Southwestern Surgical Congress

Weight-based enoxaparin dosing for venous thromboembolism prophylaxis in the obese trauma patient


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KEYWORDS: Enoxaparin; Venous thromboembolism prophylaxis; VTE prophylaxis; Anti-Xa level; Obese; Trauma

Abstract

BACKGROUND: Limited data exist regarding the efficacy of weight-based dosing of low–molecular weight heparin for venous thromboembolism (VTE) prophylaxis in obese trauma patients.

METHODS: Consecutive obese trauma patients were placed on a weight-based protocol for VTE prophylaxis (enoxaparin .5 mg/kg subcutaneously every 12 hours). Peak anti-Xa levels were drawn, and bilateral lower extremity duplex ultrasound was performed. The incidence of VTE and bleeding complications were recorded.

RESULTS: Eighty-six patients met the study criteria. Seventy-four patients achieved target prophylactic anti-Xa concentrations, with a mean level of .42 ± .01 IU/mL. Eighteen patients were found to have deep vein thrombosis. However, in 16 of these patients, deep vein thrombosis was diagnosed before weight-based low–molecular weight heparin initiation. No bleeding complications occurred, and no symptomatic pulmonary emboli were identified.

CONCLUSIONS: In obese trauma patients, weight-based enoxaparin is an efficacious regimen that provides adequate VTE prophylaxis, as measured by anti-Xa levels, and appears to be safe without bleeding complications.

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality among trauma and critically ill patients despite advances in anticoagulation therapy and is among the most preventable hospital-related complications.1–5

Patients with traumatic injuries and obesity stand out among the highest risk groups, and traumatic injury and obesity are actually independent risk factors for the development of VTE.1–7

Reported incidence varies widely in the literature, ranging from 3% to 58% after major trauma, depending on factors such as type of injury, patient demographic, surveillance method (venography vs today’s gold standard, duplex ultrasound), and medication used, if any, for prophylaxis.1,2,5

In addition to traumatic injury, obesity places patients at high risk for VTE. Obesity was found to be associated with a relative risk of 2.50 for deep vein thrombosis (DVT) compared with nonobese patients and was also identified as a risk factor for recurrent VTE.4,8 Low–molecular weight heparin (LMWH) is currently recommended for VTE prophylaxis in major trauma patients.9 Because of the predictable pharmacodynamics of LMWH, dosing guidelines are

The authors declare no conflicts of interest.

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Manuscript received March 11, 2013; revised manuscript July 26, 2013
currently standardized, and monitoring drug concentration is not recommended in most patient populations. However, weight-based dosing may be prudent in obese patients. Studies evaluating LWMH dosing in obese, trauma, and critically ill medical and surgical patients have found a strong negative correlation between weight and anti-Xa levels with fixed dosing and that weight-based dosing results in favorable anti-Xa activity.

The purpose of our study was to determine if a weight-based dosing protocol for LMWH in obese trauma patients was efficacious and safe, as measured by peak anti-Xa levels, the incidence of VTE, and bleeding complications.

Methods

All adult (≥18 years of age), obese (body mass index [BMI] ≥ 30 kg/m²) patients with traumatic injuries admitted to our level I trauma center from January 2011 to July 2012 were included for inclusion. Exclusion criteria were intracranial hemorrhage, pregnancy, active hemorrhage (as determined by the attending trauma surgeon), renal insufficiency (creatinine clearance < 30 mL/min), need for epidural anesthesia, coagulopathy, heparin allergy or history of heparin-induced thrombocytopenia, thrombocytopenia (platelet count < 50,000 or > 50% drop from baseline), or indication for therapeutic anticoagulation before initiation of enoxaparin prophylaxis.

Eligible patients were placed on a weight-based enoxaparin dosing protocol for VTE prevention and prospectively followed. Patients were given enoxaparin .5 mg/kg subcutaneously every 12 hours, rounded to the nearest 10 mg without dose capping, on the basis of actual body weight on admission. Timing of chemoprophylaxis initiation was at the discretion of the trauma service clinicians, on the basis of traumatic injuries, the timing of operative procedures, and overall clinical condition. Sequential compression devices were applied in all patients unless contraindicated by lower extremity injuries. Bilateral lower extremity duplex ultrasound was performed on hospital days 2, 4, and 7 and weekly thereafter, per standard trauma service DVT screening protocol, or at any time during hospitalization if clinically suspected. Computed tomography of the chest was obtained on the basis of clinical suspicion for pulmonary embolism (PE).

