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Prophylactic use of enoxaparin in adolescents during bariatric surgery –a prospective clinical study

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Abstract

Introduction: Severe obesity predisposes youth to a higher risk of venous thromboembolism (VTE). This study evaluates a BMI-stratified prophylactic dosing regimen of enoxaparin in adolescents with severe obesity undergoing surgery.

Methods: Adolescents aged 12-20 years received prophylactic enoxaparin at 40 mg SC (for a BMI < 50 kg/m²) and 60 mg SC (for a BMI ≥ 50 kg/m²) every 12 hours until discharge. Blood samples were drawn at pre-dose, 1, 2, 4, 6, and 12 hrs. Plasma Anti-Factor Xa (Anti-FXa) activity was used as a surrogate marker for enoxaparin pharmacokinetics.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Assent and Consent:

Informed assent and consent was obtained from all individual participants and their parents in this study.

Results: Ten female and two male obese adolescents (age range 14-19 years) had a mean BMI of 49.9 kg/m² (38.4-58 kg/m²). Four patients had a BMI of less than 50 kg/m² and received 40 mg enoxaparin, resulting in a mean dosage of 0.352 ± 0.070 mg/kg body weight. Eight patients were dosed with 60 mg enoxaparin every 12 hours, resulting in a mean dosage of 0.395 ± 0.028 mg/kg. Peak plasma anti-FXa activity (C_{max}) ranged from 0.14 to 0.30 IU/mL, median C_{max} was 0.205 IU/mL. Median T_{max} was 5.67 hours (range 3.78 to 7.52 hours). Median AUC_i was 1.00 h*IU/mL (range 0.42 to 1.67 h*IU/mL). 10 out of 12 patients (83%) reached the primary endpoint with anti-FXa activity in the range for VTE prevention (0.1-0.3 IU/mL).

Conclusions: Our dosing scheme of 40 mg vs 60 mg enoxaparin stratified according to BMI proved to be effective in reaching prophylactic anti-FXa activity in 83% of adolescent patients.

Keywords

Enoxaparin; LMWH; Obesity; Adolescents; Bariatric surgery; VTE prophylaxis

Introduction

Obesity in children and adolescents has become an important public health concern. During adolescence, obesity may cause comorbidities such as hypertension, hypercholesterolemia, and diabetes¹. Bariatric surgery can be a surgical treatment option for selected patients with a severely high body mass index (BMI).

The Bariatric Surgical Program at Children's National Health System involves a multidisciplinary team of specialists consisting of pediatric surgeons, anesthesiologists, pediatricians, nurses and child psychologists. For an adolescent to become eligible for bariatric surgery he or she should fulfill the following requirements: be of age 12-20 years, have a history of obesity for at least three years, be unsuccessful in losing weight by conventional medical intervention, have a BMI of at least 35 kg/m² with an obesity related co-morbid condition, or a BMI of at least 40 kg/m² without a comorbidity. Patients less than 12 years of age may be carefully considered.

A severely high BMI is also an independent risk factor for venous thromboembolism (VTE)³. In the United States, the prevalence of VTE and VTE-associated complications in children has dramatically increased^{4, 5}. As seen in adults, obese adolescents have a significant risk for VTE, particularly when additional risk factors, such as oral contraceptive use and cigarette smoking are present⁶.

In general, surgery is considered a risk factor for VTE, but the actual possibility is difficult to define because it depends on the severity and duration of the procedure, and the amount of post-operative immobility⁷. Because there is an increasing incidence of pediatric VTE in obese individuals, it is important to consider VTE prevention in adolescents undergoing bariatric or weight loss surgery.

VTE Prophylaxis and Treatment

Low molecular weight heparins (LMWHs) are used for the prophylaxis and treatment of VTE in obese patients. Enoxaparin is a LMWH that exerts its antithrombotic activity by

binding to and accelerating the activity of antithrombin III. Typically, after a subcutaneous injection of enoxaparin in adults of normal weight, a maximum anti-Factor Xa activity occurs 3-5 hours later⁸. Enoxaparin seems to be eliminated primarily via a dose-independent non-saturable renal mechanism. Its pharmacokinetics appears to be linear in recommended dosing regimens. Elimination half-life based on anti-Factor Xa activity is 4.5 hours after a single subcutaneous dose to about 7 hours after repeated dosing. Significant anti-factor Xa activity persists in plasma for ~ 12 h after dosing with 40 mg subcutaneously⁹.

