Optimal Dosing of Enoxaparin in Critically Ill Patients with Venous Thromboembolism

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Abstract

Background: *Evidence suggests that goal anti-Xa levels are achieved in only 33% of critically ill patients receiving standard prophylactic enoxaparin dosing. There has been limited focus on the potential suboptimal anticoagulation effect on medical intensive care unit (MICU) patients receiving therapeutic enoxaparin dosing for venous thromboembolism (VTE).*

Methods: *MICU patients receiving enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily for VTE treatment in a 350-bed community teaching hospital between 2013 and 2019 with at least one peak anti-Xa level measured were included. The primary outcome was the proportion who achieved therapeutic anti-Xa levels with standard dosing. Secondary outcomes included types of dose-adjustments required and the proportion requiring subsequent dose-adjustments. Descriptive statistics were presented for all outcomes.*

Results: *Fifty-three patients were evaluated, including those receiving either twice-daily or once-daily standard therapeutic dosing. Optimal anti-Xa levels at first measurement were recorded after the initiation of enoxaparin in 26.4% (n=14) patients. Dose adjustments were required in 70.7% (n=29) of patients receiving twice-daily dosing and in 83.3% (n=10) receiving once-daily dosing (P=0.97) to appropriately increase or decrease the enoxaparin dose. By the third anti-Xa level measurement, 3 patients remained outside of the therapeutic range.*

Conclusions: *Standard therapeutic enoxaparin dosing did not result in optimal anti-Xa levels for a majority of MICU patients regardless of dosing regimen used or patient specific factors. Future studies should identify patient factors associated with the requirement for higher or lower enoxaparin dosing.*

Keywords: critical care, optimal dosing, venous thromboembolism, enoxaparin, anticoagulation

Introduction

The incidence of first venous thromboembolism (VTE) occurrence is estimated to be approximately 104-183 people per 100,000 each year in the United States, making it one of the most common reasons patients present to the hospital.[1] In addition to cases diagnosed on presentation, hospitalization itself increases the risk for VTE development with average annual rates of VTE in hospitalized patients estimated to be 239 per 100,000 population.[2] Mortality rates remain high in these patients; as many as 10-30% of all patients with VTE will die within the first month after diagnosis.[1] Patients requiring treatment in the ICU experience higher morbidity and mortality rates, even when treated with optimal anticoagulant medications; therefore, rapid achievement of therapeutic levels of anticoagulation in these patients is of utmost importance.[3]

Enoxaparin is a low molecular weight heparin commonly used at a standard weight-based dose for the treatment of VTE. Many prescribers prefer subcutaneous enoxaparin over intravenous unfractionated heparin infusions as routine laboratory monitoring to assess anticoagulation is not needed. However, certain patient characteristics can cause unpredictable pharmacokinetic/pharmacodynamic responses to enoxaparin. In these cases, anti-Xa level monitoring can be used to ensure safe and effective anticoagulation. These characteristics include children and newborns, weight above 150 kg or below 40 kg, renal or hepatic insufficiency, pregnancy, and old age.[4] For this reason, the use of anti-Xa monitoring in these patient populations should become increasingly prevalent, and low rates of monitoring should be concerning. Emerging evidence suggests that some patient populations (e.g., critically ill, obese, renal impairment) will not achieve therapeutic anti-Xa levels with the standard recommended dose of enoxaparin. Specifically, several small studies examining enoxaparin for VTE prophylaxis in adult MICU patients have shown a significant percentage of patients, 33 to 92%, with subtherapeutic anti-Xa concentrations when receiving the standard dose.[5-10]

It is currently unknown if the suboptimal anticoagulation concerns observed in prophylactic enoxaparin studies will also be present in adult MICU patients receiving a standard therapeutic enoxaparin dose for treatment of VTE. Dosing these medications can be especially challenging in the ICU patient population due to a number of factors, such as decreased subcutaneous absorption due to decreased cardiac output or vasopressor use, alterations in drug metabolism, and changing renal function. Because morbidity and mortality rates remain high even in patients receiving optimal care, ensuring

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therapeutic anticoagulation is achieved in these patients quickly is essential. The purpose of this research is to examine whether standard therapeutic dosing of enoxaparin will result in therapeutic anti-Xa levels in MICU patients.

