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Evaluation of the Safety and Efficacy of Enoxaparin Once-Daily Versus Twice-Daily Dosing for Prophylaxis in Pediatric Patients

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OBJECTIVES Enoxaparin for the prevention of venous thromboembolism (VTE) in pediatric patients is typically dosed twice a day. The use of once-daily dosing like that used in adult patients is limited because of a lack of safety and efficacy data. The aim of this study was to evaluate the safety and efficacy of once-daily versus twice-daily dosing of enoxaparin for pediatric VTE prophylaxis based on incidence of thrombotic and bleeding events.

METHODS This was a 3-year retrospective chart review of enoxaparin received for VTE prophylaxis at Cohen Children's Medical Center, New Hyde Park, NY. Exclusion criteria were age 18 years or older, and renal dysfunction.

RESULTS A total of 177 enoxaparin courses (81 in the once-daily and 96 in the twice-daily group) were included. The median dose in the once-daily group was 0.68 mg/kg/dose with dose capping at 40 mg/dose in 70% of patients. One patient in the once-daily group had a VTE, whereas no patients in the twice-daily group experienced a VTE. One major bleeding event occurred in the once-daily group ($p = 0.46$); however, minor bleeding events were comparable between the 2 groups ($p = 0.69$).

CONCLUSIONS Once-daily enoxaparin prophylaxis appears to be safe and effective based on minimal differences in incidence of thrombotic and bleeding events when compared to twice-daily dosing. Based on this study, it may be reasonable to consider once-daily enoxaparin dosing for prophylaxis, especially in older children. A larger multicenter cohort study evaluating once-daily dosing for prophylaxis is warranted to validate the safety and efficacy specifically for risk-based dosing strategies.

ABREVIATIONS LMWH, low–molecular weight heparin; MISC, multisystem inflammatory syndrome in children; SC, subcutaneously; VTE, venous thromboembolism

KEYWORDS enoxaparin; low–molecular weight heparin; pediatrics; prophylaxis; venous thromboembolism prophylaxis

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Introduction

Enoxaparin is a low–molecular weight heparin (LMWH) anticoagulant used for prophylaxis and treatment of venous thromboembolism (VTE). Once-daily dosing at 30 to 40 mg/day has been shown to be as safe and effective as twice-daily regimens in adult patients.[1,2] Although once-daily dosing provides a key benefit of fewer subcutaneous injections, use of this dosing scheme in pediatric patients has been limited because of a lack of safety and efficacy data.[3] One study by O'Brien and colleagues[4] revealed that children have significantly lower total drug exposure with once-daily treatment dosing compared with that of adult patients using once-daily treatment dosing, leading to twice-daily dosing as the standard treatment dosing regimen for pediatric patients. However, there are currently no pediatric studies evaluating the safety and efficacy of once-daily dosing for prophylaxis. At our institution, we typically recommend using the standard enoxaparin 0.5 mg/kg/dose subcutaneously (SC) every 12 hours dosing for VTE prophylaxis in pediatric patients. However, once-daily dosing is sometimes used in older children in order to minimize injections. This study was undertaken to review our institution's use of a once-daily dosing scheme for VTE prophylaxis in pediatric patients. Our primary objectives were to evaluate the efficacy and safety of once-daily versus twice-daily dosing of enoxaparin for VTE prophylaxis in pediatric patients based on thrombotic or bleeding events. Exploratory analyses included evaluation of anti-Xa levels as well as the effect of risk factors and dose capping for enoxaparin.

Materials and Methods

Study Design. All pediatric patients, including neonates, who received enoxaparin for VTE prophylaxis within any unit of the pediatric hospital, including critical care units, between October 2018 and September 2021 were included and divided into 2 groups based on dosing frequency (i.e., once daily or twice daily). Patients ages 18 years or older and any patients with renal dysfunction during the enoxaparin course (defined as a creatinine clearance of <30 mL/min/1.73 m^2 based on the bedside Schwartz equation) were excluded. Data collection involved patient demographics (age, sex, ethnicity, weight, and height), presence of thrombosis risk factors, enoxaparin dosing schedule, and duration of prophylaxis.[5,6] Risk factors for thrombosis included presence of central venous catheters, active COVID-19 infection/multisystem inflammatory syndrome in children (MISC), systemic inflammatory disease, active malignancy, obesity (>95th percentile for age), recent trauma, recent asparaginase therapy, presence of vascular anomaly, and active use of oral contraceptives.[5,6] Anti-Xa concentrations were analyzed within the institution using a Chromogenic-ACL Top Beckman/Coulter/IL machine which was consistent throughout the study period. Dosing schemes and dose capping within both groups were per prescriber preference based on age and weight from available literature.

