?

Zoe C. Casey, MD, Alan J. Smally, MD, Robert J. Grant, MD, and Jacqueline McQuay, RN, MS

Objective: To determine the success rate of a trauma airway protocol.

Methods: This was a prospective cohort study of trauma patients requiring intubation conducted for 24 months. The study facility is a Level I trauma center serving an urban population. The protocol suggests that the first two attempts at intubation be by the third-year emergency medicine resident, a hospital-wide stat overhead page for anesthesia occurs, which results in anesthesia (occasionally a resident only, but usually an attending) presence in the trauma room in 5 to 10 minutes. After each intubation, the emergency medicine resident or the attending physician completed a data collection form indicating the number of intubation attempts and result of each one, who performed each attempt, complications related to each attempt, and airway adjuncts used.

Results: Two hundred seventy-four patients were intubated during the study period by either emergency medicine physician or anesthesiologist with a success rate of 91.6% after the third attempt. The complication and cricothyrotomy rates were 9.8% and 2.6%, respectively.

Conclusion: Our trauma airway protocol allows for the safe and effective management of the trauma airway.

Key Words: Emergency medicine, Trauma patient, Airway management, Airway protocol.


The ability to expeditiously and safely secure the airway is critical to the care of trauma victims in the emergency department (ED). Performance of intubation quickly and without complications allows the trauma team to proceed with the resuscitation, evaluation, and treatment phases of care. For a number of reasons, achieving control of the airway can be problematic.

The patient may be difficult to ventilate with a bag-valve-mask or to intubate. Ventilation problems particular to trauma patients include chest wall, pulmonary, intra-abdominal, and high cervical spine injuries. Before intubation, the inability to adequately preoxygenate the patient reduces the time until hypoxia occurs, therefore limiting the time for each intubation attempt. Intubation difficulty can arise for a number of reasons. These include neck immobility caused by cervical spine immobilization, facial injuries, distortion of the hypopharyngeal anatomy by swelling, hematoma, or burns, and the presence of blood or emesis in the airway.

Depending on the trauma center, airway management may be the responsibility of either or both emergency medicine (EM) and anesthesia physicians.1 Historically, only anesthesiologists were credentialed to use certain sedative and paralytic agents to facilitate intubation. More recently, rapid sequence induction has been used by emergency physicians (EPs) who have become responsible for the airway management of trauma patients at some trauma facilities. There has been literature published reflecting similar success rates when compared with anesthesia.2–4 The belief in the appropriateness of airway management by EP is not universally held.5

This study was conducted to determine the success rate of the trauma airway protocol when compared with other similar published data.

Patients and Methods

Hartford Hospital is a Level I trauma center located in Central Connecticut with an annual census of 80,000 that also serves as the trauma center for the adjacent Connecticut Children’s Medical Center, whose annual census is more than 40,000. The hospitals are affiliated with the University of Connecticut Integrated Emergency Medicine Residency Program (EM 1–3) and the Hartford Hospital Trauma Surgery Fellowship. They serve as the primary training site for both programs. Before 2001, there was no formal delineation of responsibility relating to intubation of the trauma patient. In May 2001, a protocol was devised by the Division of Emergency Medicine with input from the Division of Traumatology and Department of Anesthesia and accepted at a multidisciplinary forum that met monthly to discuss issues relevant to the management of trauma patients. It was agreed that the protocol would be followed for all trauma intubations and that data on each intubation would be collected prospectively, reviewed, and discussed at the forum to provide Continuous Quality Improvement.
for the trauma patient requiring intubation (Fig. 1, Trauma Intubation Algorithm).

Under the established guidelines, trauma patients are primarily intubated by senior emergency medicine residents (EMRs) or emergency medicine attending physicians (EMAs). It stipulates that the first two attempts at intubation be performed by a senior EMR with supervision by an EMA. If the patient has not been intubated after the second attempt by the EMR, anesthesia is paged and the EMA takes over subsequent attempts at intubation until anesthesia arrives. The protocol has other stipulations as well (Fig. 1), but discretion is always left to the EMA or attending trauma surgeon to provide optimal care for the patient. The EMRs who perform the first two attempts do not intubate trauma patients until they are PGY3 (postgraduate year 3) level. By the third year they have completed a 4-week anesthesia rotation, performed intubations of increasing complexity in the ED, and participated in sessions in the Simulation Center and in the animal laboratory. By the completion of their residency, our residents have recorded an average of 86 intubations in their procedure log. This experience is expected to give them adequate experience and familiarity with the difficult airway.

