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Factor Xa Levels in Patients receiving Prophylactic Enoxaparin Sodium in the Intensive Care Unit of an Academic Hospital

Mayank M Baloo[1], Juan Scribante[2], Helen Perrie[3], Daren Calleemalay[4], Shahed Omar[5]

Abstract

Background: The aim of this study was to determine the anti-factor Xa levels in patients receiving enoxaparin sodium for venous thromboembolism prophylaxis in the intensive care unit (ICU).

Patients and methods: Using a cross-sectional study methodology, 73 ICU patients receiving 40 mg enoxaparin sodium daily were enrolled in this study. Anti-factor Xa levels were measured following the second dose. Prophylactic and subprophylactic groups of patients were compared for age, sex, weight, body mass index, total bilirubin, serum albumin, and APACHE II score.

Results: Anti-factor Xa levels were prophylactic (0.2–0.6 IU/mL) in 44 (60.3%) patients and subprophylactic (<0.2 IU/mL) in 29 (39.7%) patients. The mean (SD) actual delivered dose of enoxaparin per kilogram body weight was significantly higher, at 0.59 (0.11) mg/kg in the prophylactic group compared to 0.53 (0.13) mg/kg in the subprophylactic group ($p = 0.043$). The subprophylactic group had significantly lower serum albumin levels compared to the prophylactic group. The total bilirubin levels were not found to be significantly different between the two groups ($p = 0.110$).

Conclusion: A fixed prophylactic 40 mg dose of enoxaparin was associated with a high proportion of subprophylactic anti-factor Xa levels. Weight-based dose and serum albumin level were independent predictors of achieving the prophylactic target range.

Keywords: Anesthesia, Enoxaparin, Intensive care unit, Pharmacokinetics–pharmacodynamics, Prevention of VTE, Venous thromboembolism, Venous thromboembolism (VTE) prophylaxis.

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Introduction

Venous thromboembolism (VTE) is a well-known complication in the perioperative period in patients with decreased mobility in the hospital, and a standardized drug regimen is recommended in VTE prophylaxis.[1] The drug of choice is a low-molecular-weight heparin (LMWH) such as enoxaparin sodium, commonly known as enoxaparin, and the standard dose is 40 mg subcutaneously daily.[2] Enoxaparin is used due to its ease of subcutaneous administration, monitoring is not routinely required, and it has a more advantageous side effect profile when compared to intravenously administered unfractionated heparin.[2] Despite prophylaxis, VTE remains a significant complication among immobile hospitalized patients.[3] The incidence of VTE in Australia in 2014 was 2 per 1,000 patients annually, with a mortality of 8% despite prophylaxis.[4] The survival following VTE is shown to be worse if the patient suffered a pulmonary embolism compared to a deep vein thrombosis.[5]

Enoxaparin is a low-molecular-weight heparin (LMWH).[6] LMWHs have a smaller chain structure than unfractionated heparin; therefore, they have more anti-factor Xa activity.[6] Maximal plasma doses are reached within 2 hours with a peak effect at 4 hours and a half-life of 4 hours.[6] The tests to determine the efficacy of LMWH are limited by their structure.[7] Factor Xa assays are used to monitor anti-factor Xa levels in the blood plasma.[8]

VTE prophylaxis using enoxaparin 40 mg subcutaneously daily is the standard treatment in adult patients in the intensive care unit (ICU) at our institution, provided there are no contraindications. However, it is not known whether this dose provides adequate prophylactic levels in these patients. Therefore, the aim of this study was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin in the ICU.

Methods

A cross-sectional study was conducted in a multidisciplinary ICU. The hospital is a 2,888-bed central academic hospital affiliated to a university. The ICU has 27 beds and admits both adult and pediatric patients, with approximately 750 admissions annually.

The study was approved by the Human Research Ethics Committee (Medical) of the university. Written informed consent was obtained from each patient or their surrogate before enrolling

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in this study. Deferred consent was obtained from all patients who had surrogate consent when they were able to give informed consent.

