Enoxaparin and Antifactor Xa Levels in Acute Burn Patients

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Altered pharmacokinetics in critically ill patients have been shown to result in inadequate enoxaparin dosing for venous thromboembolism (VTE) prophylaxis. In the burn unit, routine monitoring of antifactor Xa levels was implemented to ensure adequate VTE prophylaxis. The purpose of this study was to examine the appropriateness of enoxaparin dosing for VTE prophylaxis in this specialized patient population. The authors reviewed patients with acute burn injury from June 1, 2009, to October 20, 2009, who had enoxaparin therapy monitored with antifactor Xa levels. Data collection occurred prospectively. Thirty-eight patients received enoxaparin subcutaneously for prophylaxis of VTE and had antifactor Xa levels measured. Thirty (79%) patients had initial antifactor Xa levels less than 0.2 U/ml. Enoxaparin dosages were subsequently increased as needed to achieve antifactor Xa levels of 0.2 to 0.4 U/ml. Eight of 38 patients never achieved goal antifactor Xa level before enoxaparin was discontinued. The median final dose required to achieve an antifactor Xa level within therapeutic range was 50 mg every 12 hours (range 30–70 mg). In linear regression, final enoxaparin dose correlated with TBSA. Two patients had clinically significant thromboembolic events. There were no documented episodes of significant hemorrhage, thrombocytopenia, or heparin-associated allergy. The low antifactor Xa levels observed in this study demonstrate that standard dosing of enoxaparin for VTE prophylaxis is inadequate for patients with acute burns. In these patients, both a higher initial enoxaparin dose and routine monitoring of antifactor Xa levels are recommended. (J Burn Care Res 2011;32:1–5)

Venous thromboembolism (VTE) is one of the most prevalent complications in hospitalized patients, contributing to increased morbidity, mortality, and prolonged hospital length of stay. A number of risk factors are associated with VTE, including immobility, malignancy, hormone replacement, stroke or paralysis, previous VTE, trauma, obesity, major surgery, cardiac dysfunction, and indwelling central venous catheters.1 Although only a few studies examining the true incidence of VTE in burn patients are available, patients with extensive burn injury seem to be a high-risk population for VTE.2–4 In addition to sharing several of the risk factors mentioned earlier, burn victims also exhibit altered coagulability and vascular integrity. The performances of multiple operative procedures also add to VTE risks in patients with large burn injuries.5 One series showed an incidence of deep vein thrombosis (DVT) of 23% in 30 thermally injured patients, with 6 of the 7 DVT patients in that series having received low-molecular-weight heparin, compression devices, or both.6 This suggests that traditional low-molecular-weight heparin prophylaxis dose may be insufficient in preventing VTE in burn patients.

In addition to significantly altering coagulation dynamics, burns may induce several pathophysiologic changes that alter the pharmacokinetic parameters of drugs, such as volume of distribution and clearance.7 Immediately after burn injury, cardiac output decreases because of the loss of capillary integrity. As a result of this relative hypoperfusion, renal blood flow and glomerular filtration rate (GFR) are also de-
creased during this acute phase. However, within approximately 48 hours of injury, burn patients become hyperdynamic with increased cardiac output, resulting in enhanced hepatic and renal clearance of drugs. Enoxaparin, a low-molecular-weight heparin, is metabolized primarily through liver, and its active metabolites are cleared through the kidneys. The pathophysiologic changes that occur after burn injury may affect the clearance of enoxaparin and could explain the apparent reduction in effectiveness of standard dosing mentioned previously. Furthermore, the agent’s bioavailability may be reduced because of altered peripheral perfusion and edema after burn injury.

Only limited information regarding the efficacy of chemical VTE prophylaxis in burn patients exists. One observational study of four burn patients showed that standard starting dosage of enoxaparin in surgical patients was not adequate to achieve goal antifactor Xa peak levels. We hypothesized that low antifactor Xa levels would be found in our acute burn patients as well. Therefore, we began monitoring antifactor Xa levels to ensure adequate enoxaparin therapy on June 1, 2009. The purpose of this study was to examine optimal dosing of enoxaparin dosing for VTE prophylaxis in this specialized patient population.

METHODS

Patient Review

Patients older than 13 years who were admitted to our regional American Burn Association–verified burn center from June 1, 2009, through October 20, 2009, with acute burn injury, who received enoxaparin prophylaxis, and who were monitored with antifactor Xa levels were included in this institutional review board–approved review. Data collection occurred prospectively. Demographic data collected included age, gender, cause of injury or admission, weight, height, body mass index (BMI), burn size expressed as %TBSA, outcome, and hospital length of stay. GFR was calculated from admission laboratory data using the Cockcroft-Gault equation. Treatment data collected included antifactor Xa levels and enoxaparin doses. Patients were followed up until discharge for the development of any adverse effects associated with enoxaparin, such as major hemorrhage, thrombocytopenia, or heparin-associated allergy. After discharge, study investigators monitored readmissions to our institution for VTE events for 30 days.

