Adjusted-Dose Enoxaparin for VTE Prevention in the Morbidly Obese

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Abstract

Background: Venous thromboembolism (VTE) is a major health problem and common cause of morbidity and mortality in hospitalized patients. While trials in both surgical and medically ill patients have demonstrated efficacy and safety of enoxaparin for VTE prophylaxis (VTEP), they failed to adequately represent morbidly obese (body mass index > 40 kg/m²) patients. **Objective:** To assess the impact of a weight-adjusted enoxaparin dosing algorithm on anti-factor Xa levels, thrombosis, and bleeding in morbidly obese patients. **Methods:** A retrospective chart review was conducted, which included morbidly obese patients receiving VTEP with adjusted-dose enoxaparin. Patients received enoxaparin 0.5 mg/kg subcutaneously once or twice daily based on VTE risk. An anti-factor Xa level was drawn 3 to 5 hours after 2 or more consecutive doses. The primary outcome was the percentage of patients achieving target anti-factor Xa levels, defined as 0.2 to 0.6 IU/mL. Secondary outcomes included the incidence of symptomatic VTE and major bleeding. **Results:** Of the 182 charts reviewed, 141 anti-factor Xa levels from 130 patients met inclusion criteria. The study population was 44% male, and the median body mass index was 45.6 kg/m². A total of 120 anti-factor Xa levels (85.1%) were within the target prophylactic range. Sixteen anti-factor Xa levels (11.3%) were below target range, and 5 (3.4%) were above range. The only significant difference among the 3 groups was baseline renal function ($P = .035$). There were 2 thromboembolic events and 1 major bleed in the study population. **Conclusion:** A weight-based VTEP dosing strategy for morbidly obese patients is effective without an apparent increase in adverse events.

Keywords

venous thromboembolism, prophylaxis, morbidly obese, low-molecular-weight heparin, enoxaparin, anti-factor Xa level, major bleeding, pharmacokinetics

Background

Venous thromboembolism (VTE), composed of both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major public health problem and common cause of morbidity and mortality in hospitalized patients. It is estimated that 350 000 to 600 000 people develop VTE each year in the United States, with more than 100 000 eventually losing their lives.¹ When applying the observed rates of VTE by age and gender to the projected US census population, it is anticipated that rates of VTE in adults will more than double over the next 40 years, making VTE prevention essential for all at-risk patients.² Numerous clinical trials have been conducted evaluating pharmacologic agents for VTE prophylaxis (VTEP). The most extensively studied agents include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux.³

The effectiveness of LMWH for VTEP has been consistently demonstrated in surgical patients. In a meta-analysis

of 8 randomized trials comparing LMWH to placebo for VTEP in general surgery patients ($n = 5520$), a 71% reduction in symptomatic VTE was observed in the LMWH group ($P = .009$).⁴ Another meta-analysis, within the same article, comprising 51 trials ($n = 48\,624$) comparing LMWH to the active control UFH in surgical patients showed that LMWH provided a significant 41% reduction in symptomatic VTE ($P = .049$).⁴

Several landmark trials have also verified the efficacy of LMWH for the prevention of VTE in medically ill patients.

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In the MEDENOX trial ($n = 866$), Samama et al illustrated a VTE incidence of 5.5% in the enoxaparin group versus 14.9% in the placebo group ($P < .001$). The difference in major bleeds was not statistically significant between the 2 groups (1.7% in the enoxaparin group vs 1.1% in the placebo group).⁵ The PREVENT study ($n = 2991$), utilizing dalteparin, demonstrated a VTE incidence of 2.77% compared to 4.96% in the placebo group ($P = .0015$) with a nonsignificant increase in major bleeding rates (0.43% vs 0.16%, respectively; $P = .15$).⁶

While trials in both surgical and medically ill patients were pivotal in establishing the efficacy and safety of LMWH for VTEP, they failed to adequately represent morbidly obese (body mass index [BMI] $\geq 40 \text{ kg/m}^2$) patients. In trials of VTEP in surgical patients that reported BMI, fewer than 25% of enrolled subjects were obese.^{7,8} In a meta-analysis of 9 randomized controlled trials for VTEP in medically ill patients, the average BMI was 25.6 kg/m^2 .⁹ Obesity is a known risk factor for VTE, and a strong negative correlation has been shown between BMI and anti-factor Xa activity after administering standard doses of LMWH.^{10,11} Additionally, clinical trials have shown a significantly increased incidence of thrombosis with increasing BMI when standard prophylactic dosing (enoxaparin 30 mg SQ twice daily or 40 mg SQ once daily) is employed.^{12,13}

