Dosing of Enoxaparin in Morbidly Obese Patients: A Retrospective Cohort

Hospital Pharmacy
2018, Vol. 53(5) 331–337
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DOI: 10.1177/0018578718757518
journals.sagepub.com/home/hpx

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Abstract

Purpose: The purpose of this study was to evaluate odds of major bleeding, thrombosis, and ischemic stroke between different enoxaparin dosage strategies in patients weighing ≥ 120 kg. **Methods:** Patients weighing ≥ 120 kg who received therapeutic anticoagulation with enoxaparin for more than 24 hours were selected for retrospective review. Patients without a baseline weight, serum creatinine, a history of heparin-induced thrombocytopenia, or currently pregnant patients were excluded from the study. Patients with a creatinine clearance (CrCL) < 30 mL/min were analyzed separately. The incidence of major bleeding was compared between patients receiving $< 90\%$ and those receiving $\geq 90\%$ of the Food and Drug Administration (FDA)–approved dose of enoxaparin, as well as between patients weighing ≥ 150 kg and those weighing < 150 kg. Secondary outcomes included incidence of venous thromboembolism (VTE) and ischemic stroke. **Results:** A total of 462 patients were included in the primary analysis and 25 patients in the subgroup analysis. No difference in major bleeding was observed between different dosage regimens ($P = .12$) or weight groups ($P = .36$). No difference was observed in rates of VTE or ischemic stroke between different dosage regimens ($P = .52$ and $P = .60$, respectively) or weight groups ($P = .39$ and $P = .48$, respectively). Similar results were observed in the low-CrCL analysis. Results were not altered when patients were propensity matched on baseline characteristics. **Conclusion:** Reducing the dose of enoxaparin did not reduce the odds of major bleeding or increase the odds of ischemic stroke or VTE.

Keywords

anticoagulants, medication safety, monitoring drug therapy, physician prescribing

Background

The prevalence of morbid obesity in the United States has been steadily increasing since 2000.^{1–3} The American Heart Association predicts 11% of the population will be classified as morbidly obese by 2030.² Morbid obesity increases the risk of hospitalization from vascular complications including venous thromboembolism (VTE), ischemic stroke, and cardiovascular disease. The pharmacokinetics of medications used in the management of these conditions can be altered by morbid obesity.^{4–6} One such drug, enoxaparin, is a commonly prescribed anticoagulant because its favorable pharmacokinetic profile allows for less frequent monitoring than heparin. Morbid obesity may affect the volume of distribution and clearance of enoxaparin leading to a less predictable response.^{7,8} The Food and Drug Administration (FDA)–approved dose for enoxaparin in patients with creatinine clearance (CrCL) > 30 mL/min is 1 mg/kg twice daily or 1.5 mg/kg daily based on total body weight when the intent of treatment is therapeutic anticoagulation.⁹ Although patients weighing up to 159 kg have been represented in clinical trials evaluating this dosage regimen, patients weighing greater than 120 kg were minimally represented.^{10,11} No consensus

has been reached on the appropriate strategy for dosing enoxaparin in this population. Some authorities have recommended routine Factor Xa monitoring in obese patients; however, not all hospitals have the resources to obtain Factor Xa results in a timely fashion.^{12–14} Some physicians have elected to prescribe a lower dose of enoxaparin to reduce the risk of excessive anticoagulation despite some research claiming an empiric dose reduction is inappropriate.^{7,15–18} Published data analyzing the effect of less than standard doses of enoxaparin on Factor Xa levels have shown that even at a reduced dose, a majority of patients still achieve a therapeutic or supratherapeutic Factor Xa level.^{19–22} Few trials have detailed the clinical implications of a reduced dosing strategy compared with the FDA-approved dose. Thompson-Moore et al prospectively demonstrated a nonsignificant increase in bleeding risk when comparing

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enoxaparin doses of ≥ 0.95 and < 0.95 mg/kg in 41 patients with a body mass index (BMI) of ≥ 40 kg/m². No thrombotic events were documented in either group.²¹ Spinler et al demonstrated a nonsignificant increase in bleeding risk when comparing the FDA-approved enoxaparin dose with a reduced dosing strategy in non-ST segment elevation myocardial infarction (NSTEMI) patients weighing > 150 kg.¹⁵ Because major bleeding and thrombotic events are rare, more evidence is required to detect a statistical difference if one exists. The purpose of the current study was to compare the incidence of major bleeding and thrombotic events between morbidly obese patients who received enoxaparin doses $< 90\%$ of the FDA-approved dose for therapeutic anticoagulation and those who received $\geq 90\%$ of the dose. Incidence of major bleeding between morbidly obese patients weighing > 150 kg and those weighing < 150 kg was also compared.

