Alternative dosing of prophylactic enoxaparin in the trauma patient: is more the answer?

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Abstract

BACKGROUND: Inadequate anti–factor Xa levels and increased venous thromboembolic events occur in trauma patients receiving standard prophylactic enoxaparin dosing. The aim of this study was to test the hypothesis that higher dosing (40 mg twice daily) would improve peak anti-Xa levels and decrease venous thromboembolism.

METHODS: A retrospective review was performed of trauma patients who received prophylactic enoxaparin and peak anti-Xa levels over 27 months. Patients were divided on the basis of dose: group A received 30 mg twice daily, and group B received 40 mg twice daily. Demographics and rates of venous thromboembolism were compared between dose groups and patients with inadequate or adequate anti–Xa levels.

RESULTS: One hundred twenty-four patients were included, 90 in group A and 34 in group B. Demographics were similar, except that patients in group B had a higher mean body weight. Despite this, only 9% of group B patients had inadequate anti-Xa levels, compared with 33% of those in group A (P = .01). Imaging studies were available in 69 patients and revealed 8 venous thromboembolic events (P = NS, group A vs group B) with significantly more venous thromboembolic events occurring in patients with low anti-Xa levels (P = .02).

CONCLUSIONS: Although higher dosing of enoxaparin led to improved anti-Xa levels, this did not equate to a statistical decrease in venous thromboembolism.

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Methods

After institutional review board approval was obtained, a retrospective chart review was completed of all trauma patients admitted to our urban level 1 adult trauma center over a 27-month time period who received prophylactic enoxaparin (Sanofi-Aventis, Bridgewater, NJ) and appropriately timed peak anti-Xa levels. Appropriate timing required a steady-state anti-Xa level be drawn 4 hours after the 3rd (or greater) enoxaparin dose. Patients were excluded if they had histories of VTE or evidence of VTE on radiographic evaluation before receiving enoxaparin.

Patients were divided into 2 groups on the basis of initial prophylactic dose of subcutaneous enoxaparin, chosen at the discretion of the primary trauma attending: those in group A received 30 mg twice daily, and those in group B received 40 mg twice daily. Sequential compression devices were placed on the bilateral lower extremities on admission to either the operating room or hospital bed, with the exception of patients with fractured extremities. Demographic data, traumatic injuries, VTE rates (including both proximal lower extremity DVT and pulmonary embolus), and bleeding complications were compared between dose groups as well as between patients with inadequate (<.2 IU/mL) and adequate (≥.2 IU/mL) anti-Xa levels.

To be included in the VTE data set, patients had to undergo bilateral lower extremity duplex ultrasound examinations ≥1 week after initiating prophylaxis. Duplex examinations were performed by a registered vascular technologist or registered vascular sonography–certified ultrasound technician and reviewed by a board-certified attending radiologist for final interpretation. The criteria for diagnosis of DVT by ultrasound was an absence of complete compressibility or collapse on transverse view, an absence of complete color flow filling, or an absence of spontaneous phasic, augmentable spectral waveforms. Computed tomographic angiography was performed to diagnose pulmonary embolism only when clinically indicated.

Plasma anti-Xa levels were determined using a commercially available chromogenic factor Xa inhibition assay (hemosIL Heparin; Instrumentation Laboratory, Lexington, MA). Assays were performed using an ACLTOP 500 hemostasis testing system (Instrumentation Laboratory) by our hospital’s clinical laboratories.

Comparisons and analysis between groups were performed using Student’s t or chi-square tests as appropriate. P values <.05 were defined as statistically significant.

Results

Overall, 124 trauma patients met the inclusion criteria. Group A (30 mg) had 90 patients, and group B (40 mg) had 34 patients (Table 1). The groups were similar with regard to age, gender, hospital day of initiation of enoxaparin, and high-risk injury patterns, but patients in group B had a significantly greater average body weight (P < .001). Despite the increased body weight, with the increased enoxaparin dose, only 9% of patients (n = 3) in group B had inadequate anti-Xa levels, compared with 33% of patients (n = 30) in group A (P = .01). Additionally, of those with initially inadequate anti-Xa levels in group A, 88% attained adequate peak levels when dosing was increased to the group B regimen.