Treatment Protocol

Beginning in June 2009, all patients admitted to our burn unit who were anticipated to be nonambulatory for greater than 48 hours were placed on an enoxaparin dosing and monitoring protocol, which was developed specifically for the burn center (Figure 1). Exclusion criteria included contraindication to the use of enoxaparin, intracranial bleeding or hemorrhagic stroke (within 48 hours), suspected or proven hematoma, creatinine clearance <30 ml/min or serum creatinine >1.6 mg/dl, epidural anesthesia, and head injury or neurotrauma. We limited the present review to adult patients.

![Figure 1. Burn trauma intensive care unit (BTICU) low-molecular-weight heparin (LMWH) dosing algorithm. Cr Cl, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; BMI, body mass index; HIT, heparin-induced thrombocytopenia.](image-url)
The initial enoxaparin dose was 30 mg given by subcutaneous injection every 12 hours for nonobese adults and 0.5 mg/kg subcutaneous injection every 12 hours for obese adults who had BMI >35 kg/m² or weight >150 kg. The peak steady state level of antifactor Xa was drawn 4 hours after the third enoxaparin dose. The levels were measured using the Rotachrom® assay using the STA Compact instrument (Diagnostica Stago, Parsippany, NJ). All assays were performed by our hospital’s clinical laboratories. Doses of enoxaparin were then adjusted as shown on the protocol to achieve the recommended antifactor Xa level of 0.2 to 0.4 U/ml.11 The precision of the assay less than 0.2 U/ml has not been established. These levels cost approximately $80 each, and results are available within about 2 hours.

Injections were performed in the abdominal area when possible as recommended in the package insert. If injection could not be given in the abdominal area, injection site was per nursing discretion; burned areas were not used for injections. Patients having surgical procedures had their morning dose of enoxaparin held and this was resumed that night or the next morning. The decision is based on the type of procedure and physician’s decision. When this was performed, the protocol was resumed at the previous dose, and antifactor Xa levels were again checked after the third dose, as before. VTE prophylaxis was discontinued when patient was able to ambulate at least three times daily or otherwise as determined by the attending physician.

Statistical Analysis
Data were analyzed using SPSS™ version 14.0 (SPSS, Chicago, IL) software and STATA version 11.0 (StataCorp, College Station, Texas). Student’s t-test was used for continuous variables, and Fisher’s exact test was used for categorical variables. Linear regression analyses were performed to determine the appropriate injury characteristics that most influenced the enoxaparin dose received. A P value of <.05 was considered significant.

RESULTS
Thirty-eight acute adult burn patients (age ≥13 years) who received enoxaparin and had at least one correctly obtained antifactor Xa level drawn were included. The range of times from dosing at which antifactor Xa levels were drawn was 3 to 5 hours. The median patient age was 45 years, the majority of patients were male (69.2%), and the median TBSA burn was 14%. Further patient demographics are provided in Table 1. Initial therapy with enoxaparin 30 mg every 12 hours was used for 35 patients. Three obese patients started at a higher enoxaparin dose, with one patient receiving 40 mg every 12 hours and two patients receiving 50 mg every 12 hours. Thirty of 38 patients (79%) had initial antifactor Xa levels less than 0.2 U/ml. Enoxaparin dosages were subsequently increased as indicated by the protocol.

Eight of 38 patients (21%) never achieved goal antifactor Xa level before enoxaparin was discontinued. The median final dose required to achieve antifactor Xa level within therapeutic range was 50 mg every 12 hours (range 30–70 mg). Final enoxaparin doses for patients who had an antifactor Xa level within range is illustrated in Figure 2. In linear regression, enoxaparin dose was positively correlated (r = .725, P < .0001) with an increase of every 10% TBSA burned (Figure 3). The regression equation generated for enoxaparin dosing and percentage TBSA is as follows:

\[ \text{Enoxaparin dose (milligram every 12 hours)} = 36.47 + 4.3 \times (\text{TBSA/10}). \]

BMI and GFR showed no significant correlation with enoxaparin dose. One patient developed a DVT documented by venous duplex ultrasound during admission. That patient had an appropriate antifactor Xa level of 0.24 before enoxaparin was discontinued.

### Table 1. Patient demographics (n = 39)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. males</td>
<td>27 (69.2)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45 (13–90)</td>
</tr>
<tr>
<td>%TBSA</td>
<td>14 (1–66)</td>
</tr>
<tr>
<td>GFR* (ml/min)</td>
<td>120 (41–180)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (20.5–37)</td>
</tr>
<tr>
<td>Length of BTICU stays (d)</td>
<td>13.5 (1–90)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (2.6)</td>
</tr>
</tbody>
</table>

Data are shown as median (range) or n (%).

* GFR is mathematical estimated by using Cockcroft-Gault equation.

