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ORIGINAL RESEARCH ARTICLE

Stratifying Therapeutic Enoxaparin Dose in Morbidly Obese Patients by BMI Class: A Retrospective Cohort Study

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Abstract

Background Enoxaparin is a low-molecular weight heparin (LMWH) commonly used for treatment of venous thromboembolism and acute coronary syndromes. The recommended dose for these conditions is weight-based (1 mg/kg) and doesn't require dose-capping. However, previous studies have shown that in those with a body mass index (BMI) > 40 kg/m^2, this dose results in supratherapeutic levels.

Objective This study investigated enoxaparin dosing in morbidly obese patients with a goal of identifying a dose with the greatest chance of producing favorable anti-factor Xa (anti-Xa) levels.

Methods This retrospective cohort study by electronic chart review was used to record data of patients who received enoxaparin with anti-Xa level monitoring between 2012 and 2017. The primary outcome was the enoxaparin dose that results in a therapeutic anti-Xa level (0.5–1.0 IU/mL) among three BMI groups. Secondary outcomes were bleeding and thromboembolic events.

Results Two hundred forty-one patients were included in the study, and 132 achieved a therapeutic dose. For those with a BMI of 40–50 kg/m^2, the median therapeutic dose was 0.97 mg/kg every 12 h. In subjects with a BMI of 50–60 kg/m^2, the median therapeutic dose was 0.70 mg/kg. Finally, the median therapeutic dose for subjects with a BMI over 60 kg/m^2 was 0.71 mg/kg. In all three groups, 53–65% of patients had a supratherapeutic anti-Xa level while less than 10% had a subtherapeutic level. Relatively few patients (4.1%) experienced major bleeding and only one thromboembolic event was reported.

Conclusion Standard dosing of enoxaparin in morbidly obese patients will most likely lead to supratherapeutic anti-Xa levels and thus further investigation is warranted to better determine appropriate dosing.

Key Points

Our study suggests that standard treatment dosing of enoxaparin (1 mg/kg) in morbidly obese patients will lead to supratherapeutic anti-Xa levels.

The authors found the median therapeutic dose of enoxaparin in patients with a body mass index of 40–50, 50–60, and > 60 kg/m^2 to be 0.97, 0.70, and 0.71 mg/kg, respectively.

Our study warrants further investigation into lower treatment dosing strategies of enoxaparin in morbidly obese patients.

1 Introduction

Obesity rates worldwide have tripled since 1975 and it affects approximately 93.3 million adults in the USA alone and about 650 million individuals worldwide [1, 2]. Obesity puts individuals at a higher risk for development of many different health conditions including hypertension, hyperlipidemia, atrial fibrillation, and thromboembolic events such as venous thromboembolism (VTE) and stroke. Similar trends in the rates of obesity in children and adolescents also highlight the fact that obesity is occurring in a growing amount of our population, which makes solidification of dosing strategies in the population increasingly important.

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Enoxaparin is a low-molecular weight heparin (LMWH) that is frequently used in the inpatient setting for both prevention and treatment of VTE, as well as acute coronary syndromes (ACS) and stroke prevention in atrial fibrillation. When used for treatment of VTE, ACS, or for atrial fibrillation, the recommended dosing for patients with normal renal function is 1 mg/kg every 12 h [3]. In obese patients, pharmacokinetic changes, such as changes in volume of distribution due to an increase in adipose tissue and decreased tissue perfusion, and an increase in creatinine clearance (CrCl), make drug concentrations unpredictable [4]. Due to the aforementioned changes in pharmacokinetics, enoxaparin, being a hydrophilic drug, accumulates in other tissues [5]. Additionally, enoxaparin can be preferentially used in obese patients in comparison to heparin due to its fixed dosing and lack of frequent laboratory monitoring [6]. There is no maximum dose or dose adjustment provided for obese patients, but previous studies have established that, in patients with a body mass index (BMI) > 40 kg/m^2, the recommended 1 mg/kg dose is associated with an increased risk of bleeding [7], as well as supratherapeutic levels when therapy is monitored using anti-factor Xa (anti-Xa) [8, 9]. However, because no study has investigated this population using a large enough sample size to identify a dose recommendation in these patients, enoxaparin dosing in patients with BMI > 40 kg/m^2 is highly variable among locations and practitioners. Current guidelines for enoxaparin dosing in this patient population only have recommendations for monitoring, not for specific dosing strategies, such as with the American College of Chest Physicians guidelines [10].