This is a prospective cohort study conducted during 24 months from July 2002 to June 2004, with data originally collected for quality assurance purposes. As described before, the study occurred in an urban, Level I trauma center. All trauma patients requiring intubation that presented to the ED during the study period were included. All patients intubated before arrival were excluded from enrollment. The institutional review board of Hartford Hospital approved the study.

At the completion of an intubation, data sheets, which were located adjacent to the trauma rooms, were completed by the EMR or EMA. Required documentation included who performed the attempt, the route used, difficult airway adjuncts used, the result of each attempt, and any associated complications (Fig. 2, Airway Intubation Continuous Quality Improvement [CQI] Document). An attempt was considered to be the performance of laryngoscopy whether or not tube placement was attempted. No data on which medications were used for the intubation was collected.

Most data forms were filled out immediately after the intubation. In the instances that the forms were not completed in real time, 100% capture of intubated trauma patients during the study period was achieved because of redundant record keeping. A daily review of all admitted or deceased trauma patients listed those who were intubated in the ED.

In the event a CQI sheet had not been compiled, the chart was reviewed by one of the authors (J.M. or A.J.S.), and a data sheet was completed based on this review and conversation with the EMR, EMA, or attending trauma surgeon involved. This assured 100% capture. Statistical analysis was performed using nQuery 5.0 software (Elashoff, Los Angeles, CA).

**RESULTS**

During the study period, 278 trauma patients were intubated in the ED. Four patients were intubated by staff other than EM or anesthesia and were excluded from the analysis. Two patients were inadvertently extubated after successful intubation, and only the attempts before and including the first successful intubation were included in the data collected. Two hundred seventy-four patients were enrolled in the study, and there were 478 attempts at intubation. Of the enrolled patients (n = 209), 75.2% were male, and there were 16 (5.8%) pediatric patients. Blunt trauma was the mechanism of injury for 89.3% of patients. The mean Injury Severity Score was 17.6. In Table 1, the patients are grouped by Injury Severity Score.

Combined, EMRs and EMAs performed 432 intubations (90.4%) with 40 intubations (8.4%) performed by anesthesia staff. As an individual group, EMRs performed both the greatest number of intubation attempts (n = 344, 72%) and successful intubations; 76.5% of the patients were success-
### Airway Intubation CQI Document

#### First Attempt
- **By whom?**
  - EM Resident
  - EM Attending
  - Flight Nurse
  - Anesthesia
  - Trauma Resident
  - Trauma Attending
- **Time:**
- **AM/PM:**
- **Method:**
  - Orotracheal
  - Nasotracheal
  - Combitube
  - LMA
  - TTJV
  - Cricothyrotomy
  - Other: 
- **Results:**
  - Endotracheal
  - Esophageal
  - Tube not passed
  - Confirmation by: 
- **Complications of Procedure:**
  - Emesis/aspiration
  - Bleeding
  - Saturation fall > 10%
  - Saturation > 30%
  - Arrest
  - Arrhythmia
  - Hypotension (Systolic pressure <90 or BP fall 20mm Hg)
  - Bradycardia (P < 60 or fall of 20 in pulse)

#### Second Attempt
- **By whom?**
  - EM Resident
  - EM Attending
  - Flight Nurse
  - Anesthesia
  - Trauma Resident
  - Trauma Attending
- **Time:**
- **AM/PM:**
- **Method:**
  - Orotracheal
  - Nasotracheal
  - Combitube
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  - Arrest
  - Arrhythmia
  - Hypotension (Systolic pressure <90 or BP fall 20mm Hg)
  - Bradycardia (P < 60 or fall of 20 in pulse)

#### Third Attempt
- **By whom?**
  - EM Resident
  - EM Attending
  - Flight Nurse
  - Anesthesia
  - Trauma Resident
  - Trauma Attending
- **Time:**
- **AM/PM:**
- **Method:**
  - Orotracheal
  - Nasotracheal
  - Combitube
  - LMA
  - TTJV
  - Cricothyrotomy
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  - Arrhythmia
  - Hypotension (Systolic pressure <90 or BP fall 20mm Hg)
  - Bradycardia (P < 60 or fall of 20 in pulse)

