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Anti-Xa guided enoxaparin dose adjustment improves pharmacologic deep venous thrombosis prophylaxis in burn patients☆

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ABSTRACT

Introduction: Patients recovering from burn injury are at high risk of developing deep venous thrombosis (DVT). While 30-mg twice-daily enoxaparin is accepted as the standard prophylactic dose, recent evidence in injured patients suggests this dosing strategy may result in sub-optimal pharmacologic DVT prophylaxis. We hypothesized that standard enoxaparin dosing would result in inadequate DVT prophylaxis in burn patients.

Methods: A retrospective review of an ABA-verified Burn center's registry from January 2012 — December 2016 identified patients with peak plasma anti-Xa levels to monitor the efficacy of pharmacologic DVT prophylaxis. Patients ≥18 years old were included if they received at least 3 doses of enoxaparin and had appropriately timed peak anti-Xa levels. We analyzed data including patient demographics, body weight, body mass index (BMI) and total body surface area burn (TBSA). Diagnosis of DVT was collected.

Results: During the study period, 393 patients were screened with a plasma anti-Xa levels. Of the 157 patients that met inclusion criteria, 81 (51.6%) achieved target peak plasma anti-Xa levels (0.2–0.4 IU/mL) on standard 30-mg twice-daily prophylactic enoxaparin and 76 (48.4%) had sub-prophylactic levels. Sub-prophylactic patients were more likely to be male, have increased body weight and elevated BMI. 49 of the 76 sub-prophylactic patients received a dose-adjustment in order to reach target anti-Xa levels; 37 patients required 40 mg twice-daily, 10 required 50 mg twice-daily and 2 required 60 mg twice-daily. The overall DVT rate was 3.8%.

Conclusions: The current recommended prophylactic dose of 30-mg twice-daily enoxaparin is inadequate in many burn patients. Alternate dosing strategies should be considered to increase the number of burn patients achieving target prophylactic anti-Xa levels.

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Determining whether prophylactic enoxaparin dose adjustment decreases DVT rates in burn injured patients should be evaluated in future prospective trials.

1. Introduction

Deep venous thrombosis (DVT) prophylaxis continues to be a frequent complication in patients admitted following burn injury despite increasing awareness, advances in screening and implementation of prophylaxis. Depending on the screening method used, recent data indicate DVT rates of up to 23% for acute burn patients [1–6]. In the absence of prophylaxis, DVT rates up to 60% have been described, further demonstrating the importance of monitoring and aggressive prophylaxis in high risk patients [7].

While no official standardized guidelines exist for DVT prophylaxis in burn patients, pharmacologic prophylaxis strategies similar to those in trauma patients are often used [3]. While most centers utilize twice daily enoxaparin for DVT prophylaxis, additional pharmacologic adjustments are made in certain circumstances including higher dosing for obese patients and daily dosing or subcutaneous heparin for patients with renal insufficiency. Unfortunately, studies have shown that following severe injury standard doses of subcutaneous enoxaparin can result in highly variable plasma anti-Xa activity levels, a measure of enoxaparin activity in the blood [8]. As a result, standard enoxaparin dosing may not yield predictable pharmacokinetics in burn patients.

Plasma anti-Xa level monitoring in patients treated with subcutaneous enoxaparin for DVT prophylaxis is currently utilized in many centers for patients that are obese, elderly, pregnant, or have renal impairment [9,10]. However, recent evidence has shown that standard prophylactic enoxaparin dosing strategies may not result in adequate plasma anti-Xa levels in trauma patients and further research is needed to evaluate enoxaparin dose adjustment as a standard approach to DVT prophylaxis in the burn population [8,11,12].

2. Theory

The purpose of this study was to investigate the proportion of acute burn patients achieving adequate anti-Xa levels on standard enoxaparin prophylaxis. Additionally, we attempted to improve the efficacy of DVT prophylaxis by actively adjusting the enoxaparin dose based on measured plasma anti-Xa levels. We hypothesized that the majority of burn patients would be sub-prophylactic on standard enoxaparin dosing and that anti-Xa targeted dose adjustment would help achieve optimal pharmacologic DVT prophylaxis.

