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The ATLANTIC study: Anti-Xa level assessment in trauma intensive care

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ABSTRACT

Objective: To quantify the pharmacodynamic (PD) activity of daily subcutaneous (SC) enoxaparin as venous thromboembolism (VTE) prophylaxis in high-risk trauma patients admitted to the intensive care unit (ICU).

Methods: This was a prospective observational PD study conducted in the ICU of a state-wide major trauma referral centre. The study cohort included adult patients admitted to the ICU with a high risk of VTE, as defined by at least one of the following: age > 40 years, prior VTE, spinal cord injury (SCI), traumatic brain injury (TBI), major venous injury, pelvic fractures, spinal fractures requiring treatment, severe lower limb injuries, and major surgery >2 h in duration. Standard prophylactic enoxaparin dosing was 40 mg SC daily, unless amended by the treating clinician. Plasma anti-Xa activity was measured approximately 60 min before dosing (trough activity), and at 3–5 h after dosing (peak activity). Target peak and trough activity were defined as >0.2 IU/mL and >0.1 IU/mL respectively. Clinical data including the development of VTE and haemorrhagic complications were collected.

Results: Twenty-five patients were enrolled. Median [IQR] age, weight, and plasma creatinine were 59 years [36,70], 85 kg [76.5,93.5] and 70μmol/L [60.5,109] respectively. Median APACHE III and Injury Severity Score were 54 [42.5,66.5] and 27 [17,34] respectively. Thirteen patients suffered a TBI, in 12 cases surgery extended beyond two hours, and five patients had spinal fractures requiring treatment. Twenty-two patients received enoxaparin 40 mg SC daily, two 60 mg, and one 20 mg. Median peak and trough anti-Xa activity was 0.21 IU/mL [0.125,0.25] and 0.01 IU/mL [0,0.05] respectively. Twelve (12/25; 48%) patients had low peak activity ≤0.2 IU/mL. Twenty-one (21/23; 91%) patients had low trough activity (≤0.1 IU/mL) and in six (6/23; 26%) cases, these were undetectable. Eight (8/25; 32%) patients had documented VTE of whom seven had low trough activity. There were no major haemorrhagic complications.

Conclusions: In a cohort of high risk critically ill trauma patients receiving daily SC enoxaparin as VTE chemoprophylaxis, measured peak and trough plasma anti-Xa activity was inadequate in a significant proportion. On this basis, further systematic investigation concerning dose optimisation in this patient population appears warranted.

Introduction

Major trauma patients are at high risk of venous thromboembolism (VTE) due to a hypercoaguable state [1], major injuries, prolonged bed rest, and other factors [2]. Certain injuries including pelvic fractures, venous injury, traumatic brain injury (TBI), spinal cord injury (SCI), lower limb fractures, and prolonged ventilation increase this risk within the trauma population [3–7].

Chemical VTE prophylaxis can be provided by fractionated heparin, unfractionated heparin, or other factor Xa inhibitors such as fondiparinaux [8]. Factor Xa inhibitors act on the final common clotting pathway to inhibit haemostasis. In Australia and New Zealand (ANZ), subcutaneous (SC) low molecular weight heparin (LMWH), typically administered daily, is routinely provided in the ICU for this purpose [9,10]. A similar strategy is utilised in Europe [11].

Currently, it is not standard practice in ANZ to measure anti-Xa activity in patients receiving prophylactic LMWH. However, existing data suggest dose adjustment based on peak anti-Xa levels, may reduce the incidence of deep vein thrombosis (DVT) [12–16].

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Moreover, higher empirical dosing (e.g. 30 mg SC enoxaparin BD) may still provide inadequate chemoprophylaxis in many patients, as evidenced by low anti-Xa activity and the development of VTE [12–15,17,18].

Accordingly, we designed a single centre observational study to assess the pharmacodynamic (PD) activity of SC enoxaparin administered daily in major trauma patients admitted to the ICU at high risk of VTE. We hypothesised that daily exposure to SC LMWH would offer limited chemoprophylaxis, based on measured peak and trough anti-Xa activity. We also sought to explore the relationship between anti-Xa activity, clinical VTE, and haemorrhagic complications.

Methods

This was a prospective observational PD study conducted in the ICU of a state-wide major trauma referral centre. Approval to undertake the study was granted by The Alfred Hospital (Melbourne, Victoria, Australia) Human Research Ethics Committee (Project No. 213/17). Informed written consent was obtained from either the patient or a substitute decision maker in all cases.