This information prompted several investigators to evaluate the safety and efficacy of dose-adjusted LMWH for VTE prevention in obese patients. Among patients undergoing bariatric surgery, Scholten et al compared enoxaparin 40 mg every 12 hours to the standard 30 mg every 12 hours. This study demonstrated a significant decrease in DVT complications with the more aggressive dosing strategy (1.4% vs 0.6%; $P < .01$).¹⁴ In medically ill, morbidly obese patients, Freeman et al prospectively compared 3 different dosing regimens including fixed-dose enoxaparin 40 mg daily, lower dose enoxaparin 0.4 mg/kg daily, and higher dose enoxaparin 0.5 mg/kg daily. The high-dose group achieved recommended target anti-factor Xa levels more frequently than the low-dose and fixed-dose groups ($P < .05$). There were no thromboembolic or hemorrhagic events in the study population.¹⁵ Wang et al looked at 3928 morbidly obese patients with both a weight $>100 \text{ kg}$ and BMI $\geq 40 \text{ kg/m}^2$ who received either high-dose thromboprophylaxis (heparin 7500 units 3 times daily or enoxaparin 40 mg twice daily) or standard thromboprophylaxis (heparin 5000 units 2 or 3 times daily or enoxaparin 40 mg once daily). They found that the risk of symptomatic VTE was approximately halved in the high-dose group compared to the standard-dose group ($P = .05$). Additionally, the rate of hemorrhage was similar in the high-dose group compared to the standard-dose group (7.18% vs 8.44%; $P = .15$).¹⁶

Unfortunately, a consensus on optimal dosing of VTEP in morbid obesity still does not exist. The eighth edition of the American College of Chest Physicians guideline on

Figure 1. Standardized weight-adjusted VTE prophylaxis protocol.

VTE, venous thromboembolism; BID, twice daily.

antithrombotic therapy for VTEP recommends a weight-based dosing strategy in obese patients but does not highlight a specific regimen.¹⁷ Nutescu et al proposes increasing standard prophylactic doses by 30%.¹⁸

Based on available evidence in the literature, our institution implemented a standardized dose-adjusted enoxaparin strategy (stratified by VTE risk) for VTEP in morbidly obese patients in June 2009 (Figure 1).^{14-16,19-21} Morbidly obese patients considered to be very high risk for VTE (ie, hip or knee orthopedic surgery or multiple traumas) receive enoxaparin 0.5 mg/kg SQ twice daily instead of the standard 30 mg twice daily. Those considered to be at moderate risk for VTE (ie, most major general surgery or critically ill [intensive care unit, ICU] patients) receive enoxaparin 0.5 mg/kg SQ once daily instead of the standard 40 mg once daily. All doses were calculated based on the patient's total body weight.

The purpose of our study was to assess anti-factor Xa levels and clinical outcomes associated with use of a standardized dose-adjusted enoxaparin, stratified by VTE risk, for VTEP in morbidly obese patients at the University of New Mexico Hospital.

Methods

We conducted a retrospective chart review of all morbidly obese patients admitted to our institution from June 2009 to January 2014 who received VTEP with dose-adjusted enoxaparin. These patients were identified via a query of our clinical intervention software program. The inclusion criteria were as follows: age ≥ 18 years old, a BMI $\geq 40 \text{ kg/m}^2$, receipt of dose-adjusted enoxaparin (with an allowed variance of up to 20% from the standard regimens due to rounding and availability of enoxaparin dosage forms) for

VTEP, and at least one anti-factor Xa level drawn 3 to 5 hours after 2 or more consecutive doses.²² Exclusion criteria included any patient on therapeutic anticoagulation treatment, any active bleed or bleeding disorder, or a creatinine clearance <30 mL/min (based on Cockcroft-Gault using adjusted body weight) at any point during admission.

