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Reduced Dosing of Enoxaparin for Venous Thromboembolism in Overweight and Obese Adolescents: A Single Institution Retrospective Review

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Essentials

- Data is scarce on dosing enoxaparin for obese adolescents with venous thromboembolism (VTE).

- Overweight and obese adolescents treated with reduced enoxaparin dose (RD) were reviewed.

- Initial enoxaparin doses calculated using actual body weight may be greater than what is needed.

- Trials are warranted to evaluate RD enoxaparin for overweight and obese adolescents with VTE.

Abstract

Background: The global obesity epidemic has created new challenges, including venous thromboembolisms (VTE) in obese adolescents. The data on whether to reduce the dose of low-molecular heparin in obese adults is conflicting, and information on adolescent patients is scarce.

Objectives: Our primary goal was to describe dosing, anti-Xa levels, and outcomes of overweight and obese adolescents who received reduced doses of enoxaparin at the initiation of therapy. The secondary goal was to compare their outcomes to overweight and obese adolescents who received standard 1 mg/kg dosing to determine if future trials for dose reduction are warranted.

Patients/Methods: We performed a retrospective cohort study of overweight and obese patients between the ages of 12 and 18 years old diagnosed with VTE who were treated with reduced dosing (RD) of enoxaparin, comparing their dosing, anti-Xa levels, and outcomes to overweight and obese adolescents who received standard dosing (SD).

Results: RD patients (n = 19) achieved therapeutic mean initial anti-Xa levels that were similar to SD patients (n = 11). Of the RD patients, 53% did not require dose adjustments during treatment. Two RD patients had thrombus progression. A total of 25 patients ultimately completed therapy with RD.

Conclusions: Future trials are warranted to evaluate the efficacy and safety of reduced dosing of enoxaparin to treat overweight and obese adolescents with VTE.

Keywords: adolescent, enoxaparin, obesity, thromboembolism, thrombosis

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Introduction

The World Health Organization has reported an obesity epidemic affecting many countries, even developing, poor nations.[1] According to the Centers for Disease Control, the prevalence of obesity in the United States in the 12-19 year age range has already nearly doubled from 10.5% (1988-1994) to 20.6% (2013- 2014), while extreme obesity (defined as ≥ 120th percentile) has tripled from 2.6% (1988-1994) to 9.1% (2013-2014).[2] Similar to obese adults, obese adolescents have a higher risk of venous thromboembolism (VTE) compared to non-obese adolescents.[3-7] As the global obesity epidemic continues, there will be a greater need to treat overweight and obese adolescents for VTE. This population poses a dosing dilemma when prescribing low-molecular-weight heparins (LMWH) — commonly enoxaparin.

There is little data to guide providers on how to dose enoxaparin in overweight and obese adolescents. First, the recommendations by the American College of Chest Physicians (ACCP) for weight-adjusted dosing of enoxaparin to treat pediatric VTE are based largely on adult studies, despite reduced predictability of the anticoagulant effect in children compared to adults when using weight-adjusted dosing.[8, 9] Thus, enoxaparin is used off label in children. Second, obesity can affect the pharmacokinetics of enoxaparin, although it is unclear if the net effects warrant dose modifications.[10-14] Third, the therapeutic ranges recommended by the College of American Pathologists have not been validated in clinical trials.[15] Finally, the monitoring of enoxaparin utilizing anti-Xa levels in adults is controversial, and no data exist for adolescents.[16, 17]

Adolescent VTE, most commonly deep vein thrombosis (DVT) and pulmonary embolism (PE), patterns and mortality rates are different compared to adult VTE.[18]

For example, PE in adolescents is rarely fatal likely secondary to fewer comorbidities in the adolescent population.[19] In addition, adult dose-reduction strategies such as dose-capping may not apply for an obese adolescent who weighs less.[12, 13, 20] Because of these differences, data from obese adolescents is necessary and should not be extrapolated from trials designed for obese adults.