Patient selection

All adult patients (>18 years of age) admitted to the ICU following major trauma and receiving daily SC LMWH VTE chemoprophylaxis were screened for inclusion. In addition, all eligible patients had to have at least one of the following high-risk features for developing VTE [2,5]:

- Pelvic fracture
- Spinal fracture requiring operative fixation
- Spinal cord injury
- Age >40 years
- Major operative procedure > 2 h
- Major venous injury requiring repair
- Major lower limb injury with Abbreviated Injury Score (AIS) ≥3
- Traumatic brain injury with Abbreviated Injury Score (AIS) ≥3
- Past history of DVT or PE

Patients were excluded if death was deemed imminent within the next 24-hours, the clinician considered enrolment inappropriate, or they were pregnant, receiving renal replacement therapy or therapeutic anti-coagulation. The cohort therefore represents a convenience sample of critically ill trauma patients at high-risk of VTE.

LMWH dosing protocol, anti-Xa measurement, and data collection

Patients received 20 mg, 40 mg, or 60 mg daily SC enoxaparin depending on weight and renal function as per pre-existing institutional guidelines (see Supplementary Appendix 1). Patients weighing 50–130 kg with an estimated glomerular filtration rate (eGFR) > 30 ml/min were administered 40 mg SC daily; patients weighing <50 kg or with an eGFR ≤ 30 ml/min were prescribed 20 mg SC daily; patients weighing >130 kg were administered 60 mg SC daily. Peak and trough plasma anti-Xa activity were obtained between the second to eighth dose of enoxaparin. Peak activity was measured 3–5 h after the most proximate dose, and trough activity measured prior to dosing. All samples were obtained via existing intra-arterial access using standard aseptic technique, and forwarded immediately to our institutional pathology laboratory for anti-Xa assay. Adequate prophylactic peak anti-Xa activity was defined as > 0.2 IU/ml. Adequate trough activity was defined as >0.1 IU/ml [11].

Additional data concerning patient demographics, admission characteristics, illness severity including APACHE III and AIS, and treatment provided were also collected. Creatinine clearance was calculated by the Cockroft-Gault equation. Specifically, the development of VTE, haemorrhagic complications (as defined by the clinician), and red blood cell transfusion requirements were also extracted from the clinical record. Screening for VTE at our institution is regularly performed in the ICU by performing twice weekly lower leg venous ultrasonography. Additional imaging (such as computed tomography pulmonary angiography) was at the discretion the treating clinician.

Statistical analysis

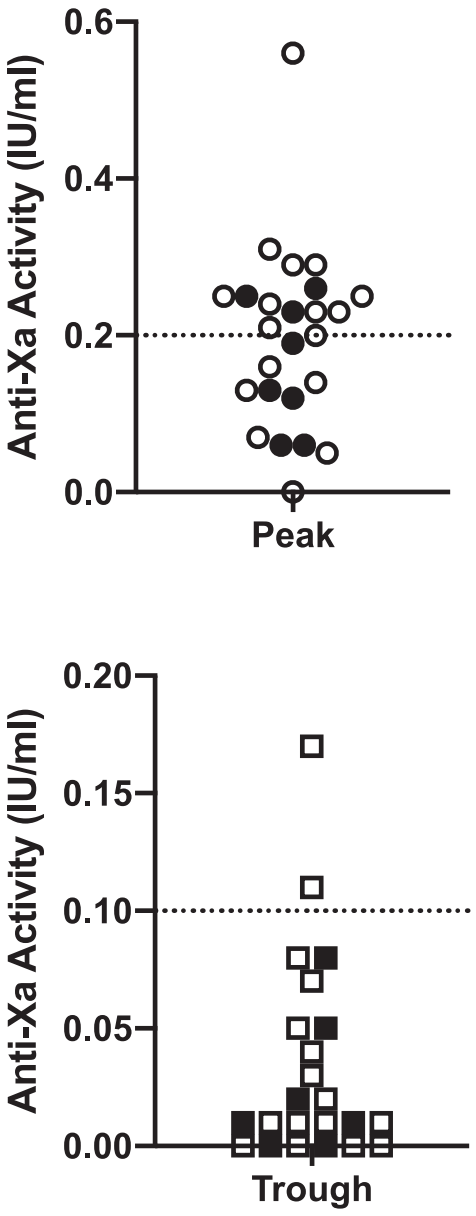
Continuous data are presented as the median [IQR]. Categorical data are provided as counts (%). Statistical reporting is as per the SAMPL Guidelines [19]. Between group comparisons utilised a Wilcoxon Rank Sum Test or Fisher's Exact Test, where analysis assumptions were met. Statistical significance was set at $p < 0.05$, and all analyses were undertaken using Stata XVIII (Texas, USA). Previous data suggests that following a single daily dose of 40 mg SC enoxaparin in ICU, approximately 80% of patients manifest subtherapeutic anti-Xa activity at 24-hours post dose [11]. As such, we calculated that a convenience sample of 25 patients would provide over 85% power (alpha 0.05) to detect a 25% absolute difference in this proportion in major trauma victims.

