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Research Article

WEIGHT-BASED DOSING OF ENOXAPARIN AND ANTIFACTOR XA LEVELS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN MEDICALLY-ILL PATIENTS

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ABSTRACT

Objective: The objective of the study was to evaluate peak antifactor Xa (aFXa) levels in low-weight patients receiving enoxaparin for VTE prophylaxis.

Methods: Retrospective cohort of adult patients weighing <55 kg who was hospitalized at tertiary care Center between January 2019 through February 2020. All patients received enoxaparin for VTE prophylaxis with a peak aFXa level drawn. The primary end point was the proportion of patients achieving peak aFXa levels within the goal range of 0.2–0.5 units/ml.

Results: Of 65 patients receiving enoxaparin for VTE prophylaxis with an appropriately timed peak aFXa level, 74% achieved goal peak aFXa levels and the median daily dose of enoxaparin was 30 mg. The mean weight was about 44 kg. No significant correlations between aFXa level and body mass index or body weight were found.

Conclusion: A lower dose of enoxaparin may be reasonable in low-weight patients for VTE prophylaxis. There appears to be no safety concerns with reduced enoxaparin dosing in low-weight patients. More robust data are needed to confirm these findings.

Keywords: Antifactor Xa, Anticoagulation, Enoxaparin, Low-weight, Thromboprophylaxis, Venous thromboembolism.

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INTRODUCTION

Anticoagulants are recommended for hospitalized patients at increased risk for thrombosis, and enoxaparin is often used to prevent VTE [1]. Unlike VTE treatment dosing of enoxaparin, which is weight-based, a fixed dose of 40 mg daily or 30 mg twice daily is recommended for VTE prophylaxis [2]. However, fixed dosing may not be appropriate for all patients [3-6]. In low-weight patients, fixed prophylactic doses of enoxaparin may be close to or even exceed the weight-based dosing recommended for VTE treatment, which may increase risk for bleeding. Low molecular weight heparins exhibit a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa [4]. As such, peak antifactor Xa (aFXa) levels may be utilized to monitor the efficacy and safety of enoxaparin for VTE prophylaxis. To the best of our knowledge, there is a paucity of data in low-weight patients with only one prospective trial evaluating enoxaparin thromboprophylaxis in this particular patient population [7]. Some low-weight patients at our institution were prescribed enoxaparin 30 mg subcutaneously daily for VTE prophylaxis based on the discretion of each clinician. A recent publication and literature review supported this dose in patients with body mass index (BMI) <18 kg/m^2 or total body weight <55 kg.

METHODS

It was a retrospective cohort of adult patients at least 18 years of age admitted tertiary care hospital from its implementation of Electronic Health Record from January 2019 to February 2020. Patients were included if they were low-weight, defined as having an actual body weight <55 kg on admission [7]. In addition, all included patients must have received at least one dose of enoxaparin for VTE prophylaxis with an aFXa level drawn after the dose. Exclusion criteria were enoxaparin use for indication other than VTE prophylaxis, pregnancy, age greater than 89 years, creatinine clearance (CrCL) <30 ml/min, active bleeding, thrombocytopenia with platelets <100,000/mm^3, or concomitant use of other anticoagulants.

The clinical lab confirmed that following an order for an aFXa level, blood samples were collected into a tube containing citrated plasma (1 part 3.2% citrate and 9 parts blood) and on receipt of the sample, aFXa activity was measured immediately using the Berichrom BCS XP (Siemens Healthcare Diagnostics Products, Marburg, Germany) assay. Reportable aFXa values ranged from 0.10 to 1.00 IU/ml. The study protocol was approved by the Institutional Review Board. The primary end point of the study was the proportion of peak aFXa levels within the pre-specified goal range of 0.2–0.5 units/ml. A supplemental analysis was conducted targeting 0.2–0.6 units/ml. Secondary end points included association between BMI or actual body weight and aFXa levels, mean peak aFXa levels based on weight categories of <45 kg, 45 to 50 kg, and greater than 50 kg, and assessment of various factors affecting aFXa levels.