To our knowledge, there has been no study describing dose modifications in obese adolescents diagnosed with VTE. Two case series described enoxaparin prophylaxis in obese adolescents, not treatment.[21, 22] The small numbers in those studies limit the interpretation of their enoxaparin pharmacokinetic data.

At our institution, the Pediatric Hematology/Oncology (PHO) team is consulted for all adolescent patients diagnosed with VTE. The initial dosing of enoxaparin is determined and ordered at a pediatric hematologist's discretion with some patients receiving doses less than the ACCP's recommendations. After approval by the institution's IRB, we performed a retrospective cohort study with the primary goal of describing dosing, anti-Xa levels, and outcomes of overweight and obese adolescents who received upfront reduced dosing (RD) of enoxaparin. We also compared these patients to overweight and obese adolescents treated at our institution who received standard dosing (SD) to determine if future trials to evaluate the efficacy and safety of dose reduction are warranted.

Materials and Methods

Study Population and Data

Our PHO team, as directed by a pediatric hematologist, manages all aspects of care for adolescents diagnosed with VTE including dosing, anti-Xa level monitoring, and follow-up. Our PHO team maintains an internal database of any new patients we encounter, captured by new consultation notes and billing records, collecting the patients names, medical record numbers, date of birth, and diagnoses.

This database was queried using the terms "thrombosis," "thrombus," "DVT," "vein," "clot," "PE," "pulmonary," "emboli," and "stroke." The electronic and written medical records from hospitalization and/or outpatient follow-ups were reviewed. Patients were included if they were ≥ 12 and ≤ 18 years old; overweight or obese, defined as a body mass index (BMI) ≥ 85th percentile for age and sex;[23] and received

enoxaparin for treatment of VTE between January 2004 and December 2014. Patients with renal disease — defined as having any pre-existing renal diagnosis, undergoing dialysis, or carrying a diagnosis of acute renal failure described in the medical records — were excluded. Patients with cerebral venous thrombosis, or who had trauma or surgery within one week of VTE diagnosis, were excluded as the associated bleeding risk may have influenced the initial enoxaparin dose selected.

Data collected include demographics, BMI, radiology reports, laboratory data, enoxaparin doses and adjustments, anti-Xa levels, and descriptions of any bleeding events. Estimated glomerular filtration rate (GFR) was calculated utilizing the creatinine–based bedside Schwartz equation.[24] DVT and PE were diagnosed using duplex ultrasonography or venography and computed tomography angiogram, respectively.

SD was defined as ≥ 0.90 mg/kg every 12 hours. This cutoff was chosen to account for doses rounded down to the nearest 10 mg increment vial. RD was defined as any dose < 0.90mg/kg every 12 hours. The duration of anticoagulation treatment varied depending on the scenario (i.e., spontaneous or provoked).[25] Furthermore, the duration of enoxaparin used during the treatment time frame varied. As current VTE treatment recommends three months of therapy, the final dose (and final anti-Xa level) in our study was defined as the last prescribed dose (and level) at 90 days of treatment.[9]

Anti-Xa Levels and Dose Adjustments

At our institution, anti-Xa levels drawn after the 2nd-5th dose at 3-5 hours post-dose are routinely obtained in all patients at the initiation of enoxaparin. In general, during outpatient follow-up, anti-Xa levels are obtained with any dose adjustment or monthly. Following ACCP guidelines, therapeutic target anti-Xa level is between 0.5-1.0 units/mL. Sub- and supra-therapeutic levels are below and above this range, respectively.[9]

For this study, a dose adjustment was defined as a change of enoxaparin dose. The rationale for adjustment was determined by a review of the medical records. The Dade Behring BCS XP instrument (Marburg, Germany) was used for measurement of

the anti-Xa level, with Diagnostica Stago (New Jersey, United States) or Quest Diagnostics™ (New Jersey, United States) anti-Xa chromogenic assays.

