

Assessment of anti-factor Xa activity of enoxaparin for venous thromboembolism prophylaxis in morbidly obese surgical patients

Nouf Al Otaib¹, Zohour Bootah¹, Maha A. Al Ammari^{1,2}, Tariq M. Aldebasi³, Abdulmalik M. Alkatheri^{1,2}, Shmeylan A. Al Harbi^{1,2}, Salah M. AbuRuz^{2,4}, Abdulkareem M. AlBekairy^{1,2}

¹Department of Pharmaceutical Care, King Abdulaziz Medical City, ²Department of Pharmacy Practice, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, ³Division of Ophthalmology, King Abdulaziz Medical City, Riyadh, Saudi Arabia, ⁴Department of Clinical Pharmacy, College of Pharmacy, University of Jordan, Amman, Jordan

Address for correspondence:

Dr. Abdulkareem M. AlBekairy,
College of Pharmacy,
King Saud Bin Abdulaziz University for Health Sciences,
Riyadh, Saudi Arabia.
E-mail: bekairy@ngha.med.sa

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Abstract:

BACKGROUND: Venous thromboembolism (VTE) can be encountered by 60% of hospitalized patients. Anticoagulants have been recommended to reduce the risk of VTE in patients with risk factors. However, no specific dosing recommendations for obese patients are provided in the current practice guidelines. The purpose of this study was to determine the efficacy and safety of weight-based dosing of enoxaparin for VTE prophylaxis among morbidly obese patients undergoing surgery.

METHODS: Adult patients were enrolled if they have a body mass index (BMI) of ≥ 35 kg/m² and were scheduled for surgery. These patients were prescribed enoxaparin (0.5 mg/kg subcutaneously [SC] once daily). Peak anti-factor Xa levels were measured 4 h after the third dose of enoxaparin. The primary outcome measure was to determine whether a weight-based dosing of enoxaparin of 0.5 mg/kg produce the anticipated peak anti-Xa levels (0.2–0.6 IU/m) among obese patients undergoing surgery. Secondary outcomes include the incidence of VTE, the incidence of minor or major bleeding, and the incidence of heparin-induced thrombocytopenia (HIT).

RESULTS: Fifty patients were enrolled in the study. The mean age was 53 ± 16 years, 74% of the patients were female. The mean BMI was 40.5 ± 5 , and the average enoxaparin dose was 50 ± 9.8 SC daily. Nearly 88% of the patients reached the target anti-factor Xa (0.427 ± 0.17). None of the patients developed HIT or VTE. There was no incidence of major or minor bleeding.

CONCLUSIONS: Weight-based enoxaparin dose led to the anticipated peak anti-Xa levels (0.2–0.6 IU/mL) in most of the morbidly obese study patients undergoing surgery without any evidence of major side effects. The weight-based dosing of enoxaparin was also effective in preventing VTE in all patients. Although these results are promising, further comparative trials are needed in the setting of morbidly obese surgical patients.

Keywords:

Low molecular weight heparin, obese, surgery, venous thromboembolism, weight-based dose

Venous thromboembolism (VTE) includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE has been shown to affect 10%–60% of hospitalized and nonhospitalized patients and is associated with a high mortality and morbidity.^[1] Hospitalized patients have a risk of up to 8 times of DVT and PE. Contributing factors

include surgery, previous history of VTE, and immobility.^[1–3] Obesity is also recognized as a major risk factor for VTE.^[1,4] The prevalence of obesity is increasing worldwide; it was found to be around 35.5% in Saudi Arabia and around 33.4% in the USA.^[5,6]

Anticoagulants, such as low molecular weight heparins (LMWHs) and unfractionated

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heparin (UFH), have been recommended for VTE prophylaxis in patients with risk factors.^[1] Appropriate use of these agents has been reported to reduce the risk of VTE by more than 50%.^[1-3,7,8] For VTE prophylaxis, fixed doses of LMWHs are recommended. No specific dosing recommendations for VTE prophylaxis for medically and surgically obese patients are provided in the current practice guidelines. Higher doses of LMWH or UFH are only recommended in bariatric surgery.^[1]