Investigating an appropriate enoxaparin dosing in patients with BMI > 40 kg/m^2 with the greatest chance of producing favorable drug concentrations in these patients is demanding. This study aims to address these dosing discrepancies in order to not only prevent bleeding issues in obese patients, but also prevent under-dosing, which can precipitate clotting events.

2 Methods

2.1 Study Design

This single-centered, retrospective cohort study was performed at Hendrick Medical Center in Abilene, Texas, USA. Hendrick Medical Center uses a pharmacist-driven anti-Xa protocol for enoxaparin dose adjustments for patients with a BMI of at least 40 kg/m^2 or total body weight (TBW) of at least 150 kg (Appendix Table 4). Pharmacists order anti-Xa level after the third dose of an enoxaparin 1 mg/kg subcutaneously every 12 h regimen. Once an anti-Xa level is available, the pharmacist contacts the physician with the new regimen based on the protocol. After the physician's approval of the new regimen, the pharmacist continues to follow the anti-Xa levels.

Patients were eligible for inclusion in the study if they were admitted to Hendrick Medical Center between 1 January 2012 and 31 December 2017. Included patients were 18 years of age or older, received at least three doses of enoxaparin 1 mg/kg subcutaneously twice daily (or once daily for patients with CrCl < 30 mL/min), and had a BMI of at least 40 kg/m^2 or a TBW of ≥ 150 kg, and had a result for at least one anti-Xa level available. Pregnant patients, prisoners, and patients who were either on dialysis or had a CrCl of < 15 mL/min were excluded from the study.

Data were collected by study authors from an electronic medical records system (AllScripts Sunrise Enterprise™) after International Review Board (IRB) approval. Patients were identified in the electronic medical records system by LMWH anti-Xa laboratory test codes. Patient data collected included age, gender, height, weight, BMI, indication for enoxaparin therapy, co-morbid conditions, concurrent medications, previous medical history, current smoking status, admission status (acute or intensive care unit), serum creatinine, enoxaparin dose(s), anti-Xa levels, which were drawn 4–6 h after the third dose of enoxaparin, and bleeding and thromboembolic information. CrCl was calculated using the Cockcroft–Gault equation using adjusted body weight. The STA® Rotachrom® Heparin kit on STA-Compact® analyzer (Diagnostics Stago, Inc., Parsippany, New Jersey) was used for all anti-Xa levels.

2.2 Outcomes

The primary outcome was the enoxaparin dose that resulted in a therapeutic anti-Xa level, defined as 0.5–1.0 IU/mL, in patients who achieved a therapeutic level during their hospital stay in each of three BMI groups: 40–50, 50–60, and > 60 kg/m^2 [11, 12]. Secondary outcomes were bleeding events and thromboembolic events in each group. Bleeding events were defined based on ISTH (International Society on Thrombosis and Haemostasis) major bleeding criteria as symptomatic bleeding in a critical area or organ (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular/pericardial, or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin level of 20 g/dL (1.24 mmol/L) or more, bleeding that led to the transfusion of two or more units of whole blood or red blood cells, or bleeding that resulted in death [13]. Thromboembolic events were identified using computed tomography (CT) angiography for pulmonary embolism and lower-extremity Doppler test for deep VTE.

2.3 Statistical Analysis

Patients included in the trial were assigned to one of three groups according to their BMI: 40–50, 50–60, and > 60 kg/m^2. Nominal data were evaluated using Chi-square or Fisher's exact tests. Continuous data were assessed using analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on whether data were parametric or non-parametric. An alpha value of 0.05 was used to determine statistical significance.

All statistical analysis was performed by using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA; 2014).