3. Materials and methods

A retrospective review of an ABA-verified Burn center's registry identified patients with peak anti-Xa levels to monitor the efficacy of pharmacologic DVT prophylaxis. Electronic medical records and pharmacy data from January 2012 — December 2016 were queried to identify patients admitted to the burn service who had at least one measured anti-Xa level during their hospital stay. The generated dataset was manually examined to include only patients with appropriate enoxaparin dosing and renal function assessment. Our standard protocol calls for pharmacologic venous thromboembolism (VTE) prophylaxis with 30 mg enoxaparin twice daily as soon as deemed safe by the attending burn physician. Alternative dosing may be utilized at the discretion of the attending physician. Peak anti-Xa levels are drawn 3–5 h following 3 serial doses of enoxaparin. Our target range for prophylactic anti-Xa levels is 0.2–0.4 IU/mL (see Fig. 1). The UC San Diego Institutional Review Board reviewed and approved this study.

3.1. *Patient selection*

Patients ≥ 18 years old were included if they received at least 3 serial doses of DVT prophylaxis with enoxaparin and had appropriately timed peak anti-Xa levels (3–5 h after at least three serial enoxaparin doses). Patients were excluded if they had a prior incident of DVT, received less than 3 doses of enoxaparin, or were treated with a non-standard dosing regimen. Patients who were pregnant or incarcerated were excluded.

3.2. *Venous duplex screening protocol*

Our screening protocol calls for lower extremity duplex within 48 h of admission and a second duplex during the first week of admission. This is followed by weekly duplex unless additional screening is clinically indicated. Screening upper extremity duplex was performed on a weekly basis.

Fig. 1 – Enoxaparin dose adjustment protocol.

3.3. Data collection

Data collection included patient demographics, body weight, body mass index (BMI), total body surface area burn (TBSA), ICU and hospital length of stay, ventilator days, peak plasma anti-Xa levels and death. Evidence of DVT and clinically significant bleeding events were analyzed.

3.4. Statistical analysis

Data are presented as mean or raw score. Student's *t*-tests and X^2 tests were used to analyze continuous and categorical data, respectively. A *p*-value of <0.05 was considered statistically significance.

4. Results

4.1. Plasma anti-Xa levels on standard enoxaparin prophylaxis

There were 157 patients that met criteria for inclusion in this study (Fig. 2). Patients were mostly male (67.5%), had a mean age of 45.1±19.5 years, and had sustained a mean total body surface area burn of 5.3±6.0% (Table 1). Of the 157 patients included in the study, 76 patients (48.4%) did not achieve goal prophylactic anti-Xa levels on standard enoxaparin dosing of 30mg twice a day. There were 81 patients (51.6%) that did achieve target prophylactic anti-Xa levels of 0.2–0.4 IU/mL on standard enoxaparin dosing. A comparison of patients reaching target anti-Xa levels on 30mg twice daily enoxaparin with those patients below target is shown in Table 2. Patients that did not reach target prophylactic anti-Xa levels were significantly more likely to be male, had increased body weight and larger body mass index (BMI). The DVT rate was 3.8% for all patients enrolled. There was no difference in screening rates between patients that achieved target prophylactic anti-Xa levels compared to patients that were below target (86.4% vs. 89.5%). DVT events for patients treated with enoxaparin 30mg twice daily are listed in Table 3.

Table 1 – Demographics of patients enrolled in study.

All patients (n=157)	
Age (yr)	45.1±19.5
Gender (male)	67.5%
Weight (lbs)	164.5±41.8
Body mass index (kg/m^2)	25.2±5.3
% TBSA burn	5.3±6.0
Hospital days	18.9±15.9
ICU days	5.4±12.4
Ventilator days	1.3±6.9
DVT	6 (3.8%)