The primary outcomes were the percentage of patients who experienced a thrombotic or bleeding event during therapy and within 30 days of discontinuation of enoxaparin therapy. A thrombotic event was defined by the presence of VTE confirmed by imaging by ultrasound, computerized tomography, or magnetic resonance imaging. Major bleeding events were defined as hemorrhage requiring a packed red blood cell transfusion, or a hemoglobin decrease of ≥2 g/dL from baseline.[4,7,8] Minor bleeding was defined as any bleeding event not meeting criteria for a major bleed

Table 1. Baseline Characteristics

	Once-Daily (n = 81)	Twice-Daily (n = 96)	p value
Sex, n (%)			
Female	43 (53.1)	37 (38.5)	0.069
Male	38 (46.9)	59 (61.5)	0.069
Age, median (range), yr	15 (0.67–17)	14 (0.17–17)	<0.001
Age 0–11 yr, n (%)	18 (22.2)	40 (41.7)	
Age 12–17 yr, n (%)	63 (77.7)	56 (58.3)	
Weight, median (range), kg	55.1 (11.5–167.5)	54.5 (3.58–162.9)	0.363
Weight <40 kg, n (%)	14 (17.3)	30 (31.3)	
Weight ≥40 kg, n (%)	67 (82.7)	66 (68.7)	
Ethnicities, n (%)			
African American	31 (38.3)	24 (25)	0.073
Asian	12 (14.8)	12 (12.5)	0.666
White	18 (22.2)	17 (17.7)	0.457
Other/multiracial	19 (23.5)	37 (38.5)	0.036
Unknown	1 (1.2)	6 (6.3)	0.127
Indications, n (%)			
Systemic inflammatory disease	29 (35.8)	5 (5.2)	<0.001
Low mobility	25 (30.9)	29 (30.2)	1.0
Vessel compression	18 (22.2)	3 (3.1)	<0.001
COVID-19/MISC	6 (7.4)	57 (59.4)	<0.001
Concern for septic emboli	1 (1.2)	0 (0)	0.458
Venous malformation	1 (1.2)	0 (0)	0.458
Stent prophylaxis	1 (1.2)	2 (2.1)	1.0
Risks for thrombosis, n (%)			
Central venous access	33 (40.2)	19 (19.8)	0.003
COVID-19/MISC	6 (7.3)	57 (59.4)	<0.001
Systemic inflammatory disease	29 (35.4)	13 (13.5)	0.001
Active malignancy	26 (31.7)	8 (8.3)	<0.001
Obesity (>95th percentile of age)	19 (23.2)	44 (45.8)	0.003
Recent trauma	15 (18.5)	20 (20.8)	0.85
Recent asparaginase therapy	10 (12.2)	1 (1)	0.003
Venous anomaly	7 (8.6)	6 (6.3)	0.575
Use of oral contraceptives	0 (0)	3 (3.1)	0.251

MISC, multisystem inflammatory syndrome in children

based on provider documentation. For the purpose of this study, peak goal anti-Xa levels were defined as 0.1 to 0.3 units/mL, drawn between 4 and 6 hours after at least the third dose.[2,9]

Statistical Analysis. Statistical comparisons were performed using Fisher exact test for categoric data and Mann-Whitney *U* tests for continuous variables through Microsoft Excel. Statistical significance for all statistical tests performed was defined as $p < 0.05$.

Results

A total of 202 patients who had received enoxaparin were identified from October 2018 through September 2021. Of these, 159 patients met inclusion criteria and used 177 courses of enoxaparin prophylaxis. The once-daily study group included 81 courses, and the twice-daily group included 96 courses. Demographic and clinical characteristics are presented in Table 1. There were significant differences in age ($p < 0.001$), indications for prophylaxis, and thrombosis risk factors between groups. The once-daily group tended to include older children, whereas the twice-daily dosing was evenly distributed among all ages. Similarly, once-daily administration was used most frequently in children weighing 40 kg or more. The indication for the patients differed as well. Those who received once-daily dosing were indicated for systemic inflammatory disease ($p < 0.001$) and vessel compression ($p < 0.001$) as compared with twice-daily recipients, who often had COVID-19/MISC ($p < 0.001$). Patients with risk factors of central venous access ($p = 0.003$), systemic inflammatory disease ($p < 0.001$), active malignancy ($p < 0.001$), and recent asparaginase therapy ($p = 0.003$) were more likely to be prescribed once-daily prophylaxis. Patients with risk factors for COVID-19/MISC and obesity ($p < 0.001$) were more likely to be prescribed twice-daily prophylaxis. The median dose in the once-daily group was 0.68 mg/kg/dose SC compared with 0.49 mg/kg/dose SC in the twice daily group, which was statistically significant ($p < 0.05$; Table 2). Of note, 2 patients younger than 2 months used 0.75 mg/kg/dose in the twice-daily group; no patients younger than 2 months received once-daily enoxaparin. In the once-daily prophylaxis group, 69.5% of doses were capped at 40 mg/dose, whereas 26% of doses were capped at either 30 mg/dose or 40 mg/dose in the twice-daily prophylaxis group.