3 Results

3.1 Patient Population

Eight hundred ninety patients were identified from electronic medical records and 241 patients met the inclusion criteria (Fig. 1). Of the patients included in the study, 169 patients had a BMI 40–50 kg/m^2, 52 patients were between 50 and 60 kg/m^2, and 20 patients were > 60 kg/m^2. The baseline characteristics are shown in Table 1. There were significant differences in the BMI of each group in the study ($P < 0.0001$). Indications for enoxaparin were well-balanced and the majority of patients had cardiovascular co-morbid conditions. The average length of enoxaparin therapy was 5.7 days.

Anti-Xa levels obtained from each group can be seen in Table 2. The mean value of the first anti-Xa level drawn for each group was > 1 IU/mL (1.07 ± 0.43 vs. 1.19 ± 0.43 vs. 1.26 ± 0.40 IU/mL for BMI groups 40–50, 50–60, and > 60 kg/m^2, respectively; $P = 0.076$). In the BMI 40–50 kg/m^2 group, 14 patients (8.3%) had a subtherapeutic anti-Xa level, 66 (39.0%) had a therapeutic level, and 89 (52.7%) had a supratherapeutic level. In the BMI 50–60 kg/m^2 group, two (3.8%) had a subtherapeutic level, 18 (34.6%) had a therapeutic level, and 32 (61.5%) had a supratherapeutic level. In the BMI > 60 kg/m^2 group, no patients had a subtherapeutic level, seven (35%) had a therapeutic level, and 13 (65%) had a supratherapeutic level.

Thirty-four patients (14.1%) in the overall study population had reduced renal clearance (CrCl < 50 mL/min). Of these, 27 were in the BMI 40–50 kg/m^2 group (16.0% of patients in this group), five were in the BMI 50–60 kg/m^2 group (9.6%), and two were in the BMI > 60 kg/m^2 group (10.0%).

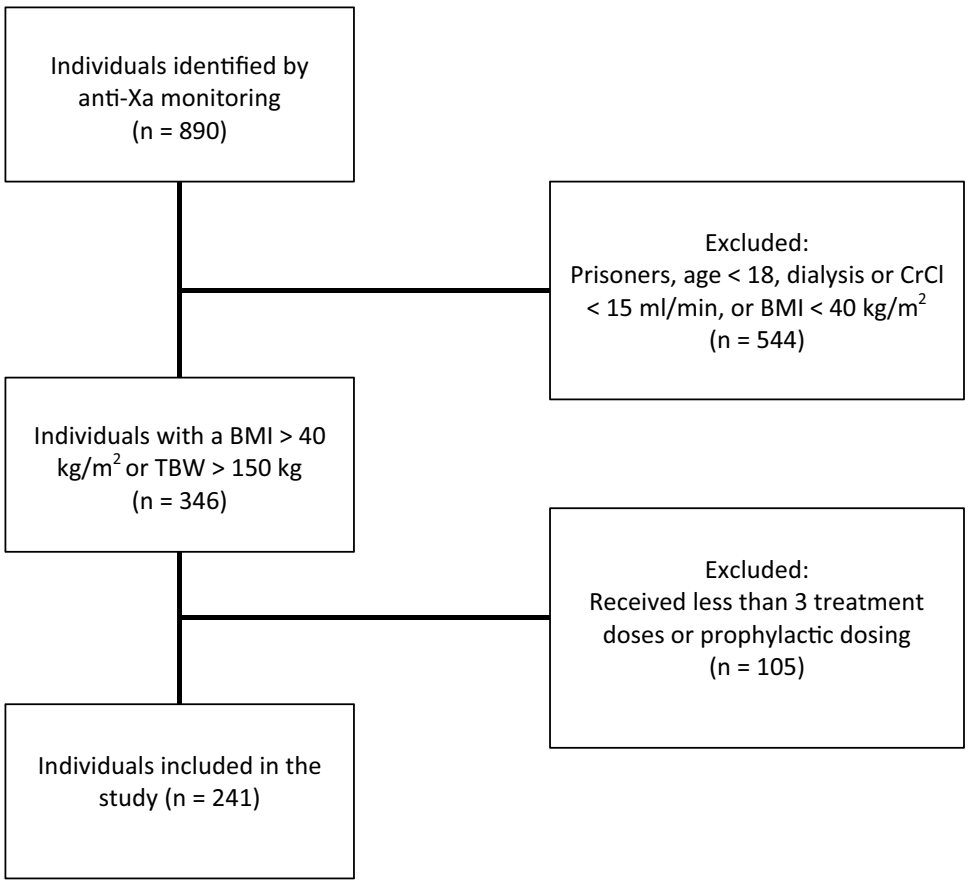

Fig. 1 Flowchart of patient enrollment. *BMI* body mass index, *CrCl* creatinine clearance, *TBW* total body weight