Outcomes

Retrospective reviews of radiology reports and medical records were performed to determine progression and bleeding, respectively. A progression was defined as thrombus extension, the development of a new PE, or re-thrombosis in a previously treated site, occurring after the initiation of enoxaparin. Based on medical record descriptions, bleeding events occurring 24 hours after enoxaparin initiation were classified as major if they were associated with a decrease in hemoglobin of ≥ 2 g/dL within 24 hours of the bleeding event or resulted in a blood transfusion. Bleeding events that did not satisfy the criteria for major based on medical record descriptions, were classified as minor.

Statistical Analyses

Summary statistics were calculated. Quantitative data were expressed as the mean ± standard deviation and nominal data as a percentage. A one sample goodness of fit test was used to compare the progression and bleeding rates of our sample relative to the mean rates reported in previous studies. Comparisons between the two groups (RD vs. SD) for quantitative variables were performed using the t-test, with the exception of the comparison of the number of anti-Xa levels. As this variable was non-normally distributed, the values were log-transformed prior to the analysis. For nominal variables, the Fisher's Exact test was used. Significance was assessed at $P < 0.05$. Analyses were performed using IBM SPSS Statistics v. 22 (Armonk, NY).

Results and Discussion

The initial database query resulted in 276 patients. Electronic and written medical record review resulted in 42 patients, 12 of which were excluded for cerebral venous thrombosis (4), recent trauma or surgery (3), or renal disease (5), leaving 30 patients in our study group. Twenty-seven patients were hospitalized for initial VTE management. Of these 27 hospitalized patients, three were transferred from outside institutions on enoxaparin plus warfarin (2) or heparin infusion (1) at the time of transfer. After four weeks of hospitalization, one patient followed up with an outside institution for continued VTE management. Serum creatinine was available in 21 patients (range

0.53-0.99 mg/dL); the estimated GFR was 97.12 mg/min/1.73m^2 (range 69.12-143.50 mg/min/1.73m^2). Available unconjugated bilirubin levels (n = 20), were below 6 mg/dL, the threshold shown to interfere with anti-Xa level assays.[26] Twenty-nine patients were reportedly negative for antithrombin III deficiency.

Nineteen patients initially received RD enoxaparin (Table 1). Mean initial anti-Xa level was within therapeutic range and 14/19 (74%) had initial therapeutic or supra-therapeutic anti-Xa levels. Five patients had initial sub-therapeutic anti-Xa levels, one of whom tested positive for a lupus anticoagulant and had a thrombus progression. Of the 19 patients, 10 (53%) did not require any dose adjustments during treatment; 23 of 27 (85%) anti-Xa levels obtained during their treatment were within therapeutic range. The mean initial and final doses were not significantly different (Fig. 1). Four RD patients' final doses were greater than their initial doses (Table 2). Of these four, two patients who were initially dosed at < 0.7 mg/kg had thrombus progression despite one patient having an initial supra-therapeutic anti-Xa level. Two bleeding events occurred, both of which were minor (Table 1).

Eleven patients received SD (Table 1). Unlike the RD patients, the SD patients' mean final dose was significantly lower than their mean initial dose (Fig. 1). Notably, in eight patients whose final doses were less than their initial doses, six (75%) were dose reduced secondary to supra-therapeutic anti-Xa levels obtained 2-16 days from initiation of therapy.

Between the two groups, no significant differences were observed in demographics, obesity status, type of VTE, and use of thrombolysis (Table 1). Despite a significantly lower mean initial dose in the RD group compared to the SD group, the mean initial anti-Xa levels and mean final doses were similar between the groups (Table 1). There were no significant differences in the percentages of patients who had initial sub-therapeutic, therapeutic, or supra-therapeutic anti-Xa levels, the number of anti-Xa levels obtained during 90 days of treatment, nor in progression or bleeding rates between the two groups (Table 1).