Methods

Study Population

A retrospective chart review was conducted from November 1, 2011, through November 1, 2016, at 3 community hospitals. After institutional review board approval, patients were identified using a report generated by the electronic medical record. Patients included in the report either had a listed dosing weight greater than or equal to 120 kg or had a total daily enoxaparin dose greater than 60 mg without a listed dosing weight. Patients were evaluated for inclusion in the primary analysis if the documented weight at baseline was greater than or equal to 120 kg, enoxaparin was administered with the intent of therapeutic anticoagulation for at least 24 hours, and evaluated outcomes were well documented. Patients with renal dysfunction, defined as a baseline CrCL less than 30 mL/min, were excluded from the primary analysis but were eligible for a separate ad hoc subgroup analysis. To provide the most conservative estimate of renal function, CrCL was calculated with the Cockcroft-Gault equation using ideal body weight (IBW). Patients were analyzed as 2 different entries if > 24 hours had passed between admissions. Patients who were pregnant, who were receiving hemodialysis or peritoneal dialysis, who were prescribed enoxaparin with the intent of VTE prophylaxis, who had documented heparin-induced thrombocytopenia (HIT), or who did not have a baseline weight or serum creatinine (SCr) documented were excluded from both the primary and subgroup analyses.

Outcomes

The primary outcome was the percentage of obese patients who experienced major bleeding within 7 days of discharge or discontinuation of enoxaparin therapy. Secondary outcomes included the percentage of patients who experienced minor bleeding, ischemic stroke, VTE, or all-cause death. Major bleeding was defined as any intracranial bleeding

(excluding microhemorrhages < 10 mm evident only on gradient-echo magnetic resonance imaging [MRI]), clinically overt signs of hemorrhage associated with a drop in hemoglobin ≥ 5 g/dL, or fatal bleeding (bleeding that directly results in death within 7 days). Bleeding was classified as fatal if a patient had both a downward trending hemoglobin and physician documentation that blood loss contributed to the patient's demise. Minor bleeding was defined as clinically overt signs of hemorrhage resulting in a hemoglobin drop of 3 to 5 g/dL. These definitions are consistent with the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria.²³ Each unit of packed red blood cells (PRBC) administered was counted as a decrease of 1 g/dL of hemoglobin. Thrombotic events were only recorded if the patient's medical record included objective proof (ie, MRI, ultrasound, ventilation and perfusion scan, or computerized tomography scan) that an event had occurred during the course of enoxaparin therapy. Outcomes were compared separately for the primary and subgroup analyses between patients who received $< 90\%$ of the FDA-approved dose of enoxaparin versus $\geq 90\%$ of the FDA-approved dose. All primary and secondary outcomes were also compared between patients who weighed ≥ 120 kg but < 150 kg versus patients who weighed ≥ 150 kg. Enoxaparin orders entered at all 3 hospitals were automatically rounded to the nearest commercially available syringe marking. Prescribers could choose to override this feature based on clinical judgment. Factor Xa values were rarely available due to the amount of time it takes for the lab to return results for this test at the studied institutions and thus were not reported. Baseline characteristics collected for each patient included age, gender, race, BMI, renal function, social and medical history linked to an increased risk of bleeding or thrombosis, and concurrent medications with a known risk of bleeding (ie, anticoagulants, antiplatelets, or nonsteroidal anti-inflammatory medications).

Statistical Analysis

Categorical variables were reported as frequencies and percentages. Continuous variables were reported as medians and interquartile ranges (IQRs). Because of the retrospective, noninterventional design of the study and the predicted low frequency of major bleeding events, no power calculation was performed. All primary and secondary outcomes were evaluated using the Pearson chi-square test as all outcome variables were binary. Odds ratios (OR) and 95% confidence intervals (CI) were reported for all comparisons when a detectable difference existed between groups. A *P* value of $< .05$ was considered to be statistically significant. To minimize the impact of baseline differences on dosage comparison data, a propensity score was generated for each patient. This score predicted the probability a patient would be prescribed a reduced or standard dose of enoxaparin accounting for all collected baseline characteristics. Patients were then matched 4-to-1 or excluded from the matched analysis if no comparable match was available. If the

Figure 1. Patient inclusion flow diagram.