Table 1 Baseline characteristics

Characteristics	All subjects ($N=241$)	BMI 40–50 kg/m^2 ($n=169$)	BMI 50–60 kg/m^2 ($n=52$)	BMI > 60 kg/m^2 ($n=20$)	*P* value
Demographics					
Age (years) [mean (± SD)]	58.9 (± 12.59)	60.1 (± 12.81)	57.71 (± 11.72)	52.15 (± 10.87)	0.020
Female [*n* (%)]	136 (56.4)	89 (52.3)	35 (67.3)	12 (60)	0.167
Height (cm) [mean (± SD)]	170.8 (± 11.50)	171.7 (± 10.72)	169.6 (± 10.47)	165.9 (± 18.04)	0.071
Weight (kg) [mean (± SD)]	140.7 (± 27.04)	130.2 (± 17.24)	157.1 (± 20.77)	187.7 (± 37.56)	< 0.001
BMI (kg/m^2) [mean (± SD)]	48.25 (± 8.02)	44.02 (± 2.67)	54.45 (± 2.99)	67.89 (± 7.34)	< 0.001
Creatinine clearance (mL/min) [median (range)]	92 (19–496)	86 (19–303)	103 (28–226)	116 (44–496)	< 0.001
Current smoker [*n* (%)]	48 (20.1)	32 (18.9)	13 (25.5)	3 (15)	0.498
Indication for therapy [*n* (%)]					
VTE	93 (38.6)	64 (37.9)	17 (32.7)	12 (60)	0.391
ACS	60 (24.9)	44 (26.0)	12 (23.1)	4 (20)	
Atrial fibrillation	77 (32.0)	52 (30.8)	21 (40.4)	4 (20)	
Other/unknown	11 (4.6)	9 (5.3)	2 (3.8)	0 (0)	
Co-morbidities [*n* (%)]					
Cardiovascular	212 (88.0)	150 (88.8)	45 (86.6)	17 (85)	0.833
Pulmonary	84 (34.9)	64 (37.9)	15 (28.8)	5 (25)	0.308
Gastrointestinal/hepatic	49 (20.3)	38 (22.5)	6 (11.5)	5 (25)	0.198
Diabetes mellitus	123 (51.0)	91 (53.8)	25 (48.1)	7 (25)	0.250
Renal	31 (12.9)	25 (14.9)	5 (9.6)	1 (5)	0.341
Musculoskeletal	52 (21.6)	39 (23.1)	11 (21.2)	2 (10)	0.404
Neurologic	23 (9.5)	18 (10.7)	5 (9.6)	0 (0)	0.385
Hematologic	22 (9.1)	19 (11.2)	3 (5.8)	0 (0)	0.208
Active cancer	18 (7.5)	12 (7.1)	4 (7.7)	2 (10)	0.781
Previous medical history [*n* (%)]					
VTE	66 (27.4)	46 (27.2)	12 (23.1)	8 (40)	0.352
CAD	53 (22.0)	43 (25.4)	9 (17.3)	1 (5)	0.074
Atrial fibrillation	71 (29.4)	48 (28.4)	17 (32.7)	6 (30)	0.837
Stroke	16 (6.6)	12 (7.1)	4 (7.7)	0 (0)	0.639
Gastrointestinal bleeding	10 (4.1)	9 (5.3)	1 (1.9)	0 (0)	0.472
Surgery/trauma within 1 month	19 (7.9)	17 (10.1)	1 (1.9)	1 (5)	0.141

ACS acute coronary syndrome, *CAD* coronary artery disease, *SD* standard deviation, *VTE* venous thromboembolism