All adult patients admitted to the ICU between November 2019 and January 2020 receiving 40 mg enoxaparin daily were considered for enrolment into the study. The exclusion criteria in this study were patients with an eGFR of <60 mL/minute, patients who did not receive a 06:00 dose of enoxaparin, blood samples collected or stored incorrectly, and patients receiving therapeutic enoxaparin dosing. Patients were classified into two groups, prophylactic and subprophylactic.

All ICU admissions were screened daily, and blood samples were taken in a sterile standardized manner 3 hours after the second prophylactic enoxaparin dose by one author (MB). Blood was collected in a 5 mL citrate tube from preferentially an arterial line or if not possible by venipuncture, stored at −20°C, and analyzed by an accredited laboratory in batches of ten. For this study, the prophylactic range was regarded as an anti-factor Xa level from 0.2 to 0.6 IU/mL[2].

The primary objective was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin following the second dose administered in the ICU. The secondary objectives were to describe and compare the following factors between the prophylactic and the subprophylactic groups: age, sex, weight, body mass index (BMI), total bilirubin, serum albumin, and severity of illness using the APACHE II score. Independent predictors of a prophylactic level were also determined.

Analysis was done in consultation with a statistician using the statistical program STATA version 13.1 (StataCorp, USA). Categorical data were described using frequencies and percentages. Independent *t*-tests were used to compare normally distributed data and Mann–Whitney tests for data not normally distributed. Regression analysis was performed on significant predictors of prophylactic anti-factor Xa levels. A *p*-value of 0.05 or less was considered statistically significant.

Results

A total of 77 patients were assessed for eligibility. Bloods for anti-factor Xa levels were taken from each patient. Four patients were excluded: one patient due to laboratory error and three patients were later found to have received therapeutic enoxaparin sodium dosing. A total of 73 patients were thus included in the study.

The anti-factor Xa levels of all patients and for those falling in the prophylactic and subprophylactic ranges are given in Table 1. A comparison of patient characteristics between the prophylactic and subprophylactic groups is provided in Table 1.

There was a statistically significant difference between the two groups regarding weight, BMI, and APACHE II score, with those in the prophylactic group having lower values for all three.

The mean (SD) actual delivered dose of enoxaparin per kilogram body weight was significantly higher, at 0.59 (0.11) mg/kg in the prophylactic group ($n = 44$) compared to 0.53 (0.13) mg/kg in the subprophylactic group ($n = 29$) ($p = 0.043$).

Patients in the subprophylactic group were found to have significantly lower serum albumin levels compared to those in the prophylactic group, while total bilirubin levels were not found to be significantly different between the two groups. See Table 2.

Using a multiple regression model that included total bilirubin, serum albumin, weight-based delivered dose of enoxaparin, and APACHE II score, only a higher serum albumin ($p = 0.013$) and a greater weight-based delivered dose ($p = 0.033$) were independent predictors of being in a prophylactic range.

Discussion

The main finding of this study was that the standard dosing of enoxaparin of 40 mg daily did not always achieve its intended prophylactic range. Only 60.3% of patients were found to be within the prophylactic range. In a group of surgical and trauma patients, Wall et al.[9] found that 41.8% of patients had an anti-factor Xa level in the prophylactic range. Their patients had a similar BMI to our patients. The lower proportion of patients that reached the prophylactic target range in their study is likely explained by the difference in the study population and dosing. Their study included only surgical and trauma patients, while our study included medical, surgical, and obstetric patients.[9] With regard to dosing of enoxaparin, our study used a 40 mg dose of enoxaparin compared to 30 mg twice daily used by Wall et al.[9] It has been demonstrated that trauma patients have a higher risk of developing augmented renal clearance.[10] This higher renal clearance could result in an increased clearance of enoxaparin and hence a lower proportion of patients reaching the desired prophylactic level. Mayr et al.[11] studied similar patients to ours, receiving 40 mg enoxaparin daily, and found 56.5% of patients to be within the recommended prophylactic range.[11] This is similar to our finding of 60.3%.