In prior LMWH studies, the reported incidence of progression ranged from 1-7%[27, 28], and the reported incidence of bleeding ranged from 0-36%.[27, 29] Utilizing a mean incidence of approximately 5% for progression, and 20% for minor bleeding, our

RD and SD groups did not differ significantly with these mean rates (progression: RD vs 5% $P = 0.25$; SD vs 5% $P = 0.43$, bleeding: RD vs 20% $P = 0.40$, SD vs 20% $P = 0.47$).

Ultimately, 83% of all patients were on RD at the end of treatment or at 90 days from diagnosis (n = 25, mean dosing 0.73 ± 0.11 mg/kg), with therapeutic or supra-therapeutic anti-Xa levels.

These findings suggest that initial doses calculated using actual body weight may be greater than what is needed, which is consistent with some previously published reports.[12, 13, 26] Therapeutic or supra-therapeutic anti-Xa levels were achieved in 74% of the RD group. However, the degree of dose reduction should be cautiously considered as the two RD progressions occurred in patients who were initially dosed at < 0.7 mg/kg.

Though the role of anti-Xa monitoring for enoxaparin in adult is controversial, monitoring in our SD patients showed supra-therapeutic levels up to 16 days from the initial dose. The significance of this is unknown as our sample size is small, but may be secondary to the effects that obesity has on enoxaparin pharmacokinetics that have yet to be clearly defined.[10-14] Until there are more studies regarding the utility of anti-Xa levels, overweight individuals should have periodic monitoring, possibly during the first two weeks of therapy.[16, 17]

All bleeding events in our study were minor. Compared to the RD group, the SD group had a higher percentage. This is more likely secondary to the small sample size and less likely secondary to overdosing in the SD group; two of the three SD group patients had therapeutic anti-Xa levels during the bleeding events.

Limitations inherent to retrospective cohort studies at a single institution pertain to this preliminary study. Furthermore, outpatient factors such as injection methods or timing of anti-Xa level testing are confounding variables. The small sample size precludes any conclusions regarding efficacy and safety. Nonetheless, as obesity rates increase globally, future trials are warranted to evaluate reduced dose enoxaparin in the treatment of overweight and obese adolescents with VTE. The information reported here offers a beginning for that research.

Addendum

S. Hoffman and C. Braunreiter contributed to the research design, data collection and analysis, and manuscript writing.

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Figure Legend

Figure 1. Mean ± standard deviation initial (blue) and final dosing (red) for the two study groups. Patients dosed initially at < 0.90 mg/kg (RD) did not significantly increase their dose, while patients dosed at ≥ 0.90 mg/kg (SD) significantly decreased their dose to maintain anti-Xa levels within therapeutic range (0.5-1.0 units/mL).