No definitive prophylactic target anti-factor Xa range has been established. A prophylactic target anti-factor Xa level of 0.2 to 0.6 IU/mL was chosen for this study based on levels suggested in previous investigations.^{19-21,23} Additionally, this target range facilitates levels that do not encroach on the therapeutic range of >0.6 to 1 IU/mL and are also not undetectable, which may leave the patient unprotected. Anti-factor Xa levels were measured 3 to 5 hours after at least the second consecutive dose to approximate steady state.²² While it is possible patients receiving BID (twice daily) dosing may not have been at steady state after only 2 doses, it was decided to measure at this point to ensure at least one level was drawn for all subjects prior to discharge. Quantitative determination of the enoxaparin anti-factor Xa activity was performed by TriCore Reference Laboratories using reagents and instruments from Diagnostica Stago (Asnières, France). The STA Liquid Anti-Xa kit uses the patient's own antithrombin potentiated by heparin to inhibit an excess of factor Xa. Residual factor Xa then hydrolyzes a synthetic chromogenic substrate causing the release of paranitroaniline. The change in absorbance (and resulting yellow color) is measured at 405 nm and relates directly to the concentration of Xa and indirectly to the concentration of heparin. The assay is calibrated with STA Multi Hep Calibrator, a kit containing both LMWH and UFH standards, allowing both types of heparin to be measured with one assay. For enoxaparin, the assay is linear from 0.10 to 2.00 anti-Xa IU/mL.

Enoxaparin administration times and anti-factor Xa level sample collections times were determined via the patient's electronic medical record. For patients who had more than one anti-factor Xa level available, only the first appropriately drawn level for each admission was included.

The primary outcome of this study was the percentage of anti-factor Xa levels drawn in morbidly obese patients that achieved the recommended peak target prophylactic level after receipt of dose-adjusted enoxaparin. The percentage of anti-factor Xa values below, within, and above target levels was determined.

Secondary outcomes included patient characteristics influencing anti-factor Xa levels, incidence of DVT or PE up to 30 days postdischarge (assessed and confirmed by Doppler ultrasonography, computed tomography [CT] scan, or ventilation/perfusion scan), and major bleeding events occurring within 5 half-lives of the last administered enoxaparin dose. Major bleeding was defined using the International Society on Thrombosis and Haemostasis definitions for both surgical and medical populations, including

any fatal bleed; symptomatic bleeding in critical areas or organs such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; hemoglobin decrease of ≥ 2 g/dL; transfusion of ≥ 2 units of blood or if medical/surgical intervention was required; surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability.^{24,25} As we had no comparator group, adverse event rates for both thrombosis and bleeding were compared to those reported in previous trials that focused on morbidly obese patients. Data on VTE risk factors (ie, active cancer, history of VTE, ICU admission, and estrogen therapy) were also collected.

This study was approved in accordance with the ethical standards of the institutional review board.

Data Analysis

Patient demographics, baseline characteristics, and outcomes were reported using descriptive statistics. Mood's median test for continuous variables and Fisher's exact test for categorical variables were used to compare the differences among the 3 anti-factor Xa level categories (ie, below, within, and above target). The a priori level of significance was .05. Statistical analysis was performed using SPSS version 19.0.

Results

A total of 182 patient charts were reviewed for 193 anti-factor Xa levels; 141 anti-factor Xa levels from 130 patients met study inclusion criteria. Eight patients had more than one anti-factor Xa level, each from a different admission. Reasons for anti-Xa level exclusion included the following: anti-factor Xa level drawn outside the specified timing ($n = 25$), enoxaparin administration time not documented in the patients chart ($n = 23$), utilization of a standard prophylactic dose of enoxaparin ($n = 2$), and BMI < 40 kg/m² ($n = 2$).

The median patient age was 48.8 years (range = 18-77). The study population included 62 males (44%) and 79 females (54%). The median body weight was 130 kg (range = 96.3-232.8), and the median BMI was 45.6 kg/m² (range = 40-90.4). The study cohort comprised 115 surgical patients (81.6%) and 26 medically ill patients (18.4%). The demographic data and baseline characteristics are summarized in Table 1.

The most prevalent VTE risk factors were active cancer (10.6%) and patients who were critically ill, which was defined as anyone residing in the ICU when enoxaparin was started (19.9%). The remaining risk factors occurred in less than 5% of patients evaluated.

The median number of doses a patient received prior to obtaining an anti-factor Xa level was 3 (range = 2-45). Approximately 15% (20 levels) of anti-factor Xa levels were drawn after the second consecutive enoxaparin dose.

Table 1. Characteristics of the Study Population^a.