Note. HIT = heparin-induced thrombocytopenia; CrCL = creatinine clearance.

absolute standardized difference between groups was less than 10% to 20% for each characteristic, matching would be considered successful. If successful, ORs would be calculated for the propensity-matched groups and compared with the prematched data. If results were not noticeably altered, prescriber bias alone could not explain observed outcomes. All statistics were analyzed using SAS version 9.4 (Cary, North Carolina).

Results

Patient Characteristics

There were 1333 patients identified by the electronic medical record report during the study period. Of those screened, 462 patients were included in the primary analysis and 25 were included in the subgroup analysis (Figure 1). Baseline characteristics for the primary analysis are presented in Table 1. The median baseline weight was 133 kg (range: 120-236 kg), and median BMI was 44.0 kg/m² (range: 26.4-92.1 kg/m²). The average age of the study cohort in years was 57 (range:

20-87), and >80% of the cohort was Caucasian. The average duration of enoxaparin therapy was 3.5 days. Over 50% of both dosing groups were on concomitant warfarin therapy. Enoxaparin was most commonly prescribed for stroke prevention in atrial fibrillation and non-acute VTE prevention while bridging a patient to warfarin. Fifty-six patients received an enoxaparin dose <90% of the FDA-approved dose compared with 406 patients who received ≥90% of the FDA-approved dose. The average total daily dose of enoxaparin in the low-dose group was 74.3% of the FDA-approved dose compared with 99.1% in the high-dose group. Baseline characteristics were similar between dosing groups, though BMI was higher in the low-dose group.

Clinical Outcomes

A total of 18 bleeding events were documented during the study period, 11 of which were classified as major bleeds and 7 as minor bleeds. No statistically significant difference was observed in the number of major bleeding events (5.4% vs 2.0%, $P = .12$) or minor bleeding events (0.0% vs 1.7%,

Table 1. Baseline Characteristics for Primary Analysis.

Demographics	<90% FDA-approved dose	>90% FDA-approved dose
	Statistics (n = 56)	Statistics (n = 406)
Age (years), median [IQR]	55.0 [46.5, 63.5]	58.0 [48.0, 67.0]
Female, n (%)	32 (57.1)	178 (43.8)
Caucasian, n (%)	44 (78.6)	336 (82.8)
BMI (kg/m ²), median [IQR]	48.8 [41.9, 60.9]	43.5 [39.1, 48.8]
Baseline SCr (mg/dL), median [IQR]	0.82 [0.71, 1.1]	0.91 [0.77, 1.2]
Baseline CrCL (mL/min), median [IQR]	85.9 [61.1, 104.1]	81.0 [59.3, 102.5]
Baseline platelets (per mL), median [IQR]	242.0 [192.0, 285.5]	211.0 [165.0, 261.0]
Baseline INR, median [IQR] ^a	1.2 [1.0, 1.4]	1.1 [1.0, 1.2]
Duration of enoxaparin (days), median [IQR]	2.5 [2.0, 4.0]	3.0 [2.0, 4.0]
Medical history		
Alcoholism, n (%)	1 (1.8)	38 (9.4)
Current smoker, n (%)	3 (5.4)	76 (18.7)
Cirrhosis, n (%)	1 (1.8)	5 (1.2)
DVT, n (%)	16 (28.6)	103 (25.4)
PE, n (%)	16 (28.6)	101 (24.9)
Stroke or TIA, n (%)	5 (8.9)	62 (15.3)
Clotting disorder, n (%)	2 (3.6)	16 (3.9)
GI bleeding/ICH, n (%)	7 (12.5)	42 (10.3)
Active malignancy, n (%)	3 (5.4)	18 (4.4)
Indication		
Atrial fibrillation/nonacute bridging, n (%)	32 (57.1)	194 (47.8)
DVT, n (%)	5 (8.9)	67 (16.5)
PE, n (%)	7 (12.5)	62 (15.3)
DVT and PE, n (%)	3 (5.4)	29 (7.1)
NSTEMI, n (%)	0 (0.0)	11 (2.7)
Other, n (%) ^b	9 (16.1)	43 (10.6)
Concomitant pharmacotherapy		
Warfarin, n (%)	35 (62.5)	277 (68.2)
P2Y12 inhibitor, n (%)	1 (1.8)	22 (5.4)
Aspirin, n (%)	22 (39.3)	154 (37.9)
NSAID, n (%)	10 (17.9)	59 (14.5)
tPA (during admission), n (%)	1 (1.8)	7 (1.7)

Note. FDA = Food and Drug Administration; IQR = interquartile range; BMI = body mass index; SCr = serum creatinine; CrCL = creatinine clearance; INR = international normalized ratio; DVT = deep vein thrombosis; PE = pulmonary embolism; TIA = transient ischemic attack; GI = gastrointestinal; ICH = intracranial hemorrhage; NSTEMI = non-ST segment elevation myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; tPA = tissue plasminogen activator.