Results

From June 2017 until November 2018, 25 patients were enrolled into the study. Demographic data, injury pattern, illness severity, and VTE risk factors are summarised in Table 1. Twenty-two (22/25; 88%) patients received 40 mg SC enoxaparin daily, one (1/25; 4%) received 20 mg, and two (2/25; 8%) received 60 mg. The median number of doses administered prior to anti-Xa plasma sampling was 2 [IQR 2,5]. The median time to first dose of enoxa-

Table 1
Patient characteristics (Median [IQR]; Number (%)).

Patient characteristic	
Age (years), median [IQR]	59 [36,70]
Weight (kg), median [IQR]	85 [76.5,93.5]
Male (%)	18/25 (72%)
APACHE III score, median [IQR]	54 [42.5,66.5]
Injury severity score (ISS), median [IQR]	27 [17,34]
Number of high risk features, median [IQR]	2 [1,3]
High risk features	
Pelvic fracture (%)	3/25 (12%)
Spinal fracture requiring treatment (%)	6/25 (24%)
Spinal cord injury (%)	0
Age > 40 years (%)	19/25 76%)
Major operative procedure >2 h (%)	12/25 (48%)
Major venous injury requiring repair (%)	0
Major lower limb injury with AIS ≥3 (%)	3/25 (12%)
Traumatic brain injury AIS ≥3 (%)	13/25 (52%)
Past history of VTE (%)	0
Mechanism of injury	
Motor vehicle accident - driver (%)	8/25 (32%)
Motorbike accident (%)	2/25 (8%)
Fall-standing (%)	4/25 (16%)
Other (%)	11/25 (44%)
Vasopressors at time of enoxaparin (%)	6 /25(24%)
Mechanically ventilated (%)	4/25 (16%)
Laboratory results	
Platelets (10^6/ml), median [IQR]	293 [190,403]
INR, median [IQR]	1.1 [1.1,1.2]
APTT (seconds), median [IQR]	31.5 [29.1,35.6]
Fibrinogen (g/L), median [IQR]	6.7 [5.5,7.7]
Creatinine (μmol/L), median [IQR]	70 [60.5,109]
Creatinine clearance (ml/min), median [IQR]	115 [76,155]
Augmented renal clearance; CrCl > 130 ml/min (%)	7/25 (28%)



Peak (3-5 h post dose, circles) and trough (60 min prior to dosing, squares) anti-Xa activity. Patients with documented DVT are represented by opaque symbols. Dotted lines represent satisfactory peak >0.2IU/ml and trough >0.1IU/ml measurements.

Fig. 1. Peak and Trough Anti-Xa Activity. Peak (3–5 h post dose, circles) and trough (60 min prior to dosing, squares) anti-Xa activity. Patients with documented DVT are represented by opaque symbols. Dotted lines represent satisfactory peak >0.2 IU/ml and trough >0.1 IU/ml measurements.

parin was 96 [52.6,175] hours. In two patients a trough level was not obtained due to logistic issues.

Anti-Xa activity

The distributions of measured peak and trough anti-Xa activity are provided in Fig. 1. The median [IQR] peak anti-Xa activity was 0.21 [0.125,0.25] IU/ml measured a median of 4.08 h [4,4.5] after dosing. Twelve (12/25; 48%) patients had peak anti-Xa activity ≤0.2 IU/ml. All of these patients had corresponding low trough activity ≤0.1 IU/mL. In univariate testing, the only difference identified between patients with adequate compared with low peak activity was the APACHE III score (median 65 [45.8–74], low peak versus 49 [38–56], adequate peak, $p = 0.03$); see Supplementary Table 1.