GFR, glomerular filtration rate; BMI, body mass index; BTICU, burn trauma intensive care unit.
Six days after discontinuation of enoxaparin, as the patient was fully ambulatory, the patient complained of left calf pain and had venous duplex ultrasound that showed a DVT of left lower extremity. This patient subsequently received therapeutic anticoagulation treatment. One patient was diagnosed with pulmonary embolism and was readmitted to our institution for management within a month of discharge from our burn unit. This patient presented with 3% TBSA burn and had a therapeutic antifactor Xa level before discontinuation of enoxaparin. One month after discharge from our burn trauma intensive care unit, this patient presented to an outside emergency room with a complaint of a 1-day history of shortness of breath. Computed tomography angiography from that facility showed bilateral pulmonary embolism. The patient was subsequently transferred to our facility secondary to increasing tachycardia because of the pulmonary embolism. The patient was obese (BMI = 37 kg/m²) and 6-week pregnant, both may contribute risks for hypercoagulability. There were no documented episodes of significant hemorrhage, thrombocytopenia, or heparin-associated allergy observed during the time of this review.

**DISCUSSION**

This analysis supports the contention that traditional enoxaparin dosing of 30 mg every 12 hours may not be sufficient for VTE prophylaxis in acutely burned patients because only 21% of patients receiving this dose had detectable antifactor Xa levels. These findings are consistent with the prior report by Yogaratnam et al that acutely burned patients require higher than typical recommended enoxaparin dose. In addition, adequate VTE prophylaxis never occurred in 21% of the study patients by the time enoxaparin was discontinued despite our escalating protocol, likely due to the low initial enoxaparin dose. Despite our aggressive regimen and intensive monitoring efforts, two patients suffered VTE episodes. Previous studies have suggested that other critically ill patients, particularly those treated with vasopressors that impair peripheral circulation, have also demonstrated decreased antifactor Xa activity.

Several other risk factors likely contribute to the altered pharmacokinetics of enoxaparin in acute burn patients, as mentioned previously. First, there is reduced bioavailability of subcutaneous enoxaparin associated with the increases in volume of distribution in burn patients after aggressive fluid resuscitation. In addition, enoxaparin half-life is reduced because of increased renal clearance during the hypermetabolic phase after significant thermal injury. Therefore, if burn patients are to receive enoxaparin for VTE prophylaxis, it is likely that dosing will need to be modified from usual surgical recommendations.

The regression equation generated by this study indicates that the constant for initial doses of enoxaparin in acute burn adult patients is 36 mg every 12 hours, with a variable adjustment based on TBSA burn injury. Our analysis did not reflect any effects of BMI on enoxaparin dose in acute burns, although obesity alone has been shown to mandate higher enoxaparin VTE prophylaxis dose in bariatric surgery patients. Our small sample size and, in particular, the very limited number of obese patients (only three with a BMI >35 kg/m²) gave us too little data to expect a significant correlation. We were also not able to correlate the GFR with enoxaparin dose, although this may be a result of the inaccuracy of mathematical estimation of GFR using Cockcroft-Gault in patients with burns. Finally, we could not determine whether enoxaparin requirements decreased as burn wounds healed.

This study is admittedly preliminary and was limited by a relatively small sample size and a paucity of documented adverse clinical outcomes. Information on DVT after discharge was difficult to obtain because of the extensive geographical catchment area of our center. Therefore, we are unable to determine whether the implementation of our protocol for enoxaparin administration and monitoring was effective in decreasing the incidence of DVT in our acute burn patients. In addition, our policy of discontinuing prophylaxis once patients are ambulatory may not provide coverage for long enough.

Although this study extends our understanding of VTE prophylaxis in acutely burned patients, additional clinical studies are needed to develop an optimal approach. An additional challenge exists because
it is unknown when the enoxaparin dose-response relationship normalizes, as the hypermetabolic phase of burn injury resolves. The current practice at our regional burn center is to obtain antifactor Xa levels weekly once an appropriate value for VTE prophylaxis has been achieved.

These findings do not necessarily mean that standard enoxaparin dosing is insufficient to protect against VTE in burn patients because antifactor Xa activity only serves as a surrogate variable for adequacy of chemical VTE prophylaxis with enoxaparin. However, a relationship between antifactor Xa levels and clinical efficacy has been established. A peak antifactor Xa level of less than 0.1 U/ml is associated with a 23% risk of thrombosis, and the authors concluded that the 4-hour peak antifactor Xa level of 0.1 to 0.4 U/ml is a reasonable range for VTE prophylaxis.11

CONCLUSION

The low antifactor Xa levels observed in this study demonstrate that standard dosing of enoxaparin for VTE prophylaxis is likely inadequate for patients with acute burns. In these patients, both a higher initial enoxaparin dose and routine monitoring of antifactor Xa levels may be beneficial.

REFERENCES