Table 2 Initial enoxaparin dose and first anti-factor Xa (anti-Xa) levels

Variable	All subjects ($N=241$)	BMI 40–50 kg/m^2 ($n=169$)	BMI 50–60 kg/m^2 ($n=52$)	BMI > 60 kg/m^2 ($n=20$)	*P* value
Median initial enoxaparin dose [mg/kg (interquartile range)]	1.00 (0.97–1.00)	1.00 (0.97–1.00)	1.00 (0.89–1.00)	1.00 (0.96–1.00)	0.187
Mean first anti-Xa level [IU/mL (± standard deviation)]	1.12 (± 0.43)	1.07 (± 0.43)	1.19 (± 0.43)	1.26 (± 0.40)	0.076
Supratherapeutic anti-Xa [*n* (%)]	134 (55.60)	89 (52.66)	32 (61.54)	13 (65)	0.565
Therapeutic anti-Xa [*n* (%)]	91 (37.76)	66 (39.05)	18 (34.62)	7 (35)	
Subtherapeutic anti-Xa [*n* (%)]	16 (6.64)	14 (8.28)	2 (3.85)	0 (0)	
Median anti-Xa test time after the initial dose [h (interquartile range)]	5.0 (4.0–5.5)	5.0 (4.0–5.5)	4.5 (4.0–5.0)	5.0 (4.75–6.0)	0.132

Supratherapeutic anti-Xa levels were defined as having an anti-Xa level > 1.0 IU/mL. Therapeutic anti-Xa levels were defined as having an anti-Xa level between 0.5 and 1.0 IU/mL. Subtherapeutic anti-Xa levels were defined as having an anti-Xa level < 0.5 IU/mL

BMI body mass index

3.2 Outcomes

The outcomes of the study can be seen in Table 3. A total of 132 patients (55%) across all three groups achieved a therapeutic anti-Xa level during the hospital stay, after dose adjustment if the first anti-Xa level was not in the therapeutic range. This total included 88 patients (52%) in the BMI 40–50 kg/m^2 group, 33 patients (65%) in the BMI 50–60 kg/m^2 group, and 11 patients (55%) in the BMI > 60 kg/m^2 group. The median dose for patients with a therapeutic anti-Xa level was 0.97 (interquartile range [IQR] 0.79–1.0) mg/kg in patients with a BMI 40–50 kg/m^2, 0.70 (0.64–0.93) mg/kg in patients with a BMI 50–60 kg/m^2, and 0.71 (0.58–0.98) mg/kg in patients with a BMI > 60 kg/m^2. There was a significant difference between the doses of each group ($P = 0.0002$).

Ten bleeding events (4.1% of all patients) occurred among patients in the study. All of the bleeding events occurred in the BMI 40–50 kg/m^2 group, but no significance was found when compared with the other BMI groups ($P = 0.136$). Six patients who experienced bleeding events had supratherapeutic anti-Xa levels and four had therapeutic levels. One new thromboembolic event occurred in one patient in the 40–50 kg/m^2 group, with no significance compared with the other BMI groups ($P = 1.000$). This patient had a therapeutic anti-Xa level, and the thromboembolic event was attributed to heparin-induced thrombocytopenia.

4 Discussion

This study showed a significant correlation between an increase in BMI and lower therapeutic dosing of enoxaparin. The study identified also a therapeutic dose of enoxaparin for each of the BMI groups, though caution should be taken in their applicability due to the small number of included patients in each group (particularly in the > 60 kg/m^2 group). No significant difference in bleeding or thromboembolic events was found between the BMI groups, although the study data are limited by the small number of patients with each outcome. Our study is unique in that it has a larger sample size ($N = 241$) than previous studies that have investigated enoxaparin in morbidly obese patients. Unlike other studies, this study categorized the BMI to identify dosing for each of the three determined BMI groups.