Methods

A single-centered, retrospective, cohort study of MICU patients receiving the standard dose of enoxaparin for the treatment of VTE within the time frame of January 2013 through December 2019 was conducted. This study was reviewed by the Piedmont Athens Regional Institutional Review Board and was determined to be exempt research. Standard dosing of enoxaparin for VTE treatment is 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours using actual body weight. Anti-Xa monitoring of enoxaparin is conducted by clinical pharmacist members of the interprofessional critical care team who provide ICU coverage seven days per week. A hospital protocol suggests anti-Xa monitoring in select patient populations, including all patients admitted to the ICU; however, the decision to monitor anti-Xa level is ultimately made at the discretion of the rounding pharmacist. Subsequent dose-adjustments of enoxaparin are also made at the discretion of the clinical pharmacist. All anti-Xa levels were drawn 3 to 5 hours after a steady-state dose, 4-5 half-lives after initiation or any dose change, with a therapeutic range considered 0.6-1 units/mL for twice-daily dosing and 1-2 units/mL for once-daily dosing. Adult patients within this time frame with at least one peak anti-Xa level drawn at the correct time interval were included in this study. Those who required renal replacement therapy were excluded from the study; however, those with a creatinine clearance less than 30 mL/min were included with dose adjustments consistent with package insert recommendations. Data collected included demographics, indication for enoxaparin, dosing information, anti-Xa levels, presence of vasoactive medications, hospital length of stay, and in-hospital mortality.

The primary outcome was the proportion of patients who achieved therapeutic anti-Xa levels with standard dosing. Secondary outcomes included describing anti-Xa level trends, dosing changes based on levels, the weight-based dose of enoxaparin required to achieve a therapeutic anti-Xa level, hospital length of stay, in-hospital mortality, and requirement of blood transfusion. Patients were subsequently divided into groups for two secondary analyses and outcomes were compared between these groups. First, patients were grouped based on whether they did or did not achieve a therapeutic anti-Xa level with standard enoxaparin dosing. Second, patients who received twice daily enoxaparin dosing were compared to those who received once daily enoxaparin dosing.

All statistical analyses were performed using IBM SPSS Statistics 26. Descriptive statistics were presented for primary and secondary outcomes. Categorical variables were presented as number and percentage and continuous variables were presented as median and interquartile range. Patient groups were compared using the Chi-squared or Fishers exact test for categorical variables and the Mann-Whitney U test for continuous variables. A binary logistic regression was applied to the primary outcome to identify patient factors associated with achievement of therapeutic anti-Xa levels. Variables included in the analysis were determined *a priori* by consensus of the investigators and included body mass index, serum creatinine, dosing regimen, and age. For all analyses, an alpha less than 0.05 was considered significant.

Results

Fifty-three patients were included, with 41 receiving twice-daily and 12 receiving once-daily enoxaparin dosing. Baseline characteristics and patient outcomes are summarized in **Table 1**. Therapeutic anti-Xa levels at first measurement were achieved with standard dosing in 14 (26.4%) patients; 12 of these were in the twice daily dosing group (85.7%). Despite the remaining 39 patients having either supra- or subtherapeutic anti-Xa levels, only 10 (18.8%) of the total group were adjusted up or down appropriately. A majority of the group at 52.8% (n=28) were indicated for dose adjustment, however, were kept at the same dose from initiation. An overview of enoxaparin dosing and initial anti-Xa levels are listed in **Table 2**.

Thirty-six percent (14/39) of remaining patients required secondary dose adjustments; however, only 3 doses were modified appropriately (2 (14.3%) dose increases and 1 (7%) dose decrease). By the third anti-Xa level measurement, 3 patients remained outside of the therapeutic range, with a median measured anti-Xa level of 0.64 (interquartile range [IQR] 0.5-0.88). The range of initial weight-based doses of enoxaparin spread from 0.68 to 1.43 mg/kg for twice daily dosing and 1.33 to 1.74 mg/kg for once daily dosing. The median hospital length of stay was 6 days with an in-hospital mortality of 1.9%. Out of the patient population, 9.4% of patients required a blood transfusion. Overall enoxaparin dose interventions are detailed in **Table 3**.