#### Fourth Attempt
- **By whom?**
  - EM Resident
  - EM Attending
  - Flight Nurse
  - Anesthesia
  - Trauma Resident
  - Trauma Attending
- **Time:**
- **AM/PM:**
- **Method:**
  - Orotracheal
  - Nasotracheal
  - Combitube
  - LMA
  - TTJV
  - Cricothyrotomy
  - Other: 
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  - Saturation fall > 10%
  - Saturation > 30%
  - Arrest
  - Arrhythmia
  - Hypotension (Systolic pressure <90 or BP fall 20mm Hg)
  - Bradycardia (P < 60 or fall of 20 in pulse)

#### Comments:

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**Person filling out form:**
fully intubated by an EMR. Of the study patients, 81% and 91.6% of patients had been successfully intubated after two and three attempts, respectively. For the majority of patients, rapid sequence intubation (RSI) was performed to facilitate intubation. The protocol does not stipulate the use of particular drugs for RSI. The exact number of patients who underwent RSI and the medications used are not available because this data were not collected. The airway adjuncts used most commonly were the gum elastic bougie followed by the Combitube. Of the 22 patients who had not been intubated after three attempts, a definitive airway was successfully placed by EM staff in seven (31.8%) of these patients.

Forty-seven of 478 intubation attempts had at least one complication. The overall complication rate was 9.8% (95% confidence interval, 7.1%–12.5%). The complication reported most frequently was fall in oxygen saturation greater than 10%. Four of the intubation attempts were associated with two complications. Further detail of complication rate by group is available in Table 2.

A total of seven patients required cricothyrotomy, two were performed after just one attempt at intubation at the discretion of the attending trauma surgeon and two were performed after 5 and 11 attempts, respectively, at intubation. In addition, cricothyrotomies were performed on three other patients after successful ventilation via Combitube. Trauma surgery performed all of the cricothyrotomies. The cricothyrotomy rate (all performed) was 2.6%.

Overall, 19 laryngoscopic attempts violated the protocol. There were 15 attempts at intubation made by EMRs after having performed laryngoscopy twice. Additionally, there were four instances in which intubation was performed by staff other than EM or anesthesia; for example flight nurses.

Most data forms were completed immediately after the intubation; an average of one form per month was forgotten. The relevant information was then obtained days later.

<table>
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<tr>
<th>Table 1 Injury Severity Scores</th>
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<td>Injury Severity Score</td>
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<td>Patient (%)</td>
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<table>
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<th>Table 2 Type of Complications by Position</th>
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Percentages and totals are based on respondents.
DISCUSSION

Our guidelines for intubation of the trauma patient produced a successful intubation in 81% of patients after the second attempt and 91.6% of patients after the third attempt. During the study period and since that time, we know of no cases of anoxic encephalopathy that occurred related to intubation of a trauma patient. In comparison with the three comparable published studies, our success rate after the second attempt was lower but was comparable after our third attempt. In 2001, Omert et al. reported a 73.7% success rate at the first attempt with 97% of patients intubated by the completion of the third attempt. The following year, Bushra et al. published a success rate of 95.2% after the second attempt at intubation. Then in 2004, Levitan et al. published data collected during 3 years that documented success rates of 87% on the first attempt, and 97% of patients intubated by the completion of the second attempt. Our success rate is slightly lower than previously published studies with quite acceptable complication rates. This may be partially explained by what we think is 100% data collection and the evaluation of all cases of multiple attempts by query of several sources. This may also be explained by our rigorous definition that laryngoscopy insertion is an attempt at intubation.

A literature search for cricothyrotomy rates in trauma patients intubated by EP revealed only a single study by Levitan et al., with a calculated cricothyrotomy rate of 0.3%. Omert et al. published a failed intubation rate of 1.9% by EP, but it was not stated whether the airway was successfully placed by anesthesia or if cricothyrotomy was necessary. More than a decade ago, Ligier and Buchman published data of trauma patients; however, all patients were intubated by anesthesia with an associated cricothyrotomy rate of 4%. Similarly, in 1994, in a study evaluating the safety of neuromuscular blockade in the intubation of trauma patients, the cricothyrotomy rate was 2.6% with only 8.3% of patients intubated by EP. Our cricothyrotomy rate of 2.6% is similar to these reports.