All patients had peak anti-Xa levels drawn with venipuncture 4 hours after the 3rd or 4th dose of enoxaparin. To quantify the anti-Xa activity for enoxaparin, all blood samples were analyzed with the STA-Compact instrument (Diagnostica Stago, Parsippany, NJ), using the Diagnostica Stago heparin anti-Xa chromogenic assay. The acceptable peak anti-Xa level for prophylaxis was considered to be .2 to .6 U/mL. If the anti-Xa level was < .2 IU/mL, the total daily dose was increased by 20 mg, and if the anti-Xa level was > .6 IU/mL, the total daily dose was decreased by 20 mg, similar to the regimen implemented by Borkgren-Oken et al. Any dose changes were discussed and approved by the clinical team, and peak anti-Xa levels were redrawn accordingly. Chemoprophylaxis was discontinued if any bleeding complications (clinically identified active hemorrhage, transfusion of ≥ 2 U of packed red blood cells, drop in hematocrit of ≥ 5 points), thrombocytopenia (platelet count < 50,000 or > 50% drop from baseline), heparin-type allergy, or VTE requiring treatment occurred. Bleeding complications were identified as follows: An initial chart review was performed. If a dose of enoxaparin was missed after initiation of the weight-based protocol, this warranted a more detailed review of clinical notes and data in search of the aforementioned events that would indicate a bleeding complication. Patients were excluded from the study if the timing of the peak anti-Xa level was incorrectly drawn or ordered.

Data collected included age, gender, height, weight, BMI, serum creatinine at admission, platelet count at admission, enoxaparin dose, peak anti-Xa level, list of injuries, Injury Severity Score, length of hospital stay, and incidence of DVT and PE.

The primary outcome measure of the study was to determine whether a weight-based enoxaparin dosing protocol was efficacious, as measured by anti-Xa levels within target range. Secondary outcome measures were the incidence of DVT and symptomatic PE, as well as bleeding complications. All data are presented either as mean ± SEM or medians with interquartile ranges, as appropriate. Unpaired Student’s t tests were used to compare normally distributed continuous variables. Continuous variables that were not normally distributed were compared using Wilcoxon’s rank-sum tests. P values < .05 were considered significant. This study has been approved by the Intermountain Healthcare Institutional Review Board and is currently recruiting patients (Salt Lake City, UT).

Results

Of all patients who met study criteria, 86 had ≥ 1 peak anti-Xa level drawn and received ≥ 3 accurate weight-based doses of enoxaparin and thus were included in the analysis. Patients were predominantly men (70%), with a mean age of 52 ± 1.78 years. The median BMI and weight were 35.3 kg/m² (interquartile range, 9.8 kg/m²) and 113.3 kg (interquartile range, 30.0 kg), respectively. Table 1 displays comprehensive patient characteristics. Target anti-Xa levels were achieved by 74 patients (86%) after the 3rd or 4th dose of enoxaparin, with a mean of .42 ± .01 IU/mL. No correlation between body weight and anti-Xa level was found ($r^2 = −.01$; Fig. 1).

Twelve patients were outside the target prophylactic anti-Xa range. Eight patients were above goal, with a mean anti-Xa level of .68 IU/mL, and 4 patients were below goal. When comparing the group above to that below the target anti-Xa range, there were no significant differences found in weight (107.9 ± 11.5 vs 104.1 ± 15.2 kg, $P = .85$) or BMI.
Upon analysis of daily weights in these 12 patients, no dramatic weight loss or gain from fluid shifts was identified that may have altered appropriate weight-based dose requirement. Enoxaparin dose was adjusted in 8 of the 12 patients out of range, and all 8 achieved target anti-Xa levels after dose adjustment. The remaining 4 patients with unacceptable anti-Xa levels failed to undergo dose adjustment per protocol because of imminent hospital discharge or, in 1 case, failure of the clinical team to change the dose.