4.2. Enoxaparin dose adjustment to reach goal anti-Xa levels

Of the 76 patients that did not achieve goal prophylactic anti-Xa levels on standard dose enoxaparin, 49 patients received an enoxaparin dose adjustment to attempt to reach target anti-Xa levels. There were 37 patients treated with enoxaparin 40mg twice daily, 10 patients treated with 50mg twice daily, and 2 patients treated with 60mg twice daily. There were no clinically significant bleeding events noted. Patients that received an enoxaparin dose adjustment were mostly male (87.8%), had a mean body weight of 190.8±37.2 lbs., BMI of 27.6 ±5.6kg/m^2, and had mean hospital LOS of 24.2±20.9days (Table 4). Based on the important contribution of body weight

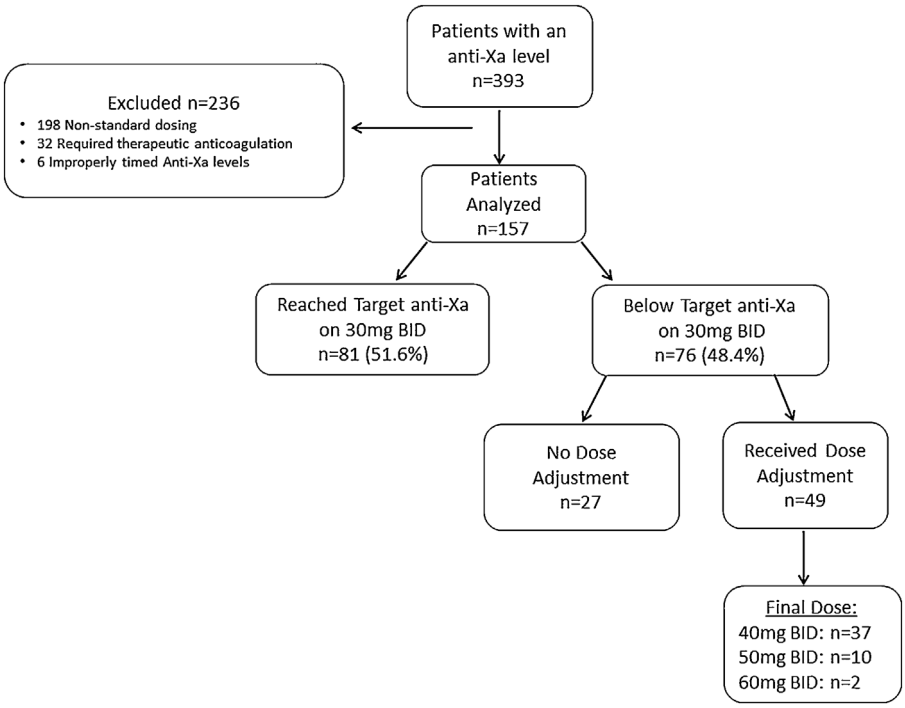

Fig. 2 – Diagram of patients enrolled in study.

Table 2 – Comparison of patients reaching target anti-Xa on 30mg twice daily enoxaparin with those below target*.

	Reached target (n=81)	Below target (n=76)	p
Age (yr)	44.7±20.6	45.4±18.5	0.85
Gender (male)	40 (49.4%)	66 (86.8%)	<0.0001
Weight (lbs)	146.7±34.7	184.4±38.9	<0.0001
Body mass index (kg/m^2)	23.7±4.5	26.9±5.7	0.0001
%TBSA burn	4.0±5.1	6.8±6.6	<0.01
TBSA >10%	8 (9.9%)	16 (21.1%)	0.075
Length of stay	16.8±12.1	21.3±19.0	0.076
ICU days	3.7±9.8	7.3±14.6	0.070
Ventilator days	0.9±6.5	1.8±7.4	0.419
Mortality	0	0	NS
DVT	1 (1.2%)	5 (6.6%)	0.108

* Target anti-Xa level 0.2–0.4 IU/ml, for prophylactic dosing of enoxaparin.

Table 3 – Deep vein thrombosis events.

Gender	Body weight (lbs)	Body mass index (kg/m^2)	Anti-Xa level	DVT location	Day of diagnosis
Male	215.6	30.1	0.11	Common femoral vein	23
Female	118.9	26.6	0.42	Internal jugular vein	28
Male	142.2	24.4	0.18	Axillary vein	19
Male	150.6	21.0	0.02	Internal jugular vein	15
Female	183.0	32.4	0.14	Common femoral vein	12
Female	158.7	28.1	0.15	Common femoral vein	7

to achieving target anti-Xa levels, we compared each patient's body weight with their final enoxaparin dose (Fig. 3). There is a clear correlation between increasing body weight and increasing enoxaparin dosing required to achieve target prophylactic anti-Xa levels.