Subsequent duplex imaging studies were available in 69 patients (56%) and revealed 8 venous thromboembolic events. Day to initiation of VTE prophylaxis between the 2 groups within the VTE data set remained statistically insignificant. In group A, 6 of 47 patients (13%) were diagnosed with venous thromboembolic episodes: 5 patients were diagnosed with proximal DVT an average of 12 days (range, 7 to 19 days) after presentation to the hospital on surveillance duplex evaluation, and an additional patient was diagnosed with a pulmonary embolus after exhibiting acute onset of shortness of breath and hypoxia. In group B, 2 of 22 patients (9%) had evidence of DVT on surveillance
duplex evaluation an average of 15 days (range, 14 to 16 days) after sustaining their injuries. No statistical difference was evident in the VTE rate between the 2 dosing groups ($P = NS$; Table 2).

However, when patients were divided on the basis of initial peak anti-Xa levels rather than initial dosing regimen, a statistically significant decrease in venous thromboembolic events was noted when the initial level was deemed adequate: 7% versus 22% ($P = .02$). In addition, as peak anti-Xa levels increased, VTE episodes decreased, without evidence of additional bleeding complications (Table 3). Of note, 3 venous thromboembolic events occurred in patients with adequate peak anti-Xa levels of $\geq .2$ IU/mL, and the only bleeding complication possibly attributed to enoxaparin therapy occurred in group A, in a patient with a peak anti-Xa level of .1 IU/mL.

### Comments

VTE remains a frequent cause of morbidity and mortality in trauma patients despite an increased awareness and practice of prophylaxis. The use of enoxaparin has become a well-accepted principle for VTE prevention in trauma patients, but controversy remains regarding appropriate dosing and monitoring of the drug effect. Prior work in orthopedic patients has shown that when started in the postoperative phase, twice-daily treatment with LMWH was more effective than once-daily therapy in decreasing the incidence of VTE.9 Additionally, once-daily dosing with 40 mg of enoxaparin was found to be inadequate in achieving recommended antithrombotic anti-Xa levels in intensive care patients.10 This finding was most pronounced in patients with high body weight or the presence of multisystem organ dysfunction. Additional studies have confirmed that this is not unique to once-daily dosing and that alterations in pharmacokinetics and pharmacodynamics occur after standard dosing of LMWH as well.7,11,12

There is evidence that anti-Xa levels are more predictive of outcomes, both thrombotic events and bleeding episodes, than the dose of LMWH alone.13 This suggests that the safety and efficacy of enoxaparin might be enhanced if anti-Xa levels were maintained within a defined range. In a study examining the relationship between anti-Xa levels and clinical outcomes in the prevention of DVT after hip replacement, the authors found a significant association between the mean anti-Xa level over the first 3 postoperative days and wound hematoma as well as between mean anti-Xa level and thrombosis. They determined that if the mean anti-Xa level was $\leq .05$ IU/mL, there were no observed hematomas but a 23.1% risk for thrombosis. Alternatively, if the mean anti-Xa level was $>.2$ IU/mL, the risk for thrombosis decreased to 3.3%, but the risk for hematoma increased to 30%. Giving both complications (bleeding and thrombosis) equal clinical weight, the authors attempted to extrapolate peak anti-Xa levels using known pharmacokinetic principles of enoxaparin. They concluded that peak anti-Xa levels between .1 and .4 IU/mL should be considered the suggested range for VTE prophylaxis.

### Table 2 VTE rate on the basis of dosing regimen

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A ($n = 47$ [52%])</th>
<th>Group B ($n = 22$ [65%])</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day to initiation of treatment</td>
<td>4.1 ± 1.2</td>
<td>3.2 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Inadequate peak anti-Xa levels</td>
<td>22 (47%)</td>
<td>2 (9%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>VTE rate</td>
<td>6 (13%)</td>
<td>2 (9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as percentages.

VTE = venous thromboembolism.
Important findings of the study include the following:

1. Increased dosing of enoxaparin improved our ability to attain peak anti-Xa levels within a predefined acceptable thromboprophylactic range. However, this did not translate to an overall decrease in the incidence of VTE. We believe that further studies are required to examine the adequacy of current anti-Xa goals for thromboprophylaxis and the safety and efficacy of higher LMWH dosing.