Eighteen patients (21%) were found to have DVT on duplex ultrasound. In 16 patients, DVT was present before or on the day of enoxaparin prophylaxis initiation. There was no significant difference in age between those with and without DVT. The DVT group had a lower mean weight than the non-DVT group (102.6 ± 8.02 vs 120.4 ± 3.63 kg, \(P = .016\)) and also a lower mean BMI (34.5 ± 1.02 vs 39.7 ± 1.3 kg/m\(^2\), \(P = .021\)). Injury Severity Scores in patients with DVT were significantly higher than in patients without DVT (23.9 ± 3.1 vs 12.7 ± .77, \(P < .001\)). There was no difference in mean anti-Xa level between groups (40.0 ± 0.2 IU/mL in the DVT group vs 42.0 ± 0.2 IU/mL in the non-DVT group, \(P = .22\)). The most common traumatic injury in the DVT group was orthopedic long bone injury, found in 12 of the 18 patients (67%). Two patients were diagnosed with DVT after weight-based enoxaparin was initiated; 1 patient with an operative left femur fracture had proximal DVT in the ipsilateral lower extremity after 3 doses of enoxaparin, and the second patient was found to have internal jugular DVT, associated with a central line, after 4 doses of enoxaparin. Both of these patients were switched to treatment dosing.

There were no cases of thrombocytopenia, heparin-induced thrombocytopenia, or development of renal dysfunction. There were no bleeding complications related to enoxaparin administration, and no symptomatic PEs were identified.

### Comments

In this study, we looked specifically at weight-based VTE prophylaxis dosing in obese trauma patients, and it is intended to contribute to a growing body of evidence that a one-size-fits-all approach is inadequate when it comes to chemoprophylaxis against VTE. Supporting preliminary evidence, our results reveal that a weight-based dosing protocol leads to favorable anti-Xa levels, without bleeding complications. No correlation was found to exist between body weight and anti-Xa level, demonstrating that weight-based dosing controls for weight differences among patients, and thus provides equal and adequate prophylaxis as measured by anti-Xa levels. Neither weight nor BMI appeared to be a predictor of anti-Xa levels above or below goal range. There was no incidence of increased bleeding or development of thrombocytopenia warranting cessation of weight-based enoxaparin. Thus, it may not be necessary to “cap” the prophylactic enoxaparin dose.

In the present study, 18 patients were diagnosed with DVT and none with PE. DVT was found in 16 of the 18 patients before starting weight-based enoxaparin; therefore, DVT incidence should not be attributed to inadequate prophylaxis. Additionally, it is difficult to evaluate for any relationship between anti-Xa level and VTE incidence. It was at the discretion of the attending trauma surgeon when to initiate the weight-based protocol, and various reasons such as hemodynamic instability and multiple trips to the operating room were the cause of this delay in most cases. When comparing patients with DVT with those without DVT, it appears that the severity of traumatic injury and delay in
chemoprophylaxis initiation outweigh patient weight or BMI as the greatest risk factors for the development of VTE.

The diagnosis of DVT in all cases was made on the basis of our current trauma service VTE prevention protocol, which constitutes routine surveillance using bilateral lower extremity duplex ultrasound. The evolving role of lower extremity duplex ultrasound should be addressed. Although it is widely acceptable to assess symptomatic patients for DVT, the role for screening asymptomatic patients with duplex scans has remained unclear. Pierce et al20 proposed the question “The more we look, the more we find?” and found that trauma centers reporting higher rates of DVT had protocols instituting higher rates of routine duplex surveillance. Haut et al21 revealed that DVT rates at their institution rose 10-fold after the implementation of routine bilateral lower extremity duplex ultrasound screening in all patients. Recently published American College of Chest Physicians guidelines now recommend against routine or periodic surveillance bilateral lower extremity duplex ultrasound in both major trauma and critically ill patients.

The 2008 American College of Chest Physicians guidelines recommended weight-based dosing in obese medical and surgical patients, although a specific dosing regimen was not delineated.11 The 2012 guidelines are less clear about dosing in obese patients, and no definitive recommendations for or against weight-based dosing are made.9 Borkgren-Okonek et al16 studied a BMI-stratified dosing regimen of enoxaparin in which bariatric surgery patients with BMIs ≤ 50 kg/m2 received 40 mg twice daily and those with BMIs > 50 kg/m2 received 60 mg twice daily. Most patients reached the target anti-Xa range, without any bleeding complications. Ludwig et al18 also reported success with a weight-based dosing regimen when they placed a group of 28 obese surgical intensive care unit patients on enoxaparin .5 mg/kg subcutaneously twice daily and found a mean anti-Xa level of .34 IU/mL, in the target range for prophylaxis. Rondina et al’ used a once-daily weight-based regimen in a group of medically ill patients with BMIs > 35 kg/m2, with a goal anti-Xa level of .2 to .6 IU/mL for prophylaxis. Peak anti-Xa levels were found to be in range; however, they fell at the low end, with a mean of .25 IU/mL. Weight-based regimens with just once-daily dosing result in mean anti-Xa levels that fall either below or at the lower end of the target range, suggesting that a twice-daily dosing protocol may be more likely to lead to favorable anti-Xa levels. This is supported by our study, as we achieved a mean anti-Xa level of .42 IU/mL with twice-daily dosing of weight-based enoxaparin.