Concerns have been raised that fixed doses are inadequate in obese patients.^[4,9,10] In fact, obese patients are not appropriately represented in clinical trials and are sometimes excluded from trials.^[11] Since obesity affects the kinetics and distribution of drugs, obese patients may respond differentially to the usual doses of anticoagulants and are at an increased risk of treatment failure with mortality and morbidity consequences. In one retrospective study, there was a significant association between patients' weights and thrombosis after enoxaparin prophylaxis ($P = 0.0002$).^[4] Frederiksen *et al.* have concluded that current doses of enoxaparin may be inadequate in obese patients.^[9]

A recent review investigated the causes of "breakthrough" (VTE) events despite the receipt of appropriate prophylaxis in surgery patients.^[12] The authors concluded that unsuccessful prophylaxis could be attributed to the inadequate enoxaparin dosing. The authors have also concluded that there is a need for more research on the utility of weight-based enoxaparin dosing for VTE in surgery patients.

The aim of the present prospective study was to investigate whether SC weight-based dosing of enoxaparin 0.5 mg/kg/day for VTE prophylaxis will lead to the anticipated peak anti-Xa level (0.2–0.6 units/mL) in morbidly obese surgical patients. The clinical efficacy and safety of the weight-based dosing were also evaluated by investigating the incidence of VTE and the incidence of minor and major bleeding.

Literature search indicated that no previous prospective study examined the clinical efficacy and safety of weight-based dosing of enoxaparin for VTE prophylaxis in obese surgical patients.

Methods

Study setting

The study was conducted at the surgical wards at King Abdulaziz Medical City, a 1025-bed tertiary care hospital in Riyadh, Saudi Arabia. The study was conducted between April 2015 and September 2015. Institutional Review Board approval was obtained from King Abdullah International Medical Research

Center. Consent for participation was obtained from all patients.

Study participants

All patients who were admitted to the surgical wards during the study period were screened for inclusion into the study. The study inclusion criteria were: adults ≥ 18 years old, males and females undergoing surgery, with body mass index (BMI) of ≥ 35 kg/m², and indication for DVT prophylaxis as per the American College of Clinical Pharmacy guidelines.^[13] Exclusion criteria were contraindication to enoxaparin (bleeding disorder, platelet count $< 100,000$ /mL, history of heparin-induced thrombocytopenia (HIT), renal impairment as determined by creatinine clearance < 30 mL/min, active bleeding), indication for therapeutic anticoagulation, and pregnancy.

Study design

This was a one-arm prospective cohort study. Study patients were prescribed enoxaparin at a dose of 0.5 mg/kg SC once daily for thromboprophylaxis by their treating physician. The choice of this particular enoxaparin dose was based on a previous report.^[14] Study patients' weights were determined on admission. Calculated enoxaparin dose was rounded to the nearest 5 mg unit.^[14] Peak anti-factor Xa levels were drawn 4 h after the third dose of enoxaparin through venipuncture. The phlebotomist drew 3.6 mL of blood in 3.2% sodium citrate.

Complete blood count was conducted daily during hospitalization. Patients were also clinically evaluated on a daily basis for signs and symptoms of adverse drug reactions such as VTE, major or minor bleeding. Major bleeding was defined as: overt bleeding, bleeding associated with a > 2 mg/dL decrease in hemoglobin from baseline, bleeding requiring medical intervention or transfusion, or bleeding at a critical site (24). Minor bleeding was defined as any bleeding that does not meet the criteria of major bleeding such as gum bleeding.

Study outcomes

The primary outcome measure was to determine whether a weight-based dosing of enoxaparin 0.5 mg/kg SC once daily led to anticipated peak anti-Xa levels of (0.2–0.6 units/mL) in obese patients undergoing surgery.

The clinical efficacy and safety of the weight-based dosing were also evaluated by investigating the incidence of VTE and the incidence of minor and major bleeding. The incidence of HIT (as defined by $\geq 50\%$ decline from baseline or platelet $< 100,000$ /mL) was also evaluated.