Although 1 thrombotic event occurred in the once-daily group and none in the twice-daily group, there was no statistical difference in the thrombotic events ($p = 0.46$; Table 3). Upon further investigation, the 1 thrombotic event in the study that occurred was a superficial catheter-associated thrombus. Because this study is retrospective in nature, only 18 of 81 of the once-daily group (22.2%) and 17 of 96 of the twice-daily group (17.7%) had imaging to confirm the lack of thrombosis during the study period (Table 4). There were no statistical differences in bleeding events, as shown in Table 3. There was 1 major bleeding event (1.2%) in the once-daily group, and no major bleeding events in the twice-daily group ($p = 0.46$). There were 2 minor bleeding events (2.4%) in the once-daily group compared with 4 minor bleeding events (4.2%) in the twice-daily group ($p = 0.69$). The 1 major bleeding event was hemorrhagic cystitis. Minor bleeding events identified included dental bleeding, hematuria, mild epistaxis, and hemoccult-positive stool tests.

Regarding exploratory outcomes, only 16 courses of enoxaparin prophylaxis included anti-Xa monitoring (2% once-daily, 15% twice-daily) because of concern for obesity and/or drug accumulation. A total of 1 of 2 patients in the once-daily group had an anti-Xa concentration within goal. Of the patients in the twice-daily group, 4 had anti-Xa concentrations within goal and 7 had concentrations above goal. Lastly, patients with 1 to 2 known risk factors for thrombosis were more likely to use once-daily dosing ($p = 0.07$) compared with patients with 3 or more risk factors.

Discussion

Once-daily enoxaparin dosing is a well-established dosing regimen for VTE prophylaxis in adult patients.

Table 2. Dosing Characteristics

	Once-Daily (n = 81)	Twice-Daily (n = 96)	p value
Dose, median (range), mg/kg/dose	0.68 (0.24–1.48)	0.49 (0.21–0.75)	<0.001
Duration of prophylaxis, n (%)			
<5 days	27 (32.9)	40 (41.7)	0.279
5–29 days	36 (43.9)	52 (54.2)	0.228
≥30 days	18 (22.2)	4 (4.2)	<0.001

Table 3. Primary Outcomes

	Once-Daily (n = 81)	Twice-Daily (n = 96)	p value
Thrombotic events, n (%)	1 (1.2)	0 (0)	0.458
Evidence of thrombosis on imaging, n (%)			
Positive findings	1 (1.2)	0 (0)	0.458
Negative findings	18 (22.2)	17 (17.7)	0.457
N/A	63 (77.8)	79 (82.3)	0.457
Bleeding events, n (%)			
Minor bleeding	2 (2.5)	4 (4.2)	0.689
Major bleeding	1 (1.2)	0 (0)	0.458

N/A, non applicable

Table 4. Exploratory Analyses

	Once-Daily (n = 81)	Twice-Daily (n = 96)	p value
Anti-Xa levels, n (%)			
No levels	79 (97.5)	82 (85.4)	0.007
<0.1 units/mL	1 (1.2)	1 (1)	1.0
0.1–0.3 units/mL	1 (1.2)	5 (5.2)	0.221
>0.3 units/mL	0 (0)	8 (8.3)	0.008
Risk factors, n (%)			
1–2 risk factors	63 (77.8)	85 (88.5)	0.067
3 risk factors	13 (15.9)	10 (10.4)	0.37
4 risk factors	5 (6.1)	1 (1.1)	0.095

Although a once-daily dosing schema would obviously be favorable in pediatric patients in order to minimize frequency of injections, there are no formal studies reviewing the use of once-daily enoxaparin dosing for VTE in pediatric patients. Additionally, weight-based dosing based on the 2008 American College of Chest Physicians guidelines of 0.5 mg/kg/dose SC every 12 hours does not indicate a max dose for adult-sized children.[2] The purpose of this retrospective study was to determine the safety and efficacy of using a once-daily dosing schema, up to a maximum of 40 mg/day, in pediatric patients.

This study demonstrated once-daily enoxaparin prophylaxis to have a similar frequency of thrombotic events compared with the twice-daily dosing cohort. Reviewing the 1 thrombotic event, prophylaxis at a capped dose of 40 mg was provided and the patient was later identified to have a superficial venous catheter–associated thrombus. Although current guidelines suggest treatment may not be necessary, treatment was initiated at the provider's discretion because of the presence of additional risk factors.[9] Most of the patients in both groups did not receive confirmatory imaging in this retrospective study; however, this is not surprising because it is not routine practice at our institution to obtain imaging to determine the duration of prophylactic enoxaparin therapy.