Achievement of Therapeutic Anticoagulation

There was no statistically significant difference in patient specific characteristics between groups that did (n=14) or did not (n=39) achieve a therapeutic anti-Xa level at first measurement. Similar findings were apparent for patient outcomes such as length of stay and inpatient mortality (**Table 1**). After the initial anti-Xa level was measured, 26.4% (n=14) of patients achieved therapeutic levels. Of the 39 remaining patients that were non-therapeutic, only 11 (28.2%) had dose adjustments made after the initial anti-Xa level and 16 (41%) had follow- up anti-Xa levels drawn. There was no significant difference in secondary outcomes including need for blood transfusion, length of hospital stay, or inpatient mortality between those who initially attained therapeutic anti-Xa levels versus those who did not. A binary logistic regression model was created to identify factors associated with initial

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achievement of therapeutic anti-Xa level. After controlling for age (OR 1.009; 95% CI 0.962 – 1.059; p=0.706), BMI (OR 0.911; 95% CI 0.813 – 1.021; p-value=0.108), and serum creatinine (OR 1.207; 95% CI 0.935 – 1.557; p=0.149), twice-daily dosing regimen (as compared to once-daily) was associated with greater odds of achieving an initial therapeutic level (OR 13.601; 95% CI 1.022 – 181.043; p=0.048).

Once versus Twice Daily Enoxaparin Dosing

There were 41 patients (77.4%) in the twice-daily dosing group and 12 patients (22.6%) in the once-daily dosing group. It was seen that there were statistically significant differences in patient admission weight ($p < 0.001$) and body mass index ($p = 0.001$) in patients receiving once verses twice daily regimens with higher weights belonging to the twice daily dosing group (**Table 1**). Dose adjustments were required in 70.7% (n=29) of patients receiving twice-daily dosing and in 83.3% (n=10) receiving once-daily dosing (*P*=0.97) after the initial anti-Xa level measurement. Therapeutic levels were obtained by 29.3% (n=12) of patients in the twice-daily dosing group; 19.5% (n=8) were supratherapeutic, and 51.2% (n=21) were subtherapeutic. Of the 29 patients outside of the therapeutic range, 12 (41.4%) received a secondary anti-Xa level with 2 patients (16.7%) achieving therapeutic levels with appropriate dose changes. Eight patients (66.7%) had a third anti-Xa level drawn with 6 (75%) achieving a therapeutic level.

Of the 12 patients in the once-daily dosing, 16.7% (n=2) achieved therapeutic anti-Xa levels after first drawn. Of the remaining 10 patients (83.3%), 4 patients (40%) had a second anti-Xa level drawn with no patients entering the therapeutic range. At the third anti-Xa level draw, 2 patients in this group were included (50%) with no therapeutic levels obtained.

Discussion

Treatment dosing of enoxaparin for VTE has been well established and is utilized widely in practice; however, there is a gap in data regarding standard dosing's effectiveness in achieving therapeutic anti-Xa levels. To the authors' knowledge, this evaluation is one of the first to evince suboptimal anticoagulation concerns associated with standard therapeutic enoxaparin dosing regimens in MICU patients.

Although it has been assumed that patients with normal renal function and body weight do not require laboratory monitoring of anti-Xa levels, previous studies were predominantly focused on the prophylactic use of low-molecular-weight heparin.[5] Notably, past data concluded that patients with an available anti-Xa assessment within 72 hours from the initiation of prophylactic low-molecular-weight heparin presented a lower overall mortality compared to those tested later.[11] There is a key role for increased anti-Xa monitoring when using enoxaparin for specific subsets of the population as patient outcomes may be improved. The results of this study highlight the necessity to monitor anti-Xa levels in patients prescribed therapeutic dosages of enoxaparin as well.

Additionally, this study supports the findings of current literature concluding that standard weight-based dosing of enoxaparin may be inadequate for those who are obese as the median BMI was 35.4 in those with subtherapeutic anti-Xa levels upon initial draw. When compared to other studies, this study's initial anti-Xa distributions reflected a greater incidence of suboptimal anticoagulation than those seen when defining obesity as a BMI of greater than or equal to 40 kg/m^2.[12, 13] These previous studies identified a correlation between obesity and supratherapeutic anti-Xa levels, leading to an increased risk of bleeding events in their study population. With a median body mass index (BMI) of 35 kg/m^2 in the study cohort, these findings further corroborate the need for dose adjustments according to anti-Xa levels in the obese population.