Statistical analysis

Data entry and analysis were carried out using IBM SPSS Statistics for Windows, Version 21.0. IBM Corp.,

Armonk, NY. Descriptive statistics were used to express the results (mean ± standard deviation and frequency [%]). Bivariate and multivariate analyses were conducted to identify factors associated with peak anti-factor Xa levels. Independent sample *t*-test and ANOVA were used to investigate the association with categorical variables (gender, BMI), and Pearson’s correlation coefficient was used for continuous variables. Multiple linear regression analyses were used to identify factors that are independently correlated with peak anti-factor Xa levels. Examined factors include weight, height, BMI, age, gender, and creatinine clearance (estimated using Cockcroft and Gault equation). Checking for outliers, normality, linearity, singularity, and multi-collinearity was carried out before linear regression analysis. All variables were entered in the regression analysis using “enter” as a method for model building. Model entry and removal were set at significance levels of 0.05 and 0.1, respectively. *P* < 0.05 was considered statistically significant.

Results

During the study period, 92 patients were screened. Fifty patients were eligible to be enrolled in the study and 42 patients were excluded from the study [Figure 1].

The clinical characteristics of the study patients are shown in Table 1. The most common reasons for admissions were total knee replacement (22%), fracture fixation (18%), and for sleeve gastrectomy (16%). The average length of hospital stay was 11 ± 7 days.

Mean enoxaparin dose was 50 ± 9.8 mg. Nearly 62% of the patients were hypertensive, 48% were diabetic, and 36% had dyslipidemia. Target anti-Xa levels were achieved in 88% of the study population (0.43 ± 0.17 IU/mL). Six (12%) patients did not achieve the target anti-Xa level (0.2–0.6 IU/mL) [Figure 2]. The anti-Xa levels were above 0.6 in two patients.

Multiple regression analyses indicated that peak anti-factor Xa levels were not associated with weight,

height, BMI, gender, age, and creatinine clearance. There was also no significant difference in BMI between patients who achieved and those who did not achieve target anti-Xa levels (42.8 ± 2 vs. 39.4 ± 4 kg/m², *P* = 0.4).

Among the study patients, there were no thrombocytopenia or symptomatic VTE or bleeding events, and there was no significant drop in hemoglobin.

Table 1: Demographic characteristics of the study patients*

Characteristic	Value
Age (years)	53±16
Gender, <i>n</i> (%)	
Male	13 (26)
Female	37 (74)
Weight (kg)	101±18 (range: 74-150)
BMI (kg/m ²)	40.5±5 (range: 35-55)
Length of hospital stay (days)	11.0±7
Platelet count (k/mcL)	274±73
Hypertension, <i>n</i> (%)	31 (62)
Diabetes, <i>n</i> (%)	24 (48)
Dyslipidemia, <i>n</i> (%)	18 (36)
Scr (µmol/L)	61±16
Crcl	82±33
ALP (U/L)	85±29
AST (U/L)	22±15
ALT (U/L)	21±13
Type of surgery, <i>n</i> (%)	
Tracheostomy	6 (12)
Pigtail insertion	6 (12)
TAH BSO	5 (10)
Fracture fixation	9 (18)
TKR	11 (22)
Sleeve gastrectomy	8 (16)
C5–C6 microdiscectomy	3 (6)
Hernia repair	2 (4)

*Data are shown as mean±SD unless otherwise specified. ALP = Alkaline phosphatase, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, TAH = Total abdominal hysterectomy, BSO = Bilateral salpingo-oophorectomy, BMI = Body mass index, TKR = Total knee replacement, SD = Standard deviation, Scr = Serum creatinine, Crcl = Creatinine clearance