2. Limitations of our findings include the small sample size as well as the retrospective nature of our study, with a lack of randomization with regard to enoxaparin dose. The initial dosing regimen was based solely on attending physician preference at the time of initiation. Similarly, no protocol existed for subsequent anti-Xa levels after adequacy was attained. In addition, although it is our practice to perform weekly duplex evaluations on patients deemed at high risk for VTE, only 56% of our initial study group had evaluable data. In most cases, this lack of data was secondary to hospital discharge. And finally, although the 2 groups were well matched with regard to age, gender, hospital day of initiation of enoxaparin, and high-risk injury patterns, differences in body weight may have led to other unknown biases.

3. Importantly, the recommendations for thromboprophylaxis in trauma patients are based on these prior data as well as general surgical data in which enoxaparin was begun preoperatively or in the immediate postoperative state. In the present study, 38% of venous thromboembolic events occurred in patients with peak anti-Xa levels of .2 IU/mL, which should have been adequate on the basis of current thromboprophylaxis recommendations. Frequently, in the case of trauma, chemical thromboprophylaxis is delayed because of injuries that are at risk for bleeding. Prior research has proved the initiation of thromboprophylaxis at 48 to 72 hours after presentation to be safe in trauma patients with either traumatic brain injuries or solid-organ injuries.14,15 In the present study, enoxaparin was initially dosed on average hospital day 3 (range, 1 to 10). This may both decrease the bleeding risk as well as increase the thrombotic risk compared with perioperative prophylactic dosing of LMWH resulting in a need to shift the acceptable thromboprophylactic range. In the present study, no patient with a peak anti-Xa level ≥.3 IU/mL had a venous thromboembolic event or a bleeding complication.

4. Our results regarding the efficacy of the current acceptable anti-Xa range for thromboprophylaxis have been confirmed in other studies. When reviewing the effect of standard enoxaparin dosing in critically ill patients, Costantini et al16 concluded that standard dosing was frequently inadequate on the basis of trough anti-Xa levels, but interestingly, 11% of patients with adequate trough anti-Xa levels had venous thromboembolic events. In addition, the average peak anti-Xa level in these patients was .27 ± .1 IU/mL. In a review of enoxaparin dosing in burn patients, the median dose required to achieve anti-Xa levels within therapeutic range was 50 mg every 12 hours (range, 20 to 70 mg). The single episode of DVT noted within the study occurred with a peak level of only .24 IU/mL.16 Finally, using a prophylactic range of .2 to .5 IU/mL, Ludwig et al17 studied the effect of .5 mg/kg twice-daily dosing of enoxaparin in the obese surgical intensive care population. The average anti-Xa level was .34 IU/mL, and only 2 patients required dose adjustment in the form of decreases. The only instance of DVT noted in the study was believed to have been preexisting. The authors reported no episodes of major bleeding or heparin-induced thrombocytopenia using this protocol of dosing. Perhaps this dosing regimen should be extrapolated to nonmorbidly obese patients as well.

5. Table 3

<table>
<thead>
<tr>
<th>Anti-Xa level (IU/mL)</th>
<th>Total patients</th>
<th>Venous thromboembolic events (% total)</th>
<th>Bleeding events (% total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;.1</td>
<td>10</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>.1</td>
<td>14</td>
<td>2 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>.2</td>
<td>24</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>.3–.5</td>
<td>21</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.

References


**Discussion**

**Christopher Dente, M.D.** (Atlanta, GA): I would like to thank the Congress for allowing me to discuss this paper and I congratulate the authors on a fine presentation. Venous thromboembolism is 1 of the great unsolved complications after trauma. The vast morass of literature on the topic is replete with studies that use prophylactic methods of varying ineffectiveness, screening studies with variable sensitivities, and use different outcome measures. One of the few things that is relatively widely accepted is that low molecular weight heparin, while not perfect, may be our best option for chemical prophylaxis. The authors present a relatively small series of patients cared for in their center with either the standard Lovenox regimen or a higher dose regimen. They note that they were able to achieve therapeutic anti-Xa levels significantly more frequently in the high dose group, although this did not change the percentage of patients diagnosed with VTE. This study has many of the same issues that much of the literature on the topic suffers from most notably the lack of standardization of screening studies. It does provide further evidence however that the dosing regimens we are using in most patients are likely inadequate. It also calls into question whether higher doses will fix the problem. I have several questions.