Our data were obtained in a broad sample of trauma patients presenting to a busy trauma center and represents all cases. We did not report the success rate of individual groups because the sequential order of intubation results in a more difficult case at each attempt. EMAs and anesthesiologists generally were given the opportunity of intubating the most difficult cases, usually after two attempts by EMRs and one or more by EMAs with resultant airway trauma. Although our success rates are not as high as those of the previous studies, we think they reflect realistic outcome numbers that other institutions can use to evaluate their outcomes.

Of the other similar studies reviewing the management of the trauma airway by EM physicians, only one published a complication rate. Our complication rate of 9.8% was lower than that published by Omert et al., which was 33%. Levitan et al. stated that there were no identified immediate complications attributable to airway management.

We think that the protocol is successful for two reasons. First and foremost, our goal is that we successfully achieve a definitive airway with minimal, acceptable, level of complications in every patient. That was achieved. Second, since developing the protocol, its consistent implementation has allowed EM, trauma, and anesthesia staff to work together in a collegial fashion. Each physician caring for our trauma patients is aware of the protocol and subsequent steps are clear to all.

Although we did not collect these data, most of our trauma intubations are performed after rapid sequence induction. This has been shown in a number of studies, including the large multicentered National Emergency Airway Registry (NEAR) trial, to be highly efficacious in facilitating intubation.

We have continued to collect the CQI intubation data since the end of the study of intubations performed in our ED, using redundant capture to collect all trauma intubations. If more than one attempt was required for intubation then additional information is obtained from the providers regarding the circumstances of the intubation. The data are reviewed annually. A 1993 survey of EM residency directors revealed that 1% of EDs always performed quality assurance checks, and 53% of EDs never performed quality assurance checks.

LIMITATIONS

Our study has the following limitations. The EMR or attending trauma surgeon performing or supervising the attempted intubation filled out the data sheets. Self-reporting may result in the under-reporting of complications or other unfavorable outcomes. The review of trauma admissions by two of our authors to ensure 100% capture of trauma intubations and the subsequent discussion with those involved in the care of the patient may allow for less accurate documentation of the events surrounding the intubation. This process, however, only occurred in instances in which the intubation was clearly problematic or if a data form was not completed, thus the data on many of the forms was taken at face value.

The completed airway forms were initially developed for the purpose of CQI. We considered an attempt to be a laryngoscopic insertion. It is possible that those completing the forms may not have counted a quick look with a laryngoscope without an attempt at passage of the tube to be an attempt at intubation.

The airway form does not require documentation of the reason for intubation, the anatomic location of trauma, or the presence or absence of a cervical collar, all of which are factors that may result in preoxygenation or make intubation markedly difficult. This information would be of added value especially in the cases in which successful tracheal intubation required more than three attempts. As a result of this study, we plan to revise the data form and add a section that will require documentation of the indication for intubation, the presence or absence of cervical collar, and the existence of facial or neck trauma.
Because this study was performed in an academic hospital, the results are applicable to only other academic centers.

Finally, we are not aware of any cases of hypoxic encephalopathy or other long-term complications as a result of intubation; however, we did not have a formal follow-up for each case. The complications mentioned in this study are all related to the events immediately pre- and postintubation.

CONCLUSION

Our trauma airway protocol allows for the safe and effective management of the trauma airway while allowing for the education and training of EMRs. We recommend it or a similar approach in all residencies that wish to involve anesthesia in the management of trauma airways.

REFERENCES

An 80-year-old man was brought to the emergency department after soft tissue damage of both the lower limbs by a mechanical agricultural device. On arrival to the emergency room he was conscious and no signs of head trauma existed. He suffered deep dirty lacerations of the lower limbs without distal ischemia. Frontal and lateral plane radiographs were taken, revealing no fracture of the femurs or the legs. An aggressive surgical debridement was performed emergently under general anesthesia and the wounds were dressed in open fashion. Two days after, hyperbaric oxygen therapy (HBO₂) was decided to prevent necroses of a soft tissue flap. Just after the end of the first session, which was completed without any problem (such as barotrauma), the patient became confused and aggressive. No metabolic blood disorder was found. An emergency CT scan of the head was performed, showing air between the skull and the brain (Figs. 1 and 2). No other session of HBO₂ was conducted and the patient’s confusion spontaneously disappeared in 2 days.