More data are emerging that shed light on inadequate VTE prophylaxis using standard dosing of enoxaparin in the trauma patient population specifically. Rutherford et al13 looked at fixed-dose enoxaparin of 40 mg subcutaneously once daily in 17 critically ill patients, 12 of whom were multiple trauma patients, and found subtherapeutic anti-Xa levels, with a mean value of .19 IU/mL. Haas et al22 studied 25 critically ill multiple trauma patients given the standard fixed dose of enoxaparin, and reported that peripheral edema resulted in significantly lower and nearly undetectable peak anti-Xa levels. Recently, Constantini et al23 published a study of 61 trauma patients who were given the standard 30-mg twice-daily dose of enoxaparin and discovered that a meager 29.5% of patients reached goal anti-Xa range, which they defined as .2 to .4 IU/mL. When the subtherapeutic group was compared with the therapeutic group, higher weight and body surface area were found to be significant predictors of low anti-Xa levels. This corroborates the negative correlation between weight and anti-Xa level in patients on fixed-dose enoxaparin previously described in the literature. This study was not powered to compare DVT rates between groups.

Despite growing evidence that fixed-dose enoxaparin in various patient populations results in subtherapeutic anti-Xa levels for VTE prophylaxis, few studies have addressed the more clinically relevant relationship between weight-based enoxaparin dosing and the incidence of VTE. Malinoski et al14 tackled this clinical question. They evaluated 54 critically ill trauma and surgical patients who received fixed-dose enoxaparin, 30 mg subcutaneously twice daily, for trough anti-Xa levels and incidence of VTE. They found that 50% of patients had low anti-Xa levels, defined as trough ≤ .1 IU/mL, and that low levels were associated with a significant increase in DVT rate (37% vs 11%, P = .026). They were unable to identify any patient characteristics that could predict a low concentration of enoxaparin and thus recommended that all critically ill trauma and surgical patients be screened with anti-Xa levels.

The pharmacology literature generally suggests measuring peak and not trough anti-Xa levels to evaluate the adequacy of chemoprophylaxis with LMWH, although sometimes this is not specified.10,22,24,25 We chose a peak anti-Xa target range of .2 to .6 IU/mL, as suggested by some authors.8 Malinoski et al14 found a relationship only between trough anti-Xa levels and VTE incidence, not peak levels. Constantini et al23 found little correlation between peak and trough levels, contributing to confusion about which level, if any, is in fact consistently associated with VTE incidence. A group took this question one step further and looked at thromboelastography compared with anti-Xa levels in intensive care unit general surgery and trauma patients. Although the thromboelastography “R time,” or time to clot formation, was shorter in patients who developed DVT, there was no relationship between anti-Xa level and DVT incidence.26 The authors failed to specify the precise timing and type (peak or trough) of anti-Xa draws, as well as any consistency in DVT screening with duplex ultrasound. Stronger evidence regarding the impact of weight-based enoxaparin dosing on incidence of VTE would make anti-Xa levels less relevant and perhaps unnecessary. Until then, clinicians are left to rely on laboratory monitoring of a surrogate marker of drug exposure to assess for adequacy of VTE prophylaxis.

Our data contribute to growing evidence that a one-size-fits-all approach with fixed-dose enoxaparin may be inappropriate for VTE prophylaxis in patients with obesity and multiple injuries. Specifically, in obese trauma patients, the
administration of enoxaparin. .5 mg/kg every 12 hours is a manageable and efficacious regimen as measured by anti-Xa levels and appears to be safe without bleeding complications. Limitations of our study include small sample size, no control group for comparison, and a single-center study. The relationship between weight-based dosing and/or anti-Xa levels with incidence of VTE warrants further investigation. Larger randomized trials are needed to assess whether weight-based dosing of enoxaparin is safer and more efficacious than standard dosing in obese trauma patients.

References


Discussion

Daniel Margulies, M.D. (Los Angeles, CA) I would like to congratulate the authors on an excellent presentation and a study. This paper explores the use of altering the dosing scheme of the low–molecular weight heparin, enoxaparin, from that of a standard BID regimen to a weight-based regimen for adult trauma patients with BMI over 30. Using .5 mg/kg of enoxaparin subcutaneously BID based on admission weight and surveying all these patients with duplex ultrasound at day 2, 4, 7 and weekly thereafter, they found that of 86 patients 74 patients had acceptable peak levels following the 3rd or 4th dose. Although 18 patients were found to have DVTs, interestingly, most of these (16 of the 18) DVTs developed before the low–molecular weight heparin was started. No bleeding complications were found.