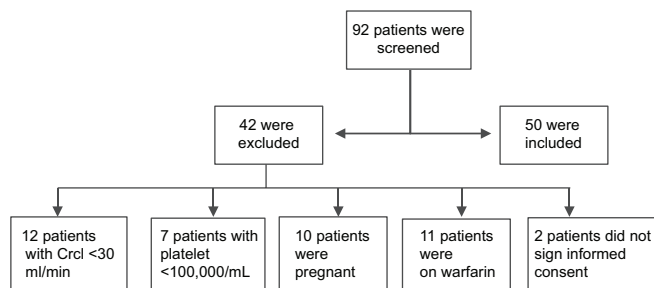


Figure 1: Reasons for patients' exclusion

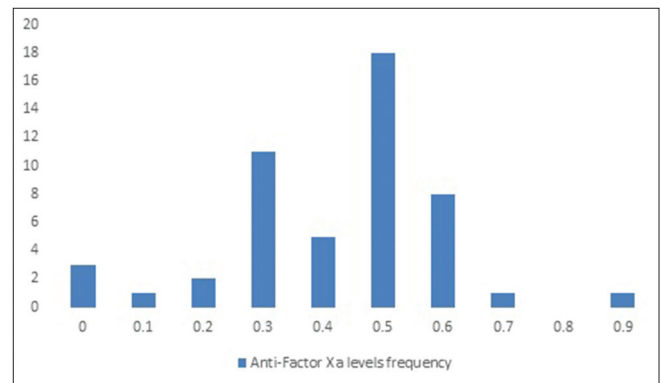


Figure 2: Peak anti-factor Xa levels' frequency (n = 50) (anti-factor Xa levels are approximated to the nearest digit)

Discussion

In the present study, the SC weight-based dosing of enoxaparin 0.5 mg/kg/day for VTE prophylaxis was found to be effective and led to the anticipated peak anti-Xa level (0.2–0.6 units/mL) in most of the study patients. Since none of the patients developed VTE, minor or major bleeding, the approach was also judged to be clinically effective and safe in the study sample of morbidly obese surgical patients. The results of this study support previous concerns that enoxaparin effect may depend on body weight and the currently recommended doses of enoxaparin may be inadequate in obese patients.^[9] Other investigators have also found similar results in obese medical patients.^[8,14,15]

Freeman *et al.* conducted a comparison of three enoxaparin dosing regimens in hospitalized, medically ill patients with extreme obesity: high dose of 0.5 mg/kg once daily, low dose of 0.4 mg/kg once daily, and a standard dose of enoxaparin 40 mg daily. Similar to our study, the high weight-based doses achieved the target anti-factor Xa levels of 0.2–0.6 u/mL in approximately 90% of patients. This study was limited by the small sample size (31 patients), the lack of clinical outcomes, and it was conducted on medical patients only.^[15]

Ludwig *et al.* conducted a retrospective study to document the efficacy of a weight-based dosing protocol of enoxaparin 0.5 mg/kg for VTE prophylaxis in obese surgical intensive care unit patients. Similar to our results, the dose was effective in achieving anti-factor Xa levels in 91% of patients. There was a single event of minor bleeding and a single VTE case. The study was limited by the retrospective nature and the small sample size (23 patients) which hinder the generalizability of the results.^[16]

Consistent with the published data, peak anti-factor Xa levels were not correlated with any of the variables.^[14,15]

The main limitation of this study is the single arm design. Future research should investigate the clinical efficacy and safety of the weight-based enoxaparin dose versus fixed-dose approach as VTE prophylaxis for morbidly obese surgical patients in a comparative design. The clinical efficacy and safety of the weight-based enoxaparin dose should also be investigated in patients at high risk for VTE. Nevertheless, this study provides evidence of the efficacy and safety of enoxaparin 0.5 mg/kg in VTE prophylaxis for morbidly obese surgical patients.

Conclusions

The results of this study indicated that weight-based dose of enoxaparin (0.5 mg/kg daily) led to the anticipated

peak of anti-factor Xa levels (0.2–0.6 IU/mL) in most of the morbidly obese study patients undergoing surgery without any evidence of major side effects. The weight-based dosing of enoxaparin was also effective in preventing VTE in all patients. Although these results are promising, further comparative trials are needed in the setting of morbidly obese surgical patients.

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Conflicts of interest

There are no conflicts of interest.

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