Two days after a CT scan of the skull base didn’t find any defect permitting communication between the intracranial content and the nasal cavity, an endonasal fibroscopy was performed. In accordance with the age of this patient, no cerebrospinal fluid imaging-cistemography was performed. His leg wounds healed in 30 days and he was able to return to his “agricultural hobby” the month after.

Pneumoencephalus after HBO₂ seems to be very rare, some cases have been described after sinus barotrauma resulting from diving activity. We did not find in the literature any case of pneumoencephalus by spontaneous communication between the intracranial content and the nasal cavity, which is the most plausible explanation in this case.

Patient confusion just after an HBO₂ session necessitates performing a CT scan of the head to look for pneumoencephalus.
Re: Predictive Value of Sputum Gram Stain for the Determination of Appropriate Antibiotic Therapy in Ventilator-Associated Pneumonia

To the Editor:

The recommendation, based on poor correlation between Gram staining of bronchoalveolar lavage and the quantitative bacterial cultures, to offer immediate broader-spectrum antibiotics irrespective of Gram’s stain and culture report has been accurate. Pending culture reports, clinicians may consider the local retrospective susceptibility of isolates toward pilot selection of antibiotics. That has been practiced in a private tertiary hospital in Delhi by working out in vitro antibiotic susceptibility profiles of isolates among hospitalized cases with grave infections toward usually prescribed parenteral antimicrobials. During the period March 2006 to April 2007, gram-negative isolates from patients in intensive care units, medical, surgical, and nursery, and those with serious infections at the Sant Parmanand Hospital were screened. One hundred fifty-six isolates obtained from the pulmonary system, urine, and purulent material included 50% extended spectrum beta-lactamase (ESBL) producers as well. The ESBL-producers were Klebsiella pneumoniae, 54%; Escherichia coli, 42%; Proteus, 40%; Pseudomonas, 50%; and Salmonella group, 67%. Among ESBL producers, 85% were susceptible to meropenem, 90% to piperacillin-tazobactam, 64% to Cefepime, 67% to aztreonam, 87% to amoxicillin-clavulanic acid, and 81% to amikacin. The respective values for non-ESBL producers were 85%, 91%, 57%, 64%, 74%, and 69% (Fig. 1). Susceptibility patterns among different bacterial species for any of the antimicrobials were similar.

The susceptibility toward Cefepime and aztreonam was much lower than other antimicrobials (Fisher’s p < 0.0001). They would not merit at the moment as the efficient pilot recipe in grave infections. Nevertheless, one ESBL producer K. pneumoniae from the lungs was susceptible only to Cefepime whereas two nonproducer K. pneumoniae of pulmonary origin were susceptible either to meropenem or aztreonam. Reduced Cefepime and aztreonam susceptibility rates to isolates from grave infections (Fig. 1) might not be an isolated incident in the present series. ESBL producer E. coli from North America had higher Cefepime susceptibility than the strains from the rest of the world had. Their susceptibility for Cefepime and piperacillin-tazobactam were 90.3% and 82.7%; whereas 89.4% Klebsiella were also sensitive to Cefepime. Presently, antibiotics with ESBL producers’ susceptibility exceeding 75% have been meropenem, piperacillin-tazobactam, amikacin, and amoxicillin-clavulanic acid (Fig. 1). A watch on the susceptibility profiles would update the identity of antibiotics that might be offered immediately after admission of patients with grave infections. Certainly that approach would supplement Gram staining-based selection of broad-spectrum antibiotics.

ACKNOWLEDGMENTS

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REFERENCES

2007

U.S. AND CANADA

November 12–13, 2007
Harvard Critical Care and Trauma Symposium.
Fairmont Copley Plaza Hotel–Boston, MA. Information: Contact 1–George Velmahos, MD, PhD, Phone: (617) 726-9591; E-mail: rmartinez3@partners.org; Website: http://massgeneral.org/trauma; Contact 2–Harvard CME, Phone: (617) 384-8600; Website: http://cme.med.harvard.edu.

INTERNATIONAL

June 28–July 2, 2008
International Shock Congress.
Gürzenich Convention Center, Cologne, Germany. Fees vary (€40–€570). Information: Post: Edmund A.M. Neugebauer, PhD, University of Witten/Herdecke, Professor and Chairman of Surgical Research, Institute for Research in Operative Medicine, Ostmerheimer Str. 200, 51109 Cologne, Germany; E-mail: science@shock2008-cologne.org; Website: http://www.shock2008-cologne.org.