An anti-FXa activity of 0.1-0.3 IU/mL measured at 4-6 hours after drug administration is usually the target range for prophylactic dosage^{10, 11} while 0.6-1.0 IU/mL is considered therapeutic for VTE treatment by the American College of Chest Physicians (ACCP)¹⁰.

We previously published a prospective pilot study examining our current dosing practice of enoxaparin using BMI stratification. Our aim was to characterize enoxaparin exposure in adolescents with a high BMI undergoing bariatric surgery. We reported preliminary results of four patients dosed with prophylactic enoxaparin and noted that peak Anti-factor Xa activity ranged from 0.20 to 0.23 IU/mL¹². Currently, we are presenting the completion of this study which now includes analysis for a total of twelve patients.

Materials and Methods

This prospective, single-center, cohort study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01587781) Identifier [NCT01587781](https://clinicaltrials.gov/ct2/show/study/NCT01587781)) was approved by the Institutional Review Board (IRB) at Children's National Health System (Washington, DC, USA). Written informed assent and consent were obtained from all study participants and their parents before inclusion in the study.

Study Population

Adolescent patients aged 12-20 years who were scheduled for laparoscopic sleeve gastrectomy were eligible for inclusion. Additionally, pneumatic compression was used for all bariatric patients until discharge from the hospital ward and early mobilization starting in the post anesthesia recovery room was encouraged. Exclusion criteria were a history of bleeding disorders, known renal failure and exposure to enoxaparin or any other anticoagulant within the past 24 hours.

Dosing and Sampling Schedule

Patients with a body mass index (BMI) < 50 kg/m² received 40 mg enoxaparin subcutaneously (SC) and those with a BMI ≥ 50 kg/m² received 60 mg SC prior to the surgical incision. Enoxaparin was administered every 12 hours for a total of 48 hours or until the patient was discharged. Standardized criteria for thromboprophylaxis greater than 48 hours (developed in conjunction with our Hematology Division) includes : 1) an age greater than 18; 2) a BMI > 60 kg/m²; 3) obstructive sleep apnea; 4) a family history of a clotting disorder; and 5) male sex. Venous blood samples were obtained to measure plasma anti-FXa activity from an indwelling peripheral venous catheter using sodium citrate vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA). The samples were centrifuged at 2500g for 10 min at 4°C, and plasma was separated and stored at -70°C until analysis. Sample

collection was discontinued if the venous access was lost, unless a blood draw was necessary for clinical purposes.

Laboratory analyses

Plasma samples (approximately 2 mL) were scheduled to be assayed at predose, as well as 1, 2, 4, 6, and up to 12 hours after the first dose of enoxaparin. Plasma anti-FXa activity was determined by an enzyme inhibition assay using a synthetic chromogenic substrate (Hybrid UFH/LMWH Curve Chromogenic Assay Liquid Method Stago STA-R Evolution, Diagnostica Stago Inc, Parsippany, NJ, USA)¹¹. The target anti-FXa activity for VTE prophylaxis was defined as 0.1-0.3 IU/mL¹.

Serum creatinine values were obtained during the preoperative laboratory assessment using a validated method in our institution's clinical laboratory and creatinine clearance was calculated using the Cockcroft-Gault formula.

Pharmacokinetic and statistical analysis

Anti-FXa activity is routinely used as surrogate marker for enoxaparin exposure. A noncompartmental pharmacokinetic analysis was performed using the software Kinetica (Kinetica 5.0, ThermoFisher Scientific, Waltham, MA, USA) to calculate individual parameters, such as the maximum Anti-FXa activity (C_{max}), time to the maximum anti-FXa activity (t_{max}), the area under the activity time curve between the first and the last sample ($AUC_{inter} = AUC_i$), and the mean residence time (MRT).

The statistical analysis was performed using GraphPad Prims 7.04 (GraphPad Software, La Jolla, California, USA).

The primary efficacy outcome was the anti-FXa activity 4-6 hours after dosing, and the primary endpoint was the proportion of patients who reached effective prophylactic anti-FXa activity levels of 0.1 to 0.3 U/mL between 4-6 hours after dosage.

