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Evaluation of Initial Enoxaparin Dosing and Antifactor Xa Levels in Infants Admitted to the Neonatal Intensive Care Unit

Rosemarie Nagy[a] Trina Hemmelgarn[b] Stephen Deptola[b]
Brianna Hemmann[b]

[a]Department of Pharmacy, Nemours Children's Hospital, Orlando, FL, USA; [b]Department of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Keywords
Enoxaparin · Antifactor Xa levels · Infants · Neonatal intensive care unit

Abstract
Introduction: Infants are at risk for thrombotic conditions due to multiple risk factors such as congenital heart defects and sepsis. According to the American College of Chest Physicians (ACCP) 2012 guidelines, enoxaparin may be given for thrombotic conditions at a dose of 1.5 mg/kg/dose every 12 h for patients less than 2 months of age and 1 mg/kg/dose every 12 h for those older than 2 months. Several studies have reported that infants typically require a higher initial dose of enoxaparin to reach therapeutic antifactor Xa levels than what is currently recommended. ***Methods:*** This is a single-center retrospective case-control study of hospitalized infants less than 12 months of age who received treatment with enoxaparin while admitted to the neonatal intensive care unit (NICU) at a freestanding children's hospital. The primary objective was the difference between the initial enoxaparin dose (mg/kg) compared to the enoxaparin dose in which the patient first achieved a therapeutic antifactor Xa level of 0.5–1.0 units/mL. ***Results:*** A total of 56 infants were included in this study. The median enoxaparin dose at initiation was 1.5 mg/kg/dose, and the median enoxaparin dose at the first therapeutic antifactor Xa level was 1.9 mg/kg/dose ($z = -12.7$, $p < 0.0001$). There was no correlation between gestational age and weight with the enoxaparin dose required to reach a therapeutic antifactor Xa level. ***Conclusion:*** Infants admitted to the NICU, specifically those less than 4 months of age, require higher initial enoxaparin dosing to reach therapeutic antifactor Xa levels than what is currently recommended.

Introduction

Estimated rates of venous thromboembolism in infants who are admitted to the neonatal intensive care unit (NICU) range from 0.1 to 5.9%. The most common locations for venous thromboembolism to occur in infants include the lower extremities and the vena cava or other thoracic veins [1]. Critically ill infants are at a higher risk than the general pediatric population for thrombotic complications, and multiple factors including central lines, congenital heart disease, disseminated intravascular coagulation, sepsis, prolonged hospitalization, and liver dysfunction exacerbate that risk [2, 3]. Enoxaparin, a low molecular weight heparin, is often the preferred agent for

karger@karger.com
www.karger.com/bmh

Correspondence to:
Brianna Hemmann, bri.hemmann@cchmc.org

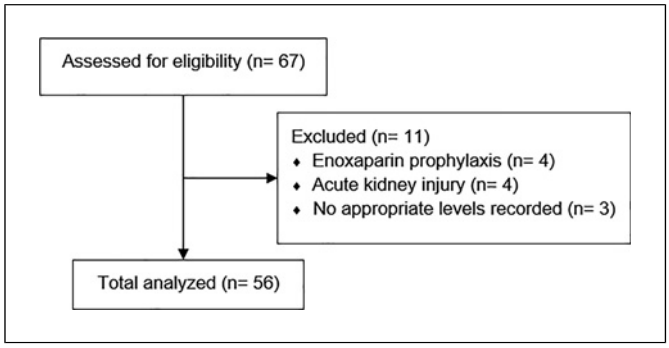

Fig. 1. Flow diagram showing patient inclusion and exclusion criteria.