5. Discussion

Burn injured patients experience a hypermetabolic response that is associated with hyperdynamic physiology, increased basal energy expenditure, alterations in protein catabolism, and a dysregulated immune response [13]. Patients recovering from burn injury have a high risk of DVT with DVT-related complications causing significant morbidity in critically ill burn patients [14]. Therefore, early, aggressive DVT prophylaxis is required to limit the occurrence of DVT in these high-risk patients. Here, we demonstrate that almost 50% of patients admitted to our burn center do not achieve target prophylactic plasma anti-Xa levels on standard 30mg twice daily dosing of enoxaparin.

Table 4 – Patients receiving enoxaparin dose adjustment.

	All patients (n=49)
Age (yr)	46.4±18.9
Gender (male)	43 (87.8%)
Weight (lbs)	190.8±37.2
Body mass index kg/m^2	27.6±5.6
%TBSA burn	7.2±7.6
Length of stay	24.2±20.9
ICU days	9.2±16.2
Ventilator days	2.3±8.7
Mortality	0
DVT	3 (6.1%)d re

Studies investigating thromboembolic events in burn patients demonstrate a wide range of DVT rates that primarily depend on screening strategies utilized to detect DVT [15]. DVT rates in burn patients are comparable to trauma patients [1–6] with the increased VTE risk after injury attributable to their hypercoagulable state [16], immobility, repeated operative procedures and frequent use of indwelling central venous catheters [17]. Though this study was not powered to show a statistically significant reduction in DVTs, there were fewer DVTs in the group with target anti-Xa levels on standard dosing. These data suggest that alternate strategies for pharmacologic prophylaxis are needed to provide high risk patients with optimal DVT prophylaxis, including personalized initial dosing strategies with additional enoxaparin dose adjustment based on anti-Xa levels.

While the 30-mg twice-daily dose of enoxaparin is accepted as the current standard prophylactic dose for most patients, several studies have shown that critically ill trauma and surgical patients are at risk of having low anti-Xa levels and raised the need for anti-Xa monitoring for VTE prevention [8,11,12,18–25]. A study of prophylactic enoxaparin dosing in critically ill trauma patients found that nearly 70% of patients had low anti-Xa levels despite receiving standard prophylactic enoxaparin doses [8]. A systematic review of 958 trauma patients receiving various enoxaparin dosing regimens reported high rates of inadequate prophylaxis (up to 92%) and VTE (5.3%) in patients on standard dosing [21]. Previous studies have also correlated low anti-Xa levels with increased DVT rate [11], and anti-Xa targeted dosing and weight-based dosing have been shown to reduce the incidence of DVT in trauma [18,20–22,26] and obese [27,28] patients.