Results

Demographics

In this prospective study, ten female and two male obese adolescents (age range 14-19 years) undergoing laparoscopic sleeve gastrectomy had a mean body weight of 140.8 kg (93.7-174 kg) and a mean BMI of 49.9 kg/m² (38.4-58 kg/m²). The mean dose of enoxaparin per kg body weight in the total study cohort was 0.381 ± 0.048 mg/kg body weight. Four patients had a BMI less than 50 kg/m² and received 40 mg enoxaparin, resulting in a mean dosage of 0.352 ± 0.070 mg/kg body weight (n=4). Eight patients were dosed with 60 mg enoxaparin every 12 hours as their BMI was equal to or greater than 50 kg/m², resulting in a mean dosage of 0.395 ± 0.028 mg/kg body weight (n=8).

All patients received the recommended enoxaparin dose based on BMI. There was one patient who had a BMI of 49.8 kg/m² despite a body weight of > 150 kg, and therefore received the lower dose of 40 mg enoxaparin SC.

The demographic characteristics of the study participants are represented in Table 1.

Clinical Outcome

All patients underwent bariatric surgery successfully without perioperative complications. No VTE and/or major bleeding (defined as bleeding causing a fall in hemoglobin level of 2 g/dL or more, leading to transfusion of erythrocyte concentrate) occurred in the study population. We routinely use clinical criteria and selectively perform imaging studies to diagnose perioperative venous thromboembolism. Of note, only one of our total cohort of > 320 patients have had a VTE. He met four of the five previously mentioned criteria (no family history of clotting disorders) for home prophylaxis and was the reason to create our experimental protocol.

Enoxaparin exposure

The individual anti-FXa activity-time profiles are shown in Figure 1. There was some considerable deviations from the scheduled times of blood sampling. This was due to technical issues related to blood retrieval from intravenous lines that became nonfunctional during the course of the study. As a result, the pharmacokinetic analysis was performed using the actual times of blood sampling in relation to dosing.

Peak plasma anti-FXa activity (C_{max}) ranged from 0.14 to 0.30 U/mL, median C_{max} was 0.205 U/mL. Median T_{max} of anti-FXa activity for enoxaparin in the total study population was 5.67 hours (range 3.78 - 7.52 hours). Median AUC_i was 1.00 (range 0.42 - 1.67) h*U/mL. Median residence time (MRT) was 3.96 hours (range 2.79 to 6.85 hours). The available PK parameters are represented in Table 2.

Ten out of 12 patients (83%), including all patients in the 40 mg dose subgroup, reached the primary endpoint with anti-FXa activity in the range for VTE prevention (0.1-0.3 IU/mL). Also the patient with a BMI of 49.8 kg/m² reached therapeutic anti-FXa activity.

There was no significant correlation found between C_{max} , T_{max} , AUC_i , MRT and body weight, as well as C_{max} , T_{max} and BMI. AUC_i and MRT correlated significantly with BMI ($p=0.04$ and 0.03 , respectively), but the correlation was only weak ($r^2=0.357$ and 0.3847 , respectively, see figures 2 and 3).

Renal function assessment

Serum creatinine and creatinine clearance were within normal limits for all patients.

Comparison of weight-based subgroups

The subgroup (n=4) receiving 40 mg enoxaparin SC, exhibited a mean peak plasma anti-FXa activity of 0.18 ± 0.04 U/mL (median 0.18 U/mL, range 0.14-0.23 U/mL); and the subgroup (n=8) dosed with 60 mg enoxaparin had a mean C_{max} of 0.22 ± 0.05 U/mL (median 0.21 U/mL, range 0.16-0.3 U/mL). All patients in the 40 mg dose subgroup reached the anti-FXa target range versus 6 patients in the 60 mg dose subgroup. The mean T_{max} of anti-FXa activity for enoxaparin dosed at 40 and 60 mg was 4.5 ± 0.84 hours (median 4.22 hours, range 3.83 to 5.72 hours); and 6.09 ± 1.3 hours (median 6.21 hours, range 3.78 to

7.52 hours) respectively. In the subgroup dosed with 40 mg enoxaparin, the mean AUC_i was 0.76 ± 0.3 h*U/mL (median 0.77 h*U/mL; range 0.42 to 1.08); and in the 60 mg subgroup the mean AUC_i was 1.14 ± 0.41 h*U/mL (median 1.15 h*U/mL; range 0.51 to 1.67 h*U/mL). Additionally, the mean residence time (MRT) was 3.25 ± 0.37 hours (median 3.27 hours, range 2.79 to 3.68 hours). and 4.8 ± 1.46 hours (median 5.03 hours, range 2.82 to 6.85 hours in the 40 and 60 mg subgroup, respectively).