1. The manuscript states that the regimen choice was based on trauma attending preference. The patient weight between the 2 groups was also markedly different, with average weights differing by upper 20 kg. My question then becomes, is the high dose regimen used specifically by 1 or a small group of faculty or did the faculty as a rule tend to use the higher dose regimen on heavier people? The answer to this question is an important determinant for interpreting the VTE rates in each group, as a different emphasis by different faculty on adjunctive methods for end VTE may cloud the results.

2. Only 56% of your patients received the duplex at 1 week and therefore qualified for subset analysis. Furthermore, you are more likely to get a duplex if you are in group B with about two thirds of these patients screened compared to group A with only about 50% screened. It is well known if you look more aggressively for VTE, you are more likely to find it. Do you think that if you had duplex information on all patients, your conclusions would be different?

3. And finally, the average data for therapy was day 3, we personally become much more aggressive with early initiation of chemoprophylaxis. Do you think that the relative delay in prophylaxis altered your results?

Again, I congratulate the authors on a fine presentation and on trying to study a difficult and vexing complication. I’d also again like to thank the Congress for the privilege of discussing this paper.

**Tammy R. Kopelman, M.D.** (Phoenix, AZ): Thank you Dr Dente. The first question you asked is: was the high dose regimen used by a particular attending and it was. It was used by myself. The purpose of this study was for me to try to show I’d achieve better goals. In addition, I think my partners, when the patients were over 100 kg, would tend to dose higher. The 2nd question was: if we had more patients in group A that had received duplex exams, would our results be different. Certainly, the more you look, like you said, the more you will find. However, statistically the makeup of the 2 groups did not appear different to our statisticians and they felt that 52% versus 65% would be an adequate representation of both groups. And finally, did our delay in initiation alter our results? It could have; in the trauma literature it is not uncommon for patients with multiple injuries to delay anticoagulation for 48 to 72 hours and that 72-hour mark is about when we started the majority of patients. So I think if we had started it sooner, could it make a difference? Yes, but I think that may be part of the issue. In the trauma population, as opposed to the isolated orthopedic or preop general surgery patients, we are initiating things later and perhaps need to be a little bit more aggressive on how much we are anticoagulating these patients.

**Robert McIntyre, M.D.** (Denver, CO): I have a couple questions that I have been struggling with in my own practice and wanted to see what your opinion was. First, I may have missed this in your presentation. How many of the VTE episodes were symptomatic versus found on routine screening? My reading of the ACCP recommendations published a year ago is that they don’t recommend routine screening duplexes or other studies. And then secondly, what is a Xa level cost?

**Dr Kopelman:** So, the only patient who was symptomatic in our study was the patient who presented with the
PE. So, 1 out of the 8. Every one of the duplex exams were on patients who we deemed asymptomatic and it was simply found on a surveillance study. The anti-Xa levels at our hospital are for our nonpay patients cost $8. So, it is not an expensive study for the hospital to run. What they charge the insurance I am not certain at this point.

Mike Corneille, M.D. (Phoenix, AZ): My question is about missed doses. Even though you measured Xa levels, did you also look at how many doses were given and how often patients go for multiple procedures—orthopedic procedures, take-backs, etc? How many missed doses of Lovenox were there?

Dr Kopelman: We did not keep track of that, but it is a common phenomenon on the service.

Randall Smith, M.D. (Temple, TX): So now what do you do based on what you discovered? What is your current management scheme?

Dr Kopelman: Our current management scheme at Maricopa is we start everyone at 40 mg twice daily. We check levels at 4 hours after the 3rd dose and we are using a goal of .3 to .5. We’ve been doing it this way for 4 months, and since that time, knock on wood, we have not had a VTE episode. So our duplex and we are still screening weekly and our duplexes have been negative.