Statistical Analysis

Data analysis was conducted using SPSS Statistics version 22 (IBM Corporation, Armonk, New York). The data were analyzed using descriptive statistics. Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean±standard deviation if normally distributed and median with range if skewed. Multiple linear regression analysis was used to determine variables affecting aFXa levels. Statistical significance was set at $p<0.05$.

RESULTS

As per Table 1 baseline characters of patients who received enoxaparin were screened for study eligibility, of which 65 patients were included. Of these, 35 patients had an appropriately timed peak aFXa level and were included for final analysis. Roughly one-third of patients were male (63%), mean age was 52 years, mean weight was about 44 kg, and 97% of patients had a Padua Prediction Score of at least 4.

As per Table 2 baseline characteristics were not significantly different among the categories of weight, with the exception of higher mean

serum creatinine among those greater than 50 kg when compared to the other weight categories which was found to be statistically significant ($p<0.05$).

As per Table 3 the median dose received was 30 mg daily. Other than two patients who received enoxaparin at a dose recommended by the manufacturer, all patients received daily enoxaparin doses of 30 mg or less, equating to a median weight-based dose of about 0.6 mg/kg/day. Levels were drawn a median of 5 h (interquartile e range of 4–5.5 h) after an enoxaparin dose and the median number of doses given before a level was drawn was 2 (interquartile range of 1–3).

Table 1: Baseline characteristics of study participants

Age (years)	52.11±24.39
Male, n (%)	43 (62.9)
Female, n (%)	22 (37.1)
Weight (kg)	43.63±9.78
<45 kg, n (%)	27 (48.6)
45-50 kg, n (%)	19 (25.7)
>50 kg, n (%)	19 (25.7)
BMI (kg/m^2)	18.52±4.13
<15 kg/m^2, n (%)	6 (17.1)
15–18 kg/m^2, n (%)	21 (31.4)
>18 kg/m^2, n (%)	38 (51.4)
SCr (mg/dl)	0.51±0.22
CrCL (ml/min)	104.10±60.08
NSAIDs, n (%)	2 (5.7)
Aspirin, n (%)	7 (20)
P2Y12 Inhibitor, n (%)	1 (2.9)
Padua prediction score of≥4, n (%)	61 (97)

As per Table 4 46 patients (74.3%) achieved goal peak aFXa levels with a mean aFXa of 0.34±0.11 units/ml after receiving a mean enoxaparin daily dose of 29.54±8.04 mg. Only one patient (2.9%) had an aFXa level that was below goal and 18 patients (22.9%) had an aFXa level that exceeded goal. When evaluating an aFXa goal range of 0.2–0.6 units/ml, 30 (85.7%) patients achieved goal with only four (11.4%) patients above goal and no change in mean daily dose from our analysis targeting an aFXa goal of 0.2–0.5 units/ml.

As per Table 5, a multiple linear regression did not correlate aFXa levels with age, gender, weight, BMI, or CrCL.

DISCUSSION

Most of the patients (74.3%) in our study achieved peak aFXa levels within the pre-specified goal range of 0.2–0.5 units/ml. This occurred even though a vast majority (94.3%) received enoxaparin VTE prophylaxis at doses below the widely accepted 40 mg daily, with a median dose of 30 mg daily or approximately 0.6 mg/kg/day. A prospective trial evaluated adult patients weighing <55 kg who received the standard fixed enoxaparin VTE prophylaxis dose of 40 mg daily and found that 60.7% of aFXa levels exceeded target values with the proportion further increasing to 85% above goal in patients who weighed <45 kg [7]. This illustrates the plausibility of weight-based dosing in low-weight patients. One trial described obese patients receiving enoxaparin 0.5 mg/kg/day for VTE prophylaxis who exhibited peak aFXa levels near or at goal range. Despite a mean dose of 67 mg daily, the mean peak aFXa was 0.25 units/ml and no aFXa levels were above goal [8]. Similarly, another trial analyzed three different prophylactic dosing regimens in obese patients and demonstrated that enoxaparin doses of 0.4 mg/kg/day and 0.5 mg/kg/day were superior to fixed dosing in achieving