Once-daily dosing appears to have similar safety outcomes compared with twice-daily dosing based on frequency of bleeding events observed in our study. All but 1 of the bleeding events were minor events. Upon further evaluation, the patient who experienced the major bleeding event was an adolescent with a history of hemorrhagic cystitis prior to enoxaparin prophylaxis. This bleeding recurred during enoxaparin prophylaxis, leading to a blood transfusion. Minor bleeding events in both groups included episodes of mild epistaxis (n = 2), mild dental bleeding following a dental procedure (n = 1), a positive hemoccult stool test (n = 1), and hematuria noted on urinalysis (n = 2).

Not surprisingly, most of the patients in both groups did not obtain anti-Xa concentrations, because anti-Xa concentrations are not routinely monitored for enoxaparin prophylaxis.[2] Although the goal anti-Xa range for LMWH treatment is well defined in literature, the anti-Xa goal range for LMWH prophylaxis, especially in the pediatric population, has not been widely reported. Based on the CHEST guideline recommendations, this study used a goal of 0.1 to 0.3 units/mL.[10] No conclusions can be drawn about the appropriateness of these dosing regimens based on anti-Xa concentrations, because the concentrations were obtained infrequently; however, it is reassuring that thrombotic and bleeding events were minimal and similar in each group.

Most patients used enoxaparin twice-daily dosing at 0.5 mg/kg/dose SC (maximum 30 or 40 mg/dose) twice-daily or 1 mg/kg/dose SC (maximum 40 mg/dose) once-daily dosing. It is not surprising that a large percentage of patients (46%) had a dose that was capped, given the prevalence of adult-sized patients at 40 kg or greater and frequency of obesity as a risk factor for thrombosis (35.4%). One case report by Lewis and colleagues presented the consideration of twice-daily dosing using a capped dose at 40 mg/dose to achieve goal anti-Xa concentrations in obese adult patients.[11] Based on the results of this study, the use of dose-capping can be considered in obese pediatric patients based on the minimal thrombotic events found. Although the 1 thrombotic event seen in the once-daily group was identified as a superficial vein catheter–associated thrombosis, the patient also had obesity as a risk factor for thrombosis. It is thought that a combination of multiple risk factors for thrombosis may be more contributory than obesity alone.[6]

There were major differences in indications and identifiable risk factors for thrombosis between prophylactic courses. This is likely due to subspecialty prescribing differences, because oncology providers were found more likely to prescribe once-daily administration compared with intensivists. This may be due to the chronic nature of the patient's risk factors, as shown by the longer duration of enoxaparin prophylaxis and its higher use when malignancy, central venous catheters, and/or history of recent asparaginase therapy were identified as indications for thromboprophylaxis. Of note, the 1 superficial VTE occurred in a patient with 4 risk factors for thrombosis, including central venous access, obesity, active oncology diagnosis, and recent asparaginase administration using enoxaparin 40 mg once daily; no anti-Xa concentrations were monitored. Risk-based dosing regimens may be considered, with twice-daily dosing preferred in patients with multiple risk factors.

There were several limitations to the study. Because of the retrospective nature of this study, information was limited to documented information. Additionally, follow-up information on patients transferred to an outside facility—that is, a rehabilitation facility—could not be obtained. Furthermore, the once-daily dosing

was more commonly used in older children and patients weighing 40 kg or more. On the other hand, COVID-19/MISC patients mostly used twice-daily dosing and may need further study. Because VTE events are rare within the pediatric population, in addition to a relatively small patient population, it is possible that a lack of differences seen between the 2 groups could be attributed to type II error. Finally, future research, including anti-Xa concentration monitoring and pharmacokinetic data, could be beneficial to further understand pharmacokinetics of once-daily prophylaxis in pediatric patients to justify its implementation into routine practice.

The opportunity to use once-daily prophylaxis dosing for pediatric patients is crucial to minimize the pain and burden of twice-daily dosing. Although further study is recommended to confirm our findings, the lack of significant thrombotic and bleeding events shown in this study may provide the opportunity to consider once-daily enoxaparin dosing for VTE prophylaxis in patients with only 1 to 2 risk factors for thrombosis.

Conclusions

Once-daily enoxaparin prophylaxis appears to have safety and efficacy outcomes similar to those of twice-daily dosing based on frequency of bleeding and clotting events observed in our study. Given the results of this study, it is reasonable to consider using once-daily enoxaparin dosing for prophylaxis, especially in older children nearing weights that align closer to adult dosing. Larger multicenter cohort studies confirming enoxaparin once-daily dosing and exploring risk-based dosing strategies for prophylaxis are warranted given the pain and burden of subcutaneous injections in this younger population.

Article Information

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