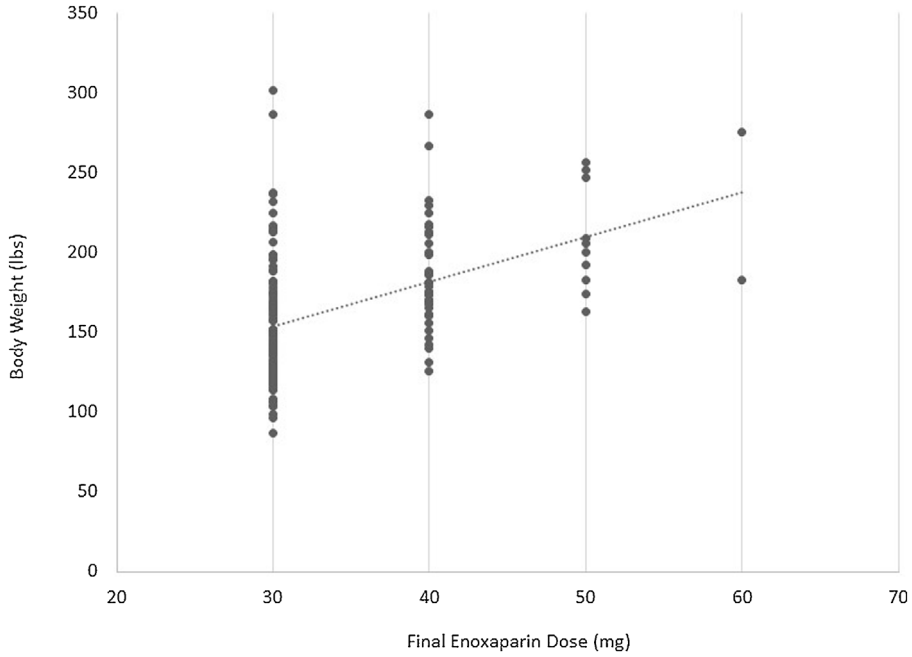

Fig. 3 – Body weight correlates with higher final enoxaparin dose.

We utilize an aggressive upper and lower extremity venous duplex surveillance protocol to screen for DVT. Previous studies have clearly demonstrated that DVT rates are increased in centers that routinely screen for DVT [15,29,30]. While this practice is controversial, the identification of asymptomatic DVTs may allow for early recognition and treatment. Further, patients can have an asymptomatic DVT during their index admission but develop long-term complications, though how often this occurs is difficult to measure [31].

Contrary to the trauma literature, there are fewer studies with much smaller cohorts studying the burn population. Yogaratnam et al. first described a reduced dose response relationship between subcutaneous enoxaparin and anti-Xa levels in acute burn patients, but only examined 4 patients [32]. Subsequently, prospective analyses investigating the effectiveness and safety of increased enoxaparin dosing based on plasma anti-Xa monitoring for DVT prophylaxis in 39 and 89 acute burn patients also demonstrated low anti-Xa levels [33,34]. Lin et al. demonstrated that they could improve anti-Xa levels by utilizing a more aggressive dosing strategy. They treated patients with 30 mg enoxaparin twice daily or utilized a weight-based dose (0.5 mg/kg twice daily) for patients with BMI > 35 kg/m^2. They actively targeted appropriate prophylactic anti-Xa levels by increasing enoxaparin dosing by 20% if patients were below target and concluded that burn patients should be started on a higher initial enoxaparin dose [33]. Inadequate anti-Xa prophylaxis has also been shown in pediatric burn patients receiving standard enoxaparin dosing [35]. Here, in 157 burn injured patients, we demonstrated that increased body weight and BMI are associated with inadequate DVT prophylaxis when standard enoxaparin dosing strategies are utilized. This results of these studies demonstrate that improved pharmacologic strategies are needed to provide optimal DVT prophylaxis to burn patients.

Limitations of this study include its retrospective nature and the exclusion of many potential patients due to non-standard dosing regimens that were utilized based on our recent data in trauma patients showing an improved ability to reach target anti-Xa levels on the first anti-Xa level with an altered dosing strategy that starts most patients at a 40 mg twice daily dose [18]. We also enrolled a limited number of patients with large TBSA burns, making it difficult to evaluate the effect of burn size on anti-Xa levels. Finally, while we did not identify an improvement in DVT rates in patients treated with enoxaparin dose adjustments, it is important to note that this study is not adequately powered for, and was not designed to find, differences in DVT rates between groups. A larger, multi-center, study will be needed to determine the effect of anti-Xa targeted enoxaparin prophylactic dosing regimens on DVT rates.

6. Conclusion

Burn patients are at high risk of DVT and are likely not receiving adequate prophylaxis with the standard prophylactic enoxaparin dosing strategy. This study demonstrates that over half of the burn patients evaluated in this study received sub-optimal DVT prophylaxis. Our findings suggest that alternate DVT prophylaxis strategies, including a weight or BMI-based enoxaparin dosing algorithm should be implemented and studied in the burn population. While it is unclear whether targeting anti-Xa levels will decrease DVT rates, the potential morbidity associated with chronic DVT, in addition to the increased scrutiny on hospital DVT rates as a metric for

hospital quality, necessitates improved treatment strategies for DVT prophylaxis.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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