^aNot available for all patients; n = 45 for <90% FDA-approved dose and n = 365 for >90% FDA-approved dose.

^bIncludes suspected but unconfirmed acute coronary syndrome, suspected but unconfirmed thrombosis, arterial thrombosis, coronary thrombosis, and portal vein thrombosis.

$P = .32$) between patients receiving <90% of the FDA-approved dose and patients who received $\geq 90\%$ of the FDA-approved dose. No statistically significant difference was observed in number of thrombotic ($P = .52$) or ischemic events ($P = .60$) between dosing groups (Table 2). All baseline characteristic propensity matches were considered successful, and results were not noticeably altered post matching. This indicates observed results were not solely the result of predictable baseline bleeding or thrombosis risk (Table 3). Patients with a documented major or minor bleed during the follow-up period were more likely to be on warfarin (77.8% vs 67.1%), to have an active malignancy (27.8% vs 3.6%), and to have a history

of gastrointestinal bleeding or intracranial hemorrhaging (27.8% vs 9.9%). Only 1 patient had an international normalized ratio above 3.0 at the time of the bleeding event. There were no statistical differences in the primary or secondary outcomes when comparing patients weighing ≥ 150 kg and those weighing ≥ 120 kg but <150 kg (Table 4).

Subgroup Analysis

Two major bleeds and 1 ischemic stroke were documented during the study period in the low-CrCL subgroup (Table 5). Both patients with a documented major bleed did not

Table 2. Unadjusted Clinical Outcomes for Primary Analysis—Dose Comparison.

	<90% FDA-approved dose n = 56 (%)	>90% FDA-approved dose n = 406 (%)	OR (95% CI)	P
Major bleeding, n (%)	3 (5.4)	8 (2.0)	2.82 (0.7-10.9)	.12
Minor bleeding, n (%)	0 (0.0)	7 (1.7)	—	.32
Major/minor bleeding, n (%)	3 (5.4)	15 (3.7)	1.48 (0.4-5.3)	.55
VTE, n (%)	0 (0.0)	3 (0.74)	—	.52
Ischemic stroke, n (%)	0 (0.0)	2 (0.49)	—	.60
All-cause death, n (%)	2 (3.6)	5 (1.2)	2.97 (0.6-15.7)	.18

Note. FDA = Food and Drug Administration; OR = odds ratio; CI = confidence interval; VTE = venous thromboembolism.

Table 3. Propensity-Matched Clinical Outcomes for Primary Analysis—Dose Comparison.

	<90% FDA-approved dose n = 43 (%)	>90% FDA-approved dose n = 153 (%)	OR (95% CI)	P
Major bleeding	3 (7.0)	3 (2.0)	3.75 (0.7-19.3)	.092
Minor bleeding	0 (0.0)	3 (2.0)	—	.35
Major/minor bleeding	3 (7.0)	6 (3.9)	1.84 (0.4-7.7)	.40
VTE	0 (0.0)	1 (0.65)	—	.60
Ischemic stroke	0 (0.0)	0 (0.0)	—	—
All-cause death	2 (4.7)	2 (1.3)	1.84 (0.4-7.7)	.17

Note. FDA = Food and Drug Administration; OR = odds ratio; CI = confidence interval; VTE = venous thromboembolism.

Table 4. Unadjusted Clinical Outcomes for Weight Comparison.

	≥150 kg n = 92 (%)	≥120 to <150 kg n = 370 (%)	OR (95% CI)	P
Major bleeding	1 (1.1)	10 (2.7)	0.67 (0.1-5.6)	.36
Minor bleeding	1 (1.1)	6 (1.6)	0.40 (0.1-3.1)	.71
Major/minor bleeding	2 (2.2)	16 (4.3)	0.49 (0.1-2.2)	.34
VTE	0 (0.0)	3 (0.81)	—	.39
Ischemic stroke	0 (0.0)	2 (0.54)	—	.48
All-cause death	1 (1.1)	6 (1.6)	0.67 (0.1-5.6)	.71

Note. OR = odds ratio; CI = confidence interval; VTE = venous thromboembolism.