Table 1. Comparison of initial treatment dose groups

	All patients (n = 30)	Initial treatment dose (mg/kg/dose)		*P* value
		< 0.90 (RD) (n = 19)	≥ 0.90 (SD) (n = 11)	
Age[a] (y)	15.3 ± 1.6	15.3 ± 1.4	15.4 ± 2.1	0.940
Male (%)	36.7	31.6	45.5	0.696
White (%)	83.3	84.2	81.8	> 0.999
Weight[a] (kg)	96.4 ± 22.1	101.8 ± 20.5	87.1 ± 22.6	0.078
Height[a] (cm)	171.3 ± 10.2	172.4 ± 10.3	169.5 ± 10.2	0.464
Obese[b] (%)	76.7	84.2	63.6	0.372
DVT[c]	36.7 (11)	36.8 (7)	36.4 (4)	> 0.999
PE[c]	26.6 (8)	21.1 (4)	36.4 (4)	0.417
DVT and PE[c]	36.7 (11)	42.1 (8)	27.2 (3)	0.466
Thrombolysis at diagnosis[c]	33.3 (10)	36.8 (7)	27.3 (3)	0.702
Initial dose[a] (mg/kg)	0.83 ± 0.14	0.74 ± 0.10	0.98 ± 0.05	< 0.001
Range (mg/kg)	(0.58 – 1.04)	(0.58 – 0.88)	(0.90 – 1.04)	---
Initial anti-Xa level[a] (units/mL)	0.70 ± 0.23	0.68 ± 0.20	0.73 ± 0.28	0.640
Sub-therapeutic (< 0.5)[c]	---	26.3 (5)	18.2 (2)	> 0.999
Therapeutic (0.5 – 1.0)[c]	---	68.4 (13)	72.7 (8)	> 0.999
Supra-therapeutic (> 1.0)[c]	---	5.3 (1)	9.1 (1)	> 0.999
Median number of anti-Xa levels[d]	---	3	4	0.404
Range	---	(1 – 8)	(1 – 14)	---
Patients who required dose adjustments[c]	---	47.4 (9)	81.8 (9)	0.063
Final dose[a] (mg/kg)	0.77 ± 0.14	0.77 ± 0.12	0.78 ± 0.18	0.829
Range (mg/kg)	(0.56 – 1.13)	(0.56 – 1.01)	(0.56 – 1.13)	---
Final dose > initial dose[c]	---	21.0 (4)	9.1 (1)	0.626
Final dose < initial dose[c]	---	21.0 (4)	72.7 (8)	0.009
Progression[c]	---	10.5 (2)	9.1 (1)	> 0.999
Bleeding (all events were minor)[c]	---	10.5 (2)	27.3 (3)	0.327

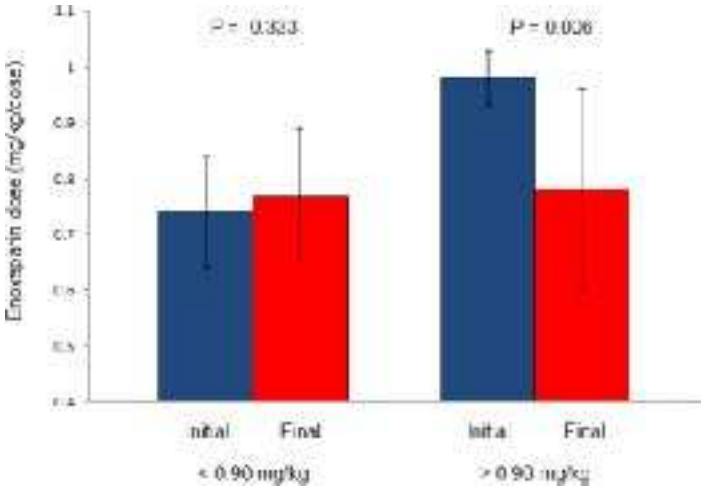
DVT, deep vein thrombosis; PE, pulmonary embolism; RD, reduced dose enoxaparin; SD, standard dose enoxaparin. [a] mean ± standard deviation; [b] body mass index ≥ 95th percentile for age and sex; [c] % (n); [d] number of anti-Xa levels obtained during 90 days of treatment. *P* values refer to comparisons between RD group and SD group.

Table 2. Outcomes for reduced dose patients whose final dose was greater than their initial dose

Weight (kg)	BMI (percentile)	Indication	Initial dose (mg/kg)	Final dose (mg/kg)	Initial anti-Xa level (units/mL)	Final anti-Xa level (units/mL)	Reason for dose adjustment(s)	Number of dose adjustments (n)	Progression or recurrence
112.3	97	PE	0.71	0.89	0.35	0.81	Sub	1	No
98.1	97	DVT	0.61	0.82	1.08	0.64	Progression	4	Yes
97.6	98	PE	0.61	0.92	0.53	0.69	Physician discretion	2	No
89.2	94	DVT, IVC extension	0.67	1.01	0.47	1.62	Sub;Progression	6+	Yes

BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; IVC, inferior vena cava; Sub, sub-therapeutic anti-Xa level < 0.5 units/mL.

Progression is defined as thrombus extension, the development of PE that was not present at diagnosis, or re-thrombosis in a previously treated site after initiation of enoxaparin and prior to completing therapy.



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