Patient Characteristics	Overweight (n = 141)
Age (years)	48.8 (18, 77)
Male, n (%)	62 (44)
Ethnicity, n (%)	
White	64 (45.4)
African American	3 (2.1)
Native American	43 (30.5)
Asian	1 (0.7)
Other ^b	30 (21.3)
Weight (kg)	130 (96.3, 232.8)
Height (cm)	168 (143, 190.5)
Body mass index (kg/m ²)	45.6 (40, 90.4)
Serum creatinine (mg/dL)	0.71 (0.40, 2.62)
Estimated CrCl (mL/min)	146.2 (52.5, 315.4)
Enoxaparin 0.5 mg/kg BID, n (%)	84 (59.6%)
Number of doses before anti-factor Xa level	3 (2-45)
Anti-factor Xa level (IU/mL)	0.31 (0.12, 0.75)
Time between dose and draw (minutes)	244 (180, 360)
Surgical indication, n (%)	115 (81.6)

Abbreviations: CrCl, creatinine clearance; BID, twice daily.

^aMedian (min, max), unless otherwise reported.

^bOther = race listed as other in patient chart.

The remaining 85% of levels were drawn after at least 3 consecutive enoxaparin doses with only 1.4% (2 levels) drawn after 10 consecutive doses. A total of 120 (85.1%) anti-factor Xa levels were within the target range of 0.2 to 0.6 IU/mL. Sixteen anti-factor Xa levels fell below the target range (11.3%) and 5 levels were above the target range (3.5%; Figure 2). There were no significant differences among the 3 groups (ie, below, within, and above target range) with respect to age, gender, race, weight, height, number of enoxaparin doses prior to anti-factor Xa laboratory draw, time between enoxaparin administration and anti-factor Xa laboratory draw, and indication for VTEP (surgical vs medically ill). There was, however, a statistically significant difference among the 3 groups in regard to renal function. Patients with anti-factor Xa concentrations below the target range had a median serum creatinine of 0.70 mg/dL (range = 0.50-0.90) while those within and above the target range had a median serum creatinine of 0.75 mg/dL (range = 0.40-2.62) and 0.80 mg/dL (range = 0.60-1), respectively; $P = .035$.

There were 2 thromboembolic events in the study population. One patient was discharged to a rehabilitation facility on a 14-day course of enoxaparin (0.5 mg/kg SQ twice daily) for VTEP. He was diagnosed with a DVT on Doppler 28 days postdischarge and started on warfarin. The second patient was discharged home after major abdominal surgery without VTEP. She was subsequently admitted 10 days later secondary to hypotension and tachycardia and was found to have

multiple pulmonary emboli on CT scan. Both patients had anti-factor Xa levels that were below target range (0.19 and 0.16 IU/mL, respectively) during the index hospitalization.

One patient developed fatal bleeding after being admitted for ileostomy closure secondary to persistent diverticulitis. The initial procedure was well tolerated; however, enoxaparin (0.5 mg/kg SQ daily) was stopped 7 days after initiation due to decreasing hemoglobin and hematocrit levels. The patient developed gastrointestinal bleeding that persisted for the next week and required multiple blood transfusions. She was eventually made comfort care and transferred to an inpatient hospice facility. The patient had an anti-factor Xa concentration that was within target range (0.23 IU/mL). Given the ongoing nature of the bleed well after enoxaparin was eliminated from her system (ie, beyond 5 half-lives), it is difficult to state with certainty that the enoxaparin was solely attributable to the adverse outcome.

Discussion

Based on the knowledge that standard dosing is not sufficient, a number of investigators have studied higher fixed doses of enoxaparin for VTEP in morbidly obese patients, specifically in patients undergoing bariatric surgery. Rowan et al looked at 52 patients undergoing laparoscopic gastric bypass who received either 30 mg or 40 mg of enoxaparin BID. The average BMI was 48.4 kg/m² and 48.5 kg/m², respectively. Neither regimen consistently achieved peak recommended anti-factor Xa levels (defined as 0.18-0.44 IU/mL). However, the 40 mg BID group was more successful in achieving target levels after the third enoxaparin dose (41.7% vs 9.1%). The investigators concluded that even 40 mg BID may not be sufficient for VTE prevention in patients undergoing bariatric surgery.²⁶

