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Evaluating chemical venous thromboembolism prophylaxis in trauma patients at a single Australian center

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Purpose: Trauma patients are at an elevated risk of developing venous thromboembolism (VTE), with the subsequent mortality in patients requiring intensive care unit admission ranging from 25% to 38%. There remains significant variability in clinical practice related to VTE prophylaxis in trauma patients due to the frequent presence of contraindications impacting the timing and consistency of application. This study aimed to assess the effectiveness of the current practice of chemical VTE prophylaxis in trauma patients at a single Australian center.

Methods: A prospective review was conducted on patients admitted to the ACT Trauma Service (Canberra, Australia) from July to November 2022. The included patients were 18 years or older, without a direct contraindication to anticoagulation, who received chemical VTE prophylaxis with low-molecular-weight heparin (enoxaparin) for at least three doses and underwent subsequent testing of anti-factor Xa (aFXa) levels.

Results: During the study period, 187 patients were admitted, of whom 63 were included in the study. Of these, 47 patients achieved therapeutic levels of anticoagulation as determined by their aFXa levels, while 16 were subtherapeutic. The only statistically significant difference between the two groups was in weight, with patients in the subtherapeutic group weighing an average of 91.9 kg compared to 79.1 kg in the therapeutic group (P<0.05).

Conclusions: A fixed-dose enoxaparin regimen was utilized, with limited individualization based on patient factors, such as injuries, comorbidities, and other biological factors. Sixteen patients (25%) had subtherapeutic VTE prophylaxis, as measured by aFXa levels. Higher weight was significantly correlated with inadequate VTE prophylaxis dosing. While age, sex, and smoking status might play important roles in clinical decision-making, weight-based dosing of low-molecular-weight heparin may be more effective in achieving adequate VTE prophylaxis.

Keywords: Wounds and injuries; Venous thromboembolism

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INTRODUCTION

Background

Trauma patients are at an elevated risk of developing venous thromboembolism (VTE), which refers to the formation of blood clots in the veins, typically presenting as deep vein thrombosis of the lower limbs and potentially leading to pulmonary embolism. The incidence of VTE after trauma can range from

5% to 63%, depending on patient risk factors, the modality of prophylaxis, and the method of detection [1,2]. Several mechanisms contribute to this risk, including a trauma-induced state of hypercoagulability resulting from disruption of the regulation of thrombin, a key enzyme in the coagulation cascade, leading to significantly increased and persistent thrombin generation [3]. In addition, trauma often results in immobilization and lower extremity venous stasis, which is a known major risk factor for VTE [4,5].

Trauma patients admitted to the intensive care unit (ICU) are at an even greater risk of VTE. Despite the frequent administration of VTE prophylaxis, which occurs in 90% of these cases, the incidence of VTE in posttraumatic ICU patients is 28%, markedly higher than the average rate of 10% in the ICU [6,7]. Moreover, trauma patients in the ICU are more susceptible to severe complications from VTE. The incidence of pulmonary embolism in this group is around 3%, with a mortality rate that varies between 25% and 38% [8,9].

There is considerable variability in clinical practice regarding VTE prophylaxis in trauma patients, often due to contraindications that significantly impact the timing and consistency of its application [10]. Although there have been several attempts to standardize pharmacologic VTE prophylaxis in these patients, the effectiveness of these protocols has yet to be studied [11,12].

Enoxaparin, a type of low-molecular-weight heparin (LMWH), is commonly used for VTE prophylaxis in trauma patients due to its superiority over unfractionated heparin in these situations. Dosing regimens can be categorized as fixed (high or low), stratified, or based on weight or body mass index (BMI); however, the dosing for the general trauma patient population remains a matter of debate [13–15]. Enoxaparin catalyzes the binding of antithrombin with coagulation factors Xa and IIa, accelerating the process and potentiating the anticoagulation effect. It can therefore be monitored by measuring anti-factor Xa (aFXa) levels [15]. However, monitoring the pharmacodynamic activity of enoxaparin via aFXa levels might sometimes be suboptimal, and weight-based dosing of enoxaparin is arguably more effective in achieving the goal aFXa levels for VTE prophylaxis, but this is difficult to observe because the timing required for level measurement and weight can be difficult to obtain in the trauma setting [16,17].