This study supports the prospect that the standardized dosing of enoxaparin should be reevaluated and does not attain therapeutic anti-Xa levels in critically ill patients. This was found to be true regardless of whether a standard once-daily or twice-daily dosing regimen was initiated. Current practice will not be sufficient in optimally treating VTE for this subgroup without anti-Xa levels as a guiding factor. While this study did demonstrate a need for change in current standard dosing of enoxaparin for VTE treatment, further studies are required to solidify this claim due to several study limitations. The small sample size (n=53) at a single institution narrows the scope of generalizability of these results. Furthermore, the distribution between the two groups were disproportionate. Anti-Xa levels were drawn at the discretion of the critical care pharmacist which could have led to bias in which patients received monitoring. Furthermore, the conclusion that standard dosing currently does not result in therapeutic anti-Xa levels in critically ill patients has not been further evaluated in populations of interest such as those who are morbidly obese, have renal or hepatic dysfunction, are of pediatric or old age, and are pregnant.[4]

Future considerations should include not only looking at attainment of therapeutic anti-Xa levels in subsets of the population, but also assess what specific patient factors led to the requirement for a subsequent dose change. Based on these study results, there were several instances where dose adjustments were required and were not performed as well as when dose adjustments were not required and were performed. This may suggest patient specific choices that can play a role in the decision making of dosing. These specific patient factors can be key factors in the unique dosing guidelines implemented going forward. Additional studies may benefit from taking a closer look at whether or not anti-Xa levels were drawn within the correct time intervals and how that may correspond to the attainment of therapeutic levels. Additionally, there were several unexplained abnormalities in

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the data that must be further explored such as dose adjustments in initially therapeutic individuals and alternately, dose adjustments that were not performed when indicated for a majority of patients. This may highlight a discordance in understanding how to best respond to anti-Xa level monitoring. Overall, the use of anti-Xa monitoring may increase with studies that address the gap in literature regarding the impact on patient outcomes with and without the use of monitoring with enoxaparin. Finally, factors such as biologic interference may have been valuable considerations to make when looking at anti-Xa levels within the critically ill population.

Conclusion

Standard therapeutic enoxaparin dosing did not result in optimal anti-Xa levels for a majority of MICU patients regardless of the regimen utilized or any patient specific factors. By obtaining additional anti-Xa levels throughout a patient's stay in the MICU, therapeutic anti-Xa levels are more likely to be obtained with the use of appropriate dose adjustments. This may lead to improved patient safety due to a reduced time outside of therapeutic anticoagulation in patients already predisposed to venous thromboembolism. Future studies should identify patient factors associated with the requirement for higher or lower enoxaparin dosing.

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Table 1. Baseline characteristics and patient outcomes

Variable	Patients (n=53)	Therapeutic anti-Xa level at first measurement (n=14)	Non-therapeutic anti-Xa level at first measurement (n=39)	*P* Value	Patients receiving 1 mg/kg every 12 hours (n=41)	Patients receiving 1.5 mg/kg every 24 hours (n=12)	*P* Value
Age, years	63 (48 – 76)	73 (50 – 81)	61 (48 – 74)	0.23	61 (48 – 75)	73 (55 – 82)	0.14
Male gender	21 (39.6)	5 (35.7)	16 (41)	0.73	16 (39.0)	5 (41.2)	0.87
Admission weight, kg	102 (82.5 – 119.9)	105.6 (83.9 – 117.9)	99.6 (81.8 – 131)	0.99	113.5 (93.5 – 127.7)	77.6 (65.0 – 86.4)	< .001
Height, cm	170 (162.6 – 182.8)	168.9 (161.9 – 184.2)	170 (162.6 – 180.3)	0.98	170 (165.1 – 188)	166.4 (160.7 – 174.6)	0.15
Body Mass Index (BMI)	35 (28.7 – 39.3)	34.4 (29.0 – 36.0)	35.4 (28.7 – 39.8)	0.57	35.8 (29.8 – 39.9)	27.5 (22.9 – 31.1)	.001
Race							
Caucasian	40 (75.5)	12 (85.7)	28 (71.8)	0.55	30 (73.2)	10 (83.3)	0.72
African American	12 (22.6)	2 (14.3)	10 (25.6)		10 (14.3)	2 (16.7)	
Unknown	1 (1.9)	0	1 (2.6)		1 (2.4)	0	
Indication for enoxaparin							
Treatment for DVT	14 (26.4)	5 (35.7)	9 (23.1)	0.49	12 (29.2)	2 (16.7)	0.46
Treatment for PE	37 (69.8)	9 (64.3)	28 (71.8)		27 (65.8)	10 (83.3)	
Treatment for DVT and PE	2 (3.8)	0	2 (5.13)		2 (4.8)	0	
BUN, mg/dL	15 (9-22)	15 (12 – 20)	13 (9 – 22)	0.50	13 (9 – 22)	17.5 (10 – 21.5)	0.73
SCr, mg/dL	0.91 (0.71 – 1.13)	0.94 (0.68 – 2.34)	0.88 (0.74 – 1.07)	0.49	0.91 (0.71 – 1.13)	0.90 (0.68 – 1.15)	0.97
Hours between SCr and last dose of enoxaparin	8 (5 – 14.5)	8 (4 – 11.8)	8 (5 – 17)	0.75	8 (5 – 13.5)	12 (6.3 – 16.3)	0.27
UOP, mL/day	1312.5 (980 – 1943.8)	1163 (463.3 – 2318.8)	1362.5 (1000 – 1906.3)	0.43	1263 (980 – 2056.3)	1550 (762.5 – 1887.5)	0.91
Dose adjustment made after initial anti-Xa result		2 (14.3)	11 (28.2)	0.58	10 (24.3)	3 (25)	0.88
Second anti-Xa level measured		7 (50)	16 (41)	0.56	19 (46.3)	4 (33.3)	0.42
Need for blood transfusion		2 (14.3)	3 (7.7)	0.49	5 (12.1)	0	0.20
Length of hospital stay, days		6 (3.7 – 12.8)	6 (3 – 8)	0.37	5 (3 – 8.5)	6 (3.25 – 9.75)	0.91
Inpatient mortality		1 (7.1)	0	0.09	1 (2.4)	0	0.59