There have been multiple studies that have assessed the use of treatment dose enoxaparin in morbidly obese patients. Spinler et al. [7] published a retrospective study investigating the differences in enoxaparin dosing among patients who were hospitalized with non-ST-segment elevation ACS at high risk for death, or myocardial infarction, in different weight and BMI ranges, using data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology-American Heart Association Guidelines) initiative. The authors observed

Table 3 Outcomes of the study

Results	BMI 40–50 kg/m^2	BMI 50–60 kg/m^2	BMI > 60 kg/m^2	*P* value
Primary results[a] ($N = 132$)	***n* = 88**	***n* = 33**	***n* = 11**	
Therapeutic enoxaparin dose (mg/kg) [median (interquartile range)]	0.97 (0.79–1.0)	0.70 (0.64–0.93)	0.71 (0.58–0.98)	0.0002
Anti-Xa level with the therapeutic dose (IU/mL) [mean (SD)]	0.79 (±0.79)	0.84 (±0.21)	0.86 (±0.10)	0.268
Anti-Xa test time after the dose (h) [mean (SD)]	4.76 (±1.22)	5.08 (±3.67)	4.77 (±1.44)	0.771
Secondary results[b] ($N = 241$)	***n* = 169**	***n* = 52**	***n* = 20**	
Bleeding [*n* (%)]	10 (5.92)	0	0	0.136
Anti-Xa level				
Supratherapeutic[c] [n (%)]	6 (60)			
Therapeutic[d] [n (%)]	4 (40)			
Subtherapeutic[e] [n (%)]	0 (0)			
VTE [n (%)]	1[f] (0.59)	0	0	1.000

BMI body mass index, *SD* standard deviation, *VTE* venous thromboembolism

[a]Primary results: evaluated from the patients who reached anti-Xa level in the therapeutic range during the hospital stay

[b]Secondary results: evaluated from all patients included in the study

[c]Supratherapeutic anti-Xa levels were defined as having an anti-Xa level > 1.0 IU/mL

[d]Therapeutic anti-Xa levels were defined as having an anti-Xa level between 0.5 and 1.0 IU/mL

[e]Subtherapeutic anti-Xa levels were defined as having an anti-Xa level < 0.5 IU/mL

[f]Patient developed HITT; first anti-Xa level 1.75, final anti-Xa level 0.79 after dose adjustment

that patients weighing more than 150 kg were frequently prescribed enoxaparin doses lower than the recommended dose (1 mg/kg), and found that patients who were prescribed the recommended dose had an elevated rate and higher risk of bleeding, relative to those who were prescribed a reduced dose, although the data were not statistically significant (11.4% vs. 6.5%, respectively; adjusted odds ratio 2.42; 95% confidence interval 0.70–8.37) [7].

Bazinet et al. [14] measured enoxaparin anti-Xa levels in the obese, in a prospective non-randomized trial. The mean anti-Xa level was 1.14 IU/mL. The authors found also that anti-Xa levels increase as BMI increases, which is similar to our results.

A case series published by Deal et al. [9] described the use of enoxaparin in patients with a BMI > 40 kg/m^2. Patients who achieved therapeutic anti-Xa levels had doses identified as 0.74 mg/kg, but the authors did not find any significant difference between this group and those who did not achieve therapeutic levels. The authors concluded that the primary difference between the two groups was length of hospital stay [9]. Based on the results of the Deal et al. [9] case series, another study, published by Lalama et al. [15], investigated the effect of a standardized protocol in which patients with a BMI > 40 kg/m^2 would be started on an enoxaparin dose of 0.75 mg/kg. The authors found that half of these patients achieved therapeutic anti-Xa levels on this initial dose, but no comparison group was included in this study [15].

A study by Thompson-Moore et al. [8] investigated enoxaparin dosing in patients with a BMI > 40 kg/m^2 or weight > 140 kg. The authors found that patients who received a dose of < 0.95 mg/kg were less likely to have supratherapeutic anti-Xa levels than those who received doses > 0.95 mg/kg, confirming the results of our trial [8]. Like the Deal et al. [9] and Lalama et al. [15] studies, the Thompson-Moore et al. [8] study was limited by a small sample size, and only determined that the optimal dose in this population is < 0.95 mg/kg, but did not identify a specific dose, which our study aimed to achieve [8, 9, 15].

Curry et al. [16] published a prospective, randomized controlled study comparing the use of reduced-dose enoxaparin (0.8 mg/kg every 12 h) to standard treatment dosing (1 mg/kg every 12 h) in achieving therapeutic anti-Xa levels in patients with a BMI ≥ 40 kg/m^2 [16]. The authors found that there was not a significant difference between the two dosing strategies in achieving therapeutic anti-Xa levels, but therapeutic levels were achieved in 89% of the patients in the reduced dosing group [16].