Objectives

This study assessed the effectiveness of the current practice of chemical VTE prophylaxis in trauma patients at a single Australian center.

METHODS

Ethics statement

This study's protocol was reviewed and approved on by the ACT Health Human Research Ethics Committee (Low Risk Research Pathway; No. 2022/ETH11550). The requirement for informed consent was waived. The study was conducted in compliance with the principles of the Declaration of Helsinki.

Study design and setting

A prospective review was performed on patients admitted to the ACT Trauma Service from July 2022 to November 2022.

Participants

The inclusion criteria were all patients aged 18 years or older who had received chemical VTE prophylaxis with enoxaparin for at least three doses. Following three doses of enoxaparin, aFXa levels were assessed daily. If two consecutive aFXa levels fell within the target range, the frequency of testing was reduced to weekly.

Patients were excluded from the study if they were under 18 years old, pregnant, incarcerated, or if death occurred within 48 hours. Exclusion criteria also included actual or suspected spinal cord injury, discharge before receiving three doses of enoxaparin, or a medical indication for therapeutic anticoagulation. Additionally, patients were excluded if the treating clinician determined a medical need for unfractionated heparin over enoxaparin for VTE prophylaxis.

Protocol

The chemical VTE prophylaxis protocol implemented involved administering subcutaneous enoxaparin at a dosage of 40 mg every 24 hours. The dose could be adjusted to either 20 or 60 mg every 24 hours, depending on the patient's weight and other biological factors, at the discretion of the treating clinician. Enoxaparin therapy was considered subtherapeutic if the trough aFXa level was below 0.1 IU/mL or if the peak level was below 0.4 IU/mL [15,17]. Obesity was defined as having a BMI greater than 30 kg/m^2. Injuries were graded using the Abbreviated Injury Scale [18,19].

Data collection

The data collected included demographic factors, comorbidities, injuries, VTE prophylaxis method, biochemistry including aFXa levels, and complications. Data collection was performed using the REDCap system (Vanderbilt University), and records were collated using Microsoft Excel (Microsoft Corp).

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Statistical analysis

Differences in demographic factors and injuries between therapeutic and subtherapeutic anticoagulation groups were assessed using the t-test for continuous variables and the Fisher exact test for categorical variables. Associations between demographic factors and subtherapeutic aFXa levels were evaluated through multivariable log-binomial regression. Data analyses were conducted using Stata BE 17 (Stata Corp).

RESULTS

The baseline characteristics of the study population are outlined in Table 1. Twenty-two patients (35%) were female. The mean BMI was 27.0 ± 5.4 kg/m^2. The prevalence of active smoking was 17%.

Differences in demographic factors and injuries related to target aFXa levels are presented in Table 2. The only statistically significant difference between the two groups was in weight, with patients in the subtherapeutic group weighing 91.9 kg compared to 79.1 kg in the other group (P < 0.05).

Three patients received a daily dose of 60 mg of enoxaparin. All three patients weighed over 90 kg and achieved target aFXa levels.

The associations between demographic factors and subtherapeutic anticoagulation are presented in Table 3.

DISCUSSION

Venous thromboembolism is a serious adverse event that has an elevated risk of occurrence in trauma patients, leading to significant morbidity and mortality [8,9,17,20]. Therefore, several measures have been implemented with the goal of preventing VTE, including mechanical and chemical prophylaxis [17]. Despite this, the ideal dosing regimen and protocol for monitoring pharmacological effects have not been established. As with many institutions, a fixed-dose regimen for enoxaparin was utilized in

Table 1. Characteristics of the study population (n=63)

Characteristic	No. of patients (%)
Sex	
Male	41 (65)
Female	22 (35)
Risk factor	
Age (yr)	58.2±21.1 (17–94)[a]
Body mass index (kg/m^2)	27.0±5.4[a]
Obesity	15 (24)
Active smoking	11 (17)
Oral contraceptive (n=22)[b]	1 (5)
Hormonal replacement therapy (n=22)[b]	1 (5)
Abbreviated Injury Scale ≥2	
Head	6 (10)
Chest	42 (67)
Abdomen	6 (10)
Enoxaparin dosing	
40 mg daily dose	58 (92)
60 mg daily dose	3 (5)
Other dosing[c]	2 (3)
aFXa monitoring	
Trough level performed	54 (86)
Peak level performed	11 (17)
Subtherapeutic anticoagulation	16 (25)
Based on trough aFXa	9 (14)
Based on peak aFXa	7 (11)

aFXa, anti-factor Xa.
[a]Values are presented as mean±standard deviation (range) or mean±standard deviation. [b]Female patients only. [c]One patient received a 10 mg daily dose, and one patient's daily dose was changed from 40 to 60 mg half-way through admission.