Data are presented as number (percentage) or median (interquartile range)
DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism, BUN = Blood Urea Nitrogen, SCr = Serum Creatinine, UOP = Urine Output

Table 2. Enoxaparin dose interventions per group

Variable	Patients (n=53)	1 mg/kg every 12 hours (n=41)	1.5 mg/kg every 24 hours (n=12)
Starting enoxaparin dose, mg	n/a	120 (100 – 125)	115 (100 – 127.5)
Starting enoxaparin dose, mg/kg	n/a	0.99 (0.94 – 1.04)	1.49 (1.44 – 1.54)
Initial anti-Xa level	n/a	0.59 (0.50 – 0.91)	0.67 (0.26 – 0.95)
Anti-Xa level at first measurement			
Therapeutic	14 (26.4)	12 (29.2)	2 (16.7)
Subtherapeutic	31 (58.5)	21 (51.2)	10 (83.3)
Supratherapeutic	8 (15.1)	8 (19.5)	0
Dose adjustment after initial anti-Xa result (n=53)	13 (24.5)	10 (24.3)	3 (25)

Table 3. Overall enoxaparin dose interventions

Variable	Patients	Variable	Patients
Dose adjustment after initial anti-Xa result (n=53)	13 (24.5)	Dose adjustment after second anti-Xa result (n=3)	
Increased appropriately	6 (11.3)	Increase, mg/kg	1.64 (1.28 – 2.30)
Decreased appropriately	4 (7.5)	Decrease, mg/kg	0.72
Dose adjusted inappropriately	2 (3.8)	Anti-Xa level at third measurement (n=14)	
Dose adjustment indicated but not performed	28 (52.8)	Therapeutic	5 (35.7)
No dose adjustment indicated	12 (22.6)	Subtherapeutic	2 (14.3)
Enoxaparin discontinued prior to dose adjustment	1 (1.9)	Supratherapeutic	1 (7.1)
Dose adjustment after initial anti-Xa result (n=10)		Third anti-Xa level not measured	6 (42.9)
Increase, mg/kg	1.31 (1.01 – 2.09)	Dose adjustment after third anti-Xa result (n=3)	
Decrease, mg/kg	0.87 (0.76 – 0.88)	Enoxaparin discontinued	2 (66.7)
Anti-Xa level at second measurement (n=39)		Dose adjustment indicated but not performed	1 (33.3)
Therapeutic	2 (5.1)	Total cumulative received enoxaparin, mg	460 (290 – 720)
Subtherapeutic	12 (30.8)		
Supratherapeutic	2 (5.1)		
Second anti-Xa level not measured	23 (59.0)		
Dose adjustment after second anti-Xa result (n=16)			
Increased appropriately	2 (12.5)		
Decreased appropriately	1 (6.2)		
Dose adjusted inappropriately	2 (12.5)		
Dose adjustment indicated but not performed	6 (37.5)		
No dose adjustment indicated	2 (12.5)		
Enoxaparin discontinued prior to dose adjustment	3 (18.8)		

Data are presented as number (percentage) or median (interquartile range)