A retrospective study published by Maclachlan et al. [17] investigated the safety of the standard enoxaparin dose (1 mg/kg) for the treatment of VTE in patients < 100 kg, in patients > 100 kg, and in patients > 100 kg that received a reduced enoxaparin dose (< 1 mg/kg) [17]. The authors found no significant differences in the number of patients with a supratherapeutic or subtherapeutic anti-Xa level in each group, and more major bleeding events occurred in patients < 100 kg, though the trial was limited by a small number of included patients [17].

Lastly, a retrospective cohort study published by Czupryn and Exline [18] investigated the use of enoxaparin in patients weighing ≥ 120 kg on the incidence of major bleeding and thromboembolic events. The authors concluded that there was no difference in major bleeding or thromboembolic events between patients given ≥ 90% of the U.S. Food and Drug Administration (FDA)-recommended dose and those who were given < 90% of the FDA-recommended dose [18].

The results of our study are consistent with studies mentioned previously that showed reduced enoxaparin dosing is needed to achieve therapeutic LMWH anti-Xa levels. Our study showed also that a reduced dosing strategy is more likely to achieve a therapeutic anti-Xa level than standard dosing. However, since our results show different therapeutic dosing in all three BMI groups, further studies are warranted to determine appropriate dosing for each group [8, 9]. Our results showed that 55% of the patients included in this study achieved an initial therapeutic anti-Xa level, which is similar to the previously mentioned trials [9, 14, 15]. As previously stated, our study included more patients than previous studies investigating enoxaparin dosing in morbidly obese patients [8–10, 15, 16]. Our study utilized a pharmacist-driven anti-Xa protocol, monitored by clinical pharmacists, and measured anti-Xa levels 4–6 h after the third dose. Our study also stratified patients into different BMI groups, a design not previously incorporated. By using BMI in lieu of weight alone, it is possible to determine the treatment for morbidly obese patients, a population in whom the safety of enoxaparin has not been established. One limitation of this design, and a limitation of the use of BMI in general, is the inclusion of individuals who have a larger muscle mass and less adipose tissue. Other limitations of our study include its retrospective, single-site design, and a small number of included patients. The applicability of bleeding and thromboembolic events in our trial is limited, due to the small number of incidences of each. VTE events were captured by diagnostic imaging, so subclinical VTE might not have been captured. Ways to improve subsequent trials investigating therapeutic dosing of enoxaparin in morbidly obese patients include continuing to utilize stratified BMI groups, increasing the number of participants in each group, and investigating the time to reach a therapeutic level of enoxaparin.

5 Conclusion

Standard treatment dosing of enoxaparin in morbidly obese patients will most likely lead to supratherapeutic anti-Xa levels. Our study suggests that lower initial treatment dosing strategies are needed in morbidly obese patients, and thus warrants further investigation.

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Compliance with Ethical Standards

Funding No funding was received in relation to the conduct of this study.

Conflict of interest Young R. Lee, Peter J. Palmere, Caitlin E. Burton, and Taylor M. Benavides declare that they have no conflict of interest.

Informed Consent For this type of study, formal consent is not required.

Ethics Approval Our study was reviewed and approved by the Texas Tech University Health Sciences Center Institutional Review Board.

Appendix

See Table 4.

Table 4 A: Pharmacist-driven anti-Xa protocol [11]

Anti-Xa	Dose titration	Time to repeat anti-Xa level
< 0.35 units/mL	Increase dose by 25%	4 h after next dose
0.35–0.49 units/mL	Increase dose by 10%	4 h after next dose
0.5–1 unit/mL	Keep same dosage	Next day, then 1 week later, then monthly (4 h after dose)
1.1–1.5 units/mL	Decrease dose by 20%	Before next dose
1.6–2 units/mL	Hold dose for 3 h and decrease dose by 30%	Before next dose, then 4 h after next dose
> 2 units/mL	Hold all doses until anti-Xa is 0.5 units/mL, then decrease dose by 40%	Before next dose and every 12 h until anti-Xa < 0.5 units/mL

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