Discussion

Unfortunately, clinicians are increasingly challenged with making dosing decisions for most anticoagulants in obese children^{13, 14} because there are limited clinical studies reviewing anticoagulant use in this population, particularly during the perioperative phase of care.

In this single center cohort study, the dosing scheme of 40 mg vs. 60 mg enoxaparin stratified according to BMI proved to be effective in reaching prophylactic anti-FXa activity in the majority of patients. This dosing scheme was specifically created for our bariatric population and is in accordance with a recent review by Sebaaly and Covert who recommend BMI-based fixed doses of enoxaparin SC in adult patients¹⁵.

Enoxaparin PK has been extensively studied in adults although conflicting data are available for the adult obese population. Gelikas et al. compared 40 mg vs. 60 mg enoxaparin given postoperatively every 24 hours, and anti-FXa activity was obtained 3-4 hours after the third dose, which was during steady-state conditions¹⁶. A prophylactic anti-FXa activity of 0.2-0.5 IU/mL was assumed and approximately 80-90% of patients reached the target range. The enoxaparin exposure was slightly higher in that study during steady state conditions compared to our data, but the adults had lower BMIs than the adolescents. Both adult groups had a comparable body weight with approximately 120-125 kg of body weight corresponding to a BMI of 42 to 44 kg/m². The body-weight adjusted dose was 0.333 mg/kg/d (40 mg) and 0.479 mg/kg/d (60 mg), respectively. There was no PK analysis performed, but the authors found a significant negative correlation between body weight and anti-FXa activity.

Tahaine et al. also used a peak anti-FXa activity of 0.2-0.5 IU/mL measured 4-6 hours after administration during steady state as prophylactic target range in obese patients with a BMI of 30-70 kg/m²¹⁷. For VTE prophylaxis, enoxaparin had been mostly administered as a fixed dose of 40 mg/day. Only 42% of patients under VTE prophylaxis reached the targeted anti-FXa activity. This is in accordance with recent literature reporting a significant negative correlation between total body weight (TBW) and anti-FXa activity in obese patients reported by Sebaaly. In contrast, we found a significant, but weak positive correlation with anti-FXa exposure (AUC_i) and MRT in our study (see figures 2 and 3). This might be due to the fact that we used BMI-stratified dosing.

There is also controversy regarding frequency of enoxaparin administration and corresponding target anti-FXa activity, since enoxaparin is given once to twice per day in the prophylactic indication. In the ITOHENOX study, patients with a BMI > 30 kg/m² (mean BMI 37.8 kg/m²) received enoxaparin 40 mg vs. 60 mg SC once daily. This study showed

that 60 mg enoxaparin SC daily provided a higher control of anti-FXa activity (target activity 0.32-0.54 IU/mL) as compared to 40 mg SC daily¹⁸. We currently prescribe enoxaparin twice daily after surgery.

Monitoring of anti-Factor Xa is currently not routinely performed for all patients. However, the ACCP recommends monitoring in children and obese persons because uncertainty exists with dose response. Because no official guidelines exist, target ranges of anti-FXa activity remains in discussion.

Conclusion

We acknowledge a major limitation of this study is the lack of an age-matched lean adolescent comparator group. This is because VTE prophylaxis is rarely performed in otherwise healthy and lean adolescents. Also, as intravenous access can be quite difficult in our obese population, we may have missed relevant PK sampling if a loss of venous access occurred before 6 hours (and peak anti-FXa activity). Additionally, due to the aforementioned, blood collection did vary from the specified PK time points.

We also suggest that because our sample size is relatively small, overall recommendations concerning a dosing scheme in this patient population would be premature. While our dosing strategy likely leads to effective thromboprophylaxis, a study directly comparing the two doses is needed to demonstrate significant PK differences.

In conclusion, our BMI-based fixed dosing scheme of enoxaparin proved to be effective in adolescents with severe obesity undergoing bariatric surgery. To our knowledge this is the first pharmacokinetic study for prophylactic use of enoxaparin in this patient population. Future analysis using a physiologically based PK/PD exploratory model may be needed to determine the efficacy and safety of different doses of enoxaparin for VTE prophylaxis in adolescent patients with extreme obesity.