Table 5. Unadjusted Clinical Outcomes for Low-CrCL Subgroup Analysis—Dose Comparison.

	<90% FDA-approved dose n = 2 (%)	>90% FDA-approved dose n = 23 (%)	P
Major bleeding	0 (0.0)	2 (8.7)	.66
Minor bleeding	0 (0.0)	0 (0.0)	—
Major/minor bleeding	0 (0.0)	2 (8.7)	.66
VTE	0 (0.0)	0 (0.0)	—
Ischemic stroke	1 (50.0)	0 (0.0)	<.001
All-cause death	0 (0.0)	0 (0.0)	—

Note. CrCL = creatinine clearance; FDA = Food and Drug Administration; VTE = venous thromboembolism.

receive an enoxaparin dose reduction for renal impairment because CrCL is calculated using adjusted body weight at all 3 institutions analyzed rather than IBW used in this study. There was technically a statistically higher risk of

ischemic stroke when patients received an enoxaparin dose <90% of the FDA-approved dose (50.0% vs 0.0%, $P < .001$); however, there were only 2 patients in total in this group. Furthermore, the one documented ischemic

stroke was in a patient experiencing refractory ischemic strokes even in the presence of a low platelet count and a therapeutic INR, and thus, the event was likely unrelated to enoxaparin failure.

Discussion

In this retrospective chart review, patients weighing ≥ 120 kg who received $<90\%$ of the FDA-approved recommended dose of enoxaparin were not shown to have a statistically lower major or minor bleeding rate, nor a statistically higher rate of thrombotic or ischemic events. BMI was higher on average in the lower dosing group; nevertheless, the observed results were not noticeably altered when patients were propensity matched for baseline characteristics indicating this difference did not have a significant impact.

The prescribing habits observed in the institutions studied support previous findings but to a lesser degree.^{15,21} Twenty-six percent of patients weighing ≥ 150 kg received a dose of enoxaparin $<90\%$ of the FDA-recommended dose and 52% received a dose $<95\%$ of the FDA-recommended dose. By comparison, 9% of patients weighing ≥ 120 kg but <150 kg received a dose of enoxaparin $<90\%$ of the FDA-recommended dose and 22% received a dose $<95\%$ of the FDA-recommended dose. This indicates that prescribers are significantly less comfortable with dosing patients >150 kg at standard dosing levels.

Warfarin use, active malignancy, and history of gastrointestinal bleeding or intracranial hemorrhaging all occurred at more than a 10% higher incidence in patients who experienced a major or minor bleed during the follow-up period. Previous studies in this population have identified both active malignancy and warfarin use as possible predictive factors for bleeding on at least 1 occasion.^{24,25} If considering enoxaparin use in a morbidly obese patient with one or more of these risk factors, a dose reduction may be more reasonable.

This is the largest study to analyze clinical outcomes for enoxaparin dosing across all indications where the intent of therapy was therapeutic anticoagulation. This trial does contain some notable limitations. Despite the large size of this trial, it is likely that with the low detection of clinical events that the data are still underpowered to detect a meaningful difference. A higher percentage of major bleeding was documented in the lower dosing group. Due to the retrospective nature of this study, it is possible that an important baseline factor was not identified, in spite of using propensity matching to control for baseline risk. The dosing cutoff used for comparison (ie, $<90\%$ of the FDA-approved dose) may have been too high. Two earlier trials both found that in morbidly obese patients, an enoxaparin dose between 70% and 75% of the recommended dose was, on average, sufficient to reach a therapeutic Factor Xa level.^{20,24} All 3 patients who experienced major bleeding in the lower dosing group had an enoxaparin dose $>80\%$ of the recommended dose—a threshold only 20 of the 56 patients in the low-dosing group surpassed.

Conclusion

There is not enough evidence to recommend an empiric enoxaparin dose reduction in all morbidly obese patients, nor to justify dose capping for all patients weighing >150 kg. More prospective, controlled trials are required to identify which morbidly obese patients may qualify for an empiric enoxaparin dose reduction and to what extent the dose of enoxaparin should be reduced. Due to existing uncertainty, if enoxaparin is used for therapeutic anticoagulation in the morbidly obese, Factor Xa monitoring should be considered. An empiric dose reduction may be considered if there are other known risk factors for bleeding present and timely Factor Xa monitoring is not available.

Acknowledgment

The authors acknowledge Matthew Karafa, PhD, for computing all reported statistics.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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