Median [IQR] trough anti-Xa activity was 0.01 IU/ml [0,0.05] at 1 h [0.8,1.2] before subsequent dose administration. Six (6/23; 26%) patients had undetectable trough anti-Xa activity. Twenty-one patients (21/23; 91%) had trough activity ≤0.1 IU/ml, which in reference to our sample size calculation, is not significantly different ($p = 0.27$) from that previously reported in the literature. The relationship between Cockcroft-Gault estimated creatinine clearance

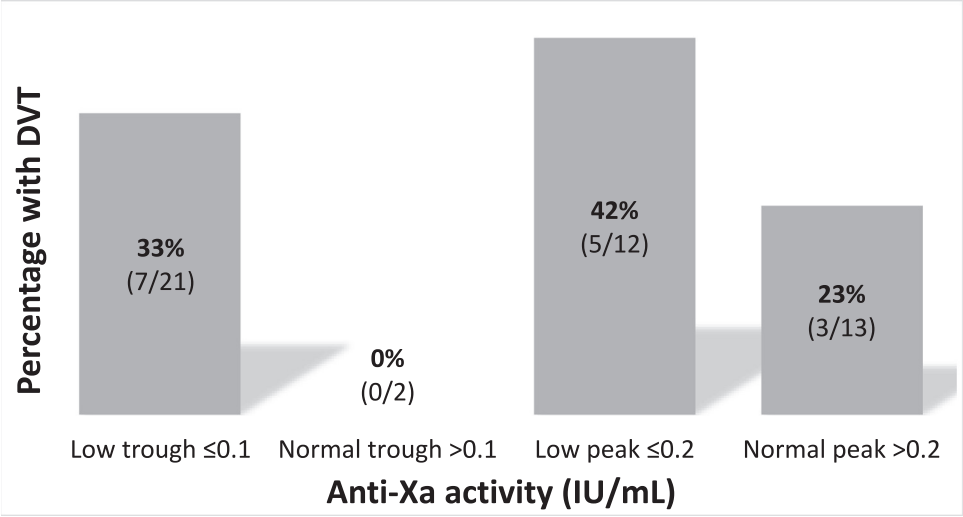


Fig. 2. Percentage of patients with DVT stratified by anti-Xa activity.

and peak and trough anti-Xa activity is provided in the supplementary appendix (Supplementary Figure 1 and Supplementary Figure 2).

Clinical outcomes

Twenty (20/25; 80%) patients had graduated compression stocks applied. IVC filters were inserted in 5 (5/25; 20%) patients. Eight (8/25; 32%) patients had a DVT of which two were above knee and six were below knee. None were in the upper limb. There were no recorded episodes of pulmonary embolism.

Median peak and trough anti-Xa activity in patients with DVT were 0.16 IU/ml [0.08,0.25] and 0.01 IU/ml [0,0.05] respectively compared with 0.23 IU/ml [0.14,0.27] and 0.02 IU/ml [0.003,0.07] in patients without DVT ($p = 0.32$ and $p = 0.68$ respectively). Amongst the 12 patients with low peak anti-Xa activity, five (42%) had documented lower limb DVT compared with three (3/13, 23%) where this was > 0.2 IU/ml (Fig. 2). One patient had a DVT but did not have a trough level measured. Of the 21 patients with low trough levels, seven (33%) had DVT. No DVTs were reported in patients with adequate trough activity (Fig. 2). Amongst the 21 patients with low trough activity, there was no difference in the incidence of DVT between those with adequate or low peak levels (3/11, 27% vs 4/10, 40%; $p = 0.66$).

A higher frequency of VTE was noted when there was $a >$ 48 h delay in commencing enoxaparin compared with earlier commencement (7/20, 35% vs 1/5, 20%), although this was not statistically significant ($p = 1.0$); Supplementary figure 3. The incidence of VTE was 35% (6/17) in patients with 1–2 high-risk features compared with 25% (2/8) in those with three or more ($p = 1.0$; Supplementary figure 4).

Ten (10/25; 40%) patients received blood products in the ICU, although no haemorrhagic complications related to LMWH administration were noted. No patient required massive transfusion after commencement of enoxaparin. A single patient was noted to have elevated peak anti-Xa activity (0.56 IU/ml), although did not require any blood products in ICU. Twenty-four patients (24/25; 96%) were alive at hospital discharge.