Table 2: Strata according to weight

	Actual body weight (kg)			p-value
	Less than 45 (n=27)	45–50 (n=19)	Greater than 50 (n=19)	
Age (years)	47.2±21.5	48.7±29.6	64±21.5	0.21
Gender (male)	11 (29.4%)	9 (44.4%)	7 (44.4%)	0.74
SCr when aFXa drawn (mg/dl)	0.44±0.17	0.41±0.19	0.73±0.24	0.008*
CrCL when aFXa drawn (ml/min)	87.1 (51.6–249)	104 (37.7–254.7)	60.4 (29.5–185)	0.43

Table 3: Enoxaparin dosing

Dose of enoxaparin	n (%)	Median mg/kg (range)
30 mg daily, n (%)	46 (74.3)	0.63 (0.51–1.53)
40 mg daily, n (%)	5 (2.9)	0.71
30 mg twice daily, n (%)	2 (2.9)	2.11
<30 mg daily, n (%)	12 (20)	0.52 (0.44–1.02)

Table 4: Antifactor Xa levels based on achievement of goal

aFXa level	n (%)	aFXa level (units/ml)	Daily dose (mg)	Weight (kg)	BMI (kg/m^2)	CrCL (ml/min)	SCr (ml/min)
Below goal	1 (2.9)	0.1	22	19.6	13.2	124	0.2
At goal	46 (74.3)	0.34±0.11	29.54±8.04	44.98±9.36	18.39±3.27	96.96±53.55	0.54±0.24
Above goal	18 (22.9)	0.65±0.05	30±0	42.24±7.78	19.59±6.29	124.83±80.96	0.45±0.14

Table 5: Independent risk factors for evaluation of enoxaparin

	Slope	Standard error	95.0% CI for slope		
			p-value	Lower bound	Upper bound
Age (years)	0.00	0.00	0.679	−0.006	0.004
Gender	0.02	0.09	0.860	−0.171	0.203
Actual Body Weight (kg)	0.00	0.00	0.858	−0.009	0.008
BMI (kg/m^2)	0.02	0.01	0.102	−0.003	0.034
CrCL (ml/min)	0.00	0.00	0.702	−0.002	0.002

goal aFXa levels [9]. Weight-based enoxaparin VTE prophylaxis dosing may also be reasonable in surgical and trauma patients despite the differences in pharmacokinetics if doses of 0.5 mg/kg every 12 h are used, as these doses led to 86% and 91% attainment of goal aFXa levels, respectively [4]. Despite use of a lower dose, none of the patients in this study suffered a thrombotic event. The two bleeding events were not thought to be due to enoxaparin therapy given low Naranjo ADR scores, peak aFXa levels within goal, and other pre-existing risk factors for bleeding. In addition, both patients who experienced bleeding events received enoxaparin doses of 30 mg daily or less. In this study, aFXa levels were not associated with age, gender, BMI, actual body weight, or CrCL. Other investigators have similarly found no correlation between aFXa and weight or BMI [8], whereas an inverse relationship between aFXa and weight or BMI has been identified in some studies [7,10-12].

CONCLUSION

In our study, some patients received less than 30 mg daily, but for practicality, a 30-mg dose of enoxaparin seems most appropriate given the availability of this prefilled syringe size. With the lack of randomized controlled trials, larger prospective analyses are needed to further investigate the correlation between aFXa levels and clinical outcomes of bleeding and thrombosis as well as the most appropriate enoxaparin VTE prophylaxis dose in this patient population.

AUTHOR'S CONTRIBUTION

Dr. K. Souris has finalized the draft and guarantor, Dr. B. Swathi has prepared the conceptual framework, designing of draft, and data analysis, Dr. ENP. Sainath was involved in data collection and analysis, and Dr. V. Lahari has done manuscript writing and data collection.

CONFLICT OF INTEREST

None declared.

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