Simone et al looked at even higher fixed doses of enoxaparin for VTEP in bariatric surgery patients and compared 40 mg BID to 60 mg BID. The average BMI was 48.8 kg/m² and 47.3 kg/m², respectively. Patients in the 40 mg BID group were unable to consistently achieve target anti-factor Xa levels (defined as 0.18-0.44 IU/mL) and had a large proportion of concentrations that were subtherapeutic after the third enoxaparin dose (44%). All patients in the 60 mg BID group reached target anti-factor Xa concentrations. While there was no increase in major bleeds, 57% of these patients had supratherapeutic anti-factor Xa concentrations, indicating that a fixed dosing strategy may not always be appropriate in all morbidly obese patients.²⁷

In our study, weight-based dosing of enoxaparin (0.5 mg/kg once or twice daily based on risk) in surgical and medically ill morbidly obese patients led to anti-factor Xa levels within the peak target range approximately 85% of the time. Two patients developed VTE (1.42%) in the 30-day postdischarge period, and 1 patient developed a major bleed (0.71%).

Figure 2. Peak anti-factor Xa levels.

Our findings are similar to what has been reported in previous studies of weight-based dosing strategies for VTEP in morbidly obese patients. Rondina et al used a weight-based dosing strategy of 0.5 mg/kg of enoxaparin once daily in 28 morbidly obese medically ill patients. Anti-factor Xa levels were consistently within or near recommended range (reported as 0.08-0.59 IU/mL) without any episodes of VTE or hemorrhage.²¹ Freeman et al also demonstrated that weight-based dosing (0.4 and 0.5 mg/kg once daily) of enoxaparin more consistently produces target anti-factor Xa levels (defined as 0.2-0.5 IU/mL) without an increase in hemorrhagic events when compared to fixed adjusted-dose or standard dosing regimens. Eighty-two percent of patients in the fixed-dose group fell below the target range compared to only 13% in the high-dose group.¹⁵

Our study expands on previous literature regarding VTEP in morbidly obese patients by including real-world data on both surgical and medically ill patients using a standardized, risk-stratified dosing strategy. To our knowledge, this is the largest reported study cohort to date utilizing weight-based dosing for VTEP in morbidly obese patients. There was no cap on enoxaparin dosing and patients weighing as much as 232 kg were evaluated.

While not sufficiently powered to study clinical outcomes of thrombosis or hemorrhage, rates of adverse outcomes in our study are similar to what has been seen in other trials looking specifically at dose-adjusted enoxaparin for VTEP in morbidly obese patients (Table 2).^{14-16,21,27}

Our study has several limitations. This was a single-center study and subjects may not be representative of populations at other health facilities. Retrospective cohorts are inherently more prone to bias. Some anti-factor Xa levels were drawn after the second dose, which may not be

Table 2. Thrombotic and Bleeding Events Compared to Other Morbidly Obese Trials.

Trials	Symptomatic VTE, n/N (%)	Major Bleeding, n/N (%)
Parikh et al	2/141 (1.42)	1/141 (0.71)
Freeman et al ¹⁵	0/20 (0)	0/20 (0)
Rondina et al ²¹	0/28 (0)	0/28 (0)
Scholten et al ¹⁴	2/389 (0.51)	1/389 (0.26)
Simone et al ²⁷	0/40 (0)	1/40 (2.5)
Wang et al ¹⁶	12/1559 (0.77)	112/1559 (7.18)

Abbreviation: VTE, venous thromboembolism.

representative of steady state. However, the majority of anti-factor Xa levels (85%) were drawn after at least 3 doses, and thus these patients were likely at steady state. While larger than all previous studies on this topic, we did have a small sample size. Also, we did not have a comparator group. Follow-up was limited and we were only able to track thrombosis or bleeding events among patients who returned to our institution. We only evaluated a single anti-factor Xa level, which did not allow us to determine potential drug accumulation over time. Finally, it is important to note that our primary outcome, anti-factor Xa levels, have not been correlated with clinical outcomes of bleeding or thrombosis.

Conclusion

Our findings suggest that using standardized weight-based dosing (stratified by VTE risk) of enoxaparin for VTEP in surgical and medically ill morbidly obese patients consistently

produces peak anti-factor Xa levels within the recommended target prophylactic range and does not appear to lead to increased adverse events.

Authors' Note

The study was presented at the 2013 American Society of Health-System Pharmacists Midyear Clinical Meeting in Orlando, FL, December 2013 (Abstract No. 9-133); and the 2014 Western States Pharmacy Conference in San Diego, CA, May 2014 (Abstract No. 426).

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.

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