Discussion

Key findings

In this single-centre prospective observational PD study of critically ill high-risk trauma patients receiving daily SC enoxaparin as VTE chemoprophylaxis, over 40% had low peak plasma anti-Xa activity, over 90% had inadequate trough anti-Xa activity, and in approximately a quarter ($n = 6$) trough anti-Xa activity was undetectable. Numerically higher rates of VTE were noted in those with low PD indices. These results imply that LMWH administered in this manner, in this patient group, may offer only limited VTE chemoprophylaxis.

Relationship with previous studies

Other studies have also demonstrated low peak anti-Xa activity with SC LMWH administration [11,13,20]. However, the clinical implications of such findings are uncertain. A large retrospective study in trauma patients from North America demonstrated no reduction in VTE with twice daily fractionated heparin dosed to achieve peak anti-Xa levels of 0.2–0.4 IU/ml [18]. In comparison, several other studies in trauma patients, including one prospective cohort study, have demonstrated that prophylactic anti-Xa activity can be achieved by up-titrating doses and that these adjustments were associated with a reduction in DVT [13,15,16]. Doses in these trials have been increased to a maximum of 0.55 mg/kg or 60 mg enoxaparin BD to minimise bleeding. In our cohort, DVTs were numerically more common in patients with low measured anti-Xa activity although there was no statistically significant association between the two variables.

The incidence of DVT in our cohort was 32%. This is higher than the range of 16–18% quoted in the EPO-TBI trial [7], and higher than the 12% reported by Barrera et al. in a systematic review of VTE in trauma patients not receiving prophylaxis [21]. This is likely due to pre-selection of high-risk patients and our institutional policy of twice weekly ultrasound surveillance in this cohort.

Study implications

These data imply that the administration of a fixed daily dose of SC enoxaparin in high risk critically ill trauma patients may not confer adequate VTE chemoprophylaxis, and that this practice warrants further investigation. The results remind the prescriber of the importance of considering anthropometric or physiological variables (such as renal function) in empirical dose selection. Indeed, others have described lower anti-Xa activity in patients receiving enoxaparin with augmented renal clearance [22], which is a common finding in this cohort of patients [23]. As such, major trauma patients may benefit from twice daily SC administration, as is routine in North America [18], although this has not been

the subject of a high-quality randomised controlled clinical trial. Moreover, simply increasing the daily dose may expose patients to higher peak anti-Xa activity, and therefore a greater risk of haemorrhagic complications.

As such, our data imply a potential role for routine anti-Xa monitoring, so as to allow dose optimisation. In this respect, the cost of processing an anti-Xa level at our institution is ~$40 AUD per occasion, representing an affordable sum in comparison to the total daily cost of delivering intensive care. Indeed, given the high proportion of patients with very low or undetectable trough anti-Xa activity in the study cohort, and the relative cost implications, further controlled clinical investigation utilising such an approach appears justified.

Strengths and limitations

This was an observational PD study conducted in a single major trauma centre only. However, it is one of only a few prospective investigations measuring anti-Xa activity in patients receiving VTE prophylaxis, and the first from ANZ. The study cohort was a homogenous group of major trauma victims, at high risk of VTE, receiving 'standard' chemoprophylaxis. Although renal function and body mass did vary between patients (resulting in different clinician directed prophylactic doses), the vast majority of participants received 40 mg enoxaparin SC daily.

There was also some degree of temporal heterogeneity in when anti-Xa activity was assessed (second to eighth dose of enoxaparin). In addition, we only sampled one peak and trough level per patient, and therefore cannot comment on what happens to anti-Xa activity over time. Ward patients were not included in this study, and although these patients potentially have a similar VTE risk, we are not able to comment on the anti-Xa activity routinely achieved in this setting, with this dosing strategy. Finally, enoxaparin is not the only fractionated heparin, and other agents may have different pharmacokinetics warranting different dosing protocols.

Conclusions

In a cohort of high risk critically ill trauma patients receiving daily SC enoxaparin as VTE chemoprophylaxis, measured peak and trough plasma anti-Xa activity was sub-optimal in approximately 50% and 90% respectively, which may infer a greater VTE risk. Further systematic investigation concerning dose optimisation in this patient population appears warranted.

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Declaration of Competing Interest

We disclose that there is no conflict of interest, be it financial or personal, that could inappropriately bias our work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2019.10.066.

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