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Figure 1:
Individual profiles of plasma anti-FXa activity. The anti-FXa activity target range is indicated by the shaded area. Patients who received the 40 mg dose are marked with open symbols, patients who received the 60 mg dose are marked with closed symbols.

Figure 2:

A significant, but weak correlation between BMI and AUC_i was observed ($p=0.04$). The vertical gray line marks a BMI of 50 kg/m² which was the cut-off for 40 mg vs. 60 mg. enoxaparin dosing.

Figure 3:

A significant, but weak correlation between BMI and MRT was observed ($p=0.03$). The vertical gray line marks a BMI of 50 kg/m² which was the cut-off for 40 mg vs. 60 mg. enoxaparin dosing.

Table 1.

Demographic and baseline characteristics.

Parameter (mean /median)	N= 12, total study population	N=4, subgroup BMI < 50 kg/m ² , 40 mg	N=8, subgroup BMI > 50 kg/m ² , 60 mg	P value
Age (y) median (range)	17 (14 - 19)	16 (15-19)	17.0 (14 – 18)	0.5838
Gender	10f, 2 m	3f, 1m	7f, 1m	
Race	6 African American 3 Caucasian 2 Hispanic 1 other	1 African American 2 Caucasian 1 Hispanic	5 African American 1 Caucasian 1 Hispanic 1 other	
BMI (kg/m ²) median	50.9 (38.4 – 58)	41.7 (38.4 – 49.8)	53.02 (50.08 – 58.0)	0.0040
Body weight (kg) median	147.3 (93.7 – 174.0)	111.5 (93.7 – 152.5)	149.4 (139.8 – 174.0)	0.0727
Body height (cm) median	168 (156 – 178)	164 (156 – 175)	169 (158 – 178)	0.3434
IDW (kg) median	60.5 (49 – 73)	58 (49 – 66)	60.5 (51 – 73)	0.6545
BSA (m ²) median	2.45 (1.93 – 2.70)	2.15 (1.93 – 2.57)	2.46 (2.30 – 2.70)	0.1091
Creatinine (mg/dl) median	0.7 (0.5 – 0.9)	0.7 (0.7 – 0.9)	0.7 (0.5 – 0.9)	0.6429
Creatinine Clearance (mL/min) median	267 (149 – 451)	198 (149 – 246)	299 (233 – 451)	0.2857
<u>Enoxaparin dose:</u>				
Dose in mg, median	60 (40 – 60)	40	60	0.0020
Dose mg/kg TBW, median	0.39 (0.26 – 0.43)	0.36 (0.26 – 0.43)	0.40 (0.35 – 0.43)	0.2828
Dose mg/kg IDW, median	0.95 (0.61 – 1.18)	0.69 (0.61 – 0.82)	0.99 (0.82 – 1.18)	0.0040
Dose mg/m ² BSA, median	22.9 (15.6 – 26.1)	18.7 (15.6 – 20.8)	24.4 (22.2 – 26.1)	0.0040

p values for subgroup comparison calculated using Mann Whitney test.

Table 2:

Anti-FXa activity as surrogate marker for enoxaparin

Parameter (mean /median)	N= 12, total study population	N=4, subgroup BMI < 50 kg/m ² , 40 mg	N=8, subgroup BMI > 50 kg/m ² , 60mg	p value
C _{max} (U/mL) median	0.21 (0.14 – 0.30)	0.18 (0.14 – 0.23)	0.21 (0.16 – 0.30)	0.1758
T _{max} (hours) median	5.67 (3.78 – 7.52)	4.22 (3.83 – 5.72)	6.21 (3.78 – 7.52)	0.1818
AUQ _i (h*U/mL) median	1.00 (0.42 – 1.67)	0.77 (0.419 – 1.081)	1.15 (0.509 – 1.67)	0.1333
MRT (hours) median	3.96 (2.79 – 6.85)	3.27 (2.79 – 3.68)	5.03 (2.82 – 6.85)	0.1333
Patients in anti-FXa target range @ 4-6 hours after dosing (n)	10	4	6	

p values for subgroup comparison calculated using ann Whitney test.