Table 2. Difference between the therapeutic and subtherapeutic aFXa groups (n=63)

Anticoagulation	aFXa		P-value[a]
	Therapeutic (n=47)	Subtherapeutic (n=16)	
Demographic factor			
Mean age (yr)	58.6	56.8	0.767
Mean weight (kg)	79.1	91.9	0.016*
Mean BMI (kg/m^2)	26.3	29.2	0.059
Abbreviated Injury Scale ≥2			
Head (%)	12.8	0	0.324
Chest (%)	66.0	68.8	>0.999
Abdomen (%)	10.6	6.3	>0.999

aFXa, anti-factor Xa; BMI, body mass index
[a]P-value from the t-test for continuous variables and the Fisher exact test for categorical variables.
*P<0.05.

Table 3. Associations between demographic factors and subtherapeutic anti-factor Xa levels

Factor	RR[a]	95% CI	P-value
Weight (kg)	1.027	1.001–1.053	0.042*
Age (yr)	1.014	0.987–1.042	0.323
Male sex	1.725	0.524–5.678	0.370
Smoking (active)	1.441	0.506–4.107	0.494

RR, relative risk; CI, confidence interval.
[a]Results from multivariable log-binomial regression with subtherapeutic coagulation as the dependent variable.
*P<0.05.

this study, with limited individualization based on patient factors such as injuries, comorbidities, and other biological factors. In total, 25% of patients had subtherapeutic VTE prophylaxis, as measured by aFXa levels. Higher weight was significantly correlated with inadequate VTE prophylaxis dosing. This is supported by research by Nunez et al. [20], in which patients received increased dosing based on weight and 76% of patients achieved the goal aFXa levels compared to 8% on a standard dosing regimen. In 2015, Rostas et al. [13] proposed that a potential mechanism underlying this observation may be that higher weight and associated abdominal wall thickness (including from peripheral oedema) decrease the absorption of any subcutaneously administered medication, including LMWH. However, other studies have suggested that the critically ill trauma population is likely to have an acquired deficiency in antithrombin, along with an increased volume of distribution in patients of a higher weight [13,17]. Several trials have proposed implementing a higher initial dosing regimen and shown that the incidence of subtherapeutic aFXa levels was lower in these groups than in patients who received standard dosing (9% vs. 39%) [17]. The aFXa levels are a surrogate biomarker, with target levels aiming to strike a balance between the likelihood of VTE development and an elevated risk of bleeding [14,20]. In studies where patients received increased dosing regimens, the incidence of bleeding remained low, indicating that this approach is likely to be safe in critically ill trauma patients [15,17,20]. While age, sex, and smoking status might play important roles in clinical decision-making, no differences in these parameters were detected between the two groups in this study population.

Limitations

This study was limited by the inclusion of only a small number of patients, attributable to the brief duration of the study and its single-center design. This limitation also restricted the extent of subgroup analysis for patients with more severe injuries. The limited timeframe was primarily due to the extensive burden of data collection and resource utilization. Patient assessments were conducted exclusively during hospital admissions, with no outpatient evaluations or follow-up data gathered. Additionally, other potential factors that could influence the pharmacokinetics of enoxaparin, such as the use of vasopressors, were not collected.

Conclusions

Higher body weight is significantly associated with subtherapeutic aFXa levels. BMI was not associated with subtherapeutic aFXa levels. Weight-based dosing of enoxaparin (LMWH) may be more effective in achieving adequate VTE prophylaxis.

ARTICLE INFORMATION

Author contributions

Conceptualization: SWC; Data curation: NQ, SWC; Formal analysis: all authors; Methodology: all authors; Project administration: NQ, SWC; Writing–original draft: NQ, MTV; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Data availability

Data analyzed in this study are available from the corresponding author upon reasonable request.

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