When calculating the delivered dose of enoxaparin per kilogram body weight in our study group, a significant difference was found with the group achieving prophylactic levels receiving a dose of 0.59 mg/kg, while the subprophylactic group received only

Table 1: Comparison of patient characteristics

	Groups			
Characteristics	*All (n = 73)*	*Prophylactic*	*Subprophylactic*	*p value*
		n (%)		
Male	41 (56.2)	23 (56.1)	18 (43.9)	0.475
Female	32 (43.8)	21 (65.6)	11 (34.4)	
		Mean (SD)		
Anti-factor Xa levels	0.25 (0.12)	0.33 (0.09)	0.13 (0.03)	N/A
Age (years)	39.7 (16.2)	37.9 (16.9)	42.3 (15.0)	0.253
Weight (kg)	74.1 (19.4)	68.9 (13.4)	80.5 (25.0)	0.043
BMI (kg/m^2)	27.1 (7.8)	25.3 (5.0)	29.8 (10.3)	0.036
APACHE II score	11.5 (6.0)	10.4 (4.6)	13.2 (7.3)	0.045

Table 2: Comparisons between groups for serum albumin and total bilirubin levels

	Groups			
Test	*All*	*Prophylactic*	*Subprophylactic*	*p value*
		Median (IQR)		
Total bilirubin (μmol/L)	8.0 (5.5–13.0)	8.0 (5.0–10.0)	11.0 (6.0–21.5)	0.110
		Mean (SD)		
Serum albumin (gm/L)	31 (10.4)	34.4 (10.5)	27.8 (9.0)	0.007

0.53 mg/kg. The relevance of this weight-based delivered dosing is confirmed by Celik et al.[12] Using a morbidly obese group of patients with a mean BMI of 42.2 kg/m^2, the authors showed that a daily dose of 0.63 mg/kg was able to reduce the subprophylactic group to 11.8%,[12] which is lower than found in our study (39.7%) and other studies.[9,11]

Freeman et al.[13] compared three dosing regimens, a fixed dose of 40 mg enoxaparin daily, a low weight-based dose of 0.4 mg/kg daily, and a higher weight-based dose of 0.5 mg/kg daily.[13] Only 18% of the fixed-dose group achieved target anti-factor Xa levels compared to 64% of the low-dose group and 87% of the high-dose group.[13]

In our study, a subprophylactic anti-factor Xa level was associated with a lower serum albumin level (mean 27.8 gm/L) when compared to patients who achieved a prophylactic anti-factor Xa level (mean serum albumin 34.4 gm/L). Pharmacokinetic studies for protein-bound drugs indicate that the protein levels impact on free drug concentration and on elimination rate constants.[14] Chi et al.[15] showed an increasing incidence of VTE from 3.5% among medical patients with serum albumin levels greater than 45 gm/L to 20% among patients with serum albumin levels of less than 25 gm/L.[15] Regression analysis in our study confirmed that low serum albumin level was an independent predictor of a subprophylactic anti-factor Xa level.

APACHE II score is used as a surrogate for severity of illness in ICU patients and in this study was significantly associated with low anti-factor Xa levels. However, APACHE II score was shown not to be an independent predictor of anti-factor Xa prophylactic levels by regression analysis. The mean APACHE II score in this study was low, mean 11.5, as patients with a higher APACHE II score did not meet the inclusion criteria for the study.

A limitation to this study was that it was a single center, which may reduce generalizability to other populations. The authors suggest that weight-based dosing and cognizance of lower serum albumin levels may provide solutions to adequate dosing and recommend further research in this regard.

Conclusion

In this study, a fixed prophylactic 40 mg dose of enoxaparin was associated with a high proportion of subprophylactic anti-factor Xa levels. Weight-based dose and serum albumin level were independent predictors of achieving the prophylactic target range.

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