I have 2 comments and 3 questions for the authors.

Even with this very robust prevention protocol you found a 21% DVT rate. My comment is that this paper adds to the mounting evidence that despite all our efforts at prophylaxis, we still haven’t the foggiest as to how to stop DVTs from occurring. Ultimately we need to do better with this high risk population of trauma patients and I don’t have the answer here.

Secondly, a word of caution in interpreting these data. Although the authors show that therapeutic levels of low–molecular weight heparin were achieved using weight-based dosing, one cannot conclude that there was an actual
impact on the DVT rate as the paper was designed to show this.

Questions for the authors: (1) What was the average time from admission to the start of the Enoxaparin in these patients? With those 17 or 18 DVTs that occurred, it could have occurred at any point along the way. (2) Twelve patients or 26% did fall outside the therapeutic range, with some below and some above despite this specific regimen; yet, whether they were low or high was not predicted by their weight. How do you explain that? Does edema fluid in the tissues affect the absorption? (3) Lastly, have you altered your practice to include measuring anti-Xa levels for all high-BMI patients or for that matter, for all trauma patients, routinely?

I would like to thank the Program Committee for the opportunity to discuss this paper.

Annika Bickford, P.A.-C. (Murray, UT): Thank you Dr Margulies. I appreciate your questions. First of all, in response to the question of what was the average time to initiation of chemoprophylaxis, in our retrospective analysis we found it very challenging to obtain, so I don't have that answer for you right now. We are hoping to be able to have that obtained by the time the manuscript is published. It would certainly be interesting to look at if the timing of chemoprophylaxis, particularly if early chemoprophylaxis contributes to the success of our patients in addition to the adjusted dose. Secondly, for the 12 patients that were out of range, we did not find that weight was a predictor. I think it is multifactorial. First of all, there is inherent variability in the anti-Xa test itself. We did our best to control that, by handling and analyzing all blood samples the same way and in the same laboratory. Additionally, we excluded patients with a creatinine clearance <30; however, there is of course variability in renal function among patients which I am sure was a contributing factor. Your question about whether edema affects absorption, the answer is yes. There is actually a paper looking at multiple trauma patients showing that patients who were edematous had lower and nearly undetectable anti-Xa levels compared to nonedematous patients. When looking at the 12 patients in our study that were out of range, none experienced significant weight gain which could potentially represent edema and contribute to the altered pharmacokinetics and anti-Xa levels. Then of course weight measured in kilograms and BMI does not account for body composition and I am sure this also contributes to the variability in the anti-Xa results given the subcutaneous administration of enoxaparin. And then finally, what are we doing at our institution? We have implemented this weight-based regimen on our trauma service, for patients with a BMI > 30, administering weight-based doses of enoxaparin and checking anti-Xa levels. Again, this is only in obese and not in all patients. However, we are in the early phase at our institution of initiating a prospective randomized trial which will include all trauma patients and will randomize them to a weight-based versus the standard enoxaparin regimen for prophylaxis. Thank you.

Walter Biffl, M.D. (Denver, CO): I want to congratulate you on a very nice presentation. I first want to reiterate what Dr Margulies said. It appears that if you've got 90% of your DVTs occurring before you start enoxaparin, then perhaps your greatest opportunity to impact the patients' outcomes is by looking at your protocol and implementing it earlier. In our unit, we find that the vast majority of DVT and PE events occur in patients who have a delay before we start heparin. I have a question about the ultrasound. You are doing routine duplex screening. Is that identifying enough DVT that you consider it worthwhile to continue it as a cost-effective measure?

Ms Bickford: The role of routine duplex ultrasound is controversial. We are continuing to ultrasound all high risk patients at our institution. My personal opinion is that in patients who we appropriately identify as “high risk” based on multiple factors, we should continue to routinely survey with ultrasound. The latest ACCP guidelines actually recommend against routine surveillance ultrasound, but the literature is varied on that issue. With the ISS as high as it was in all of our DVT patients, you can clearly see being between a rock and a hard place with these critically injured patients who aren't able to be chemoprophylaxed as clinically dictated, but are the highest risk of DVT. This is certainly a problem that I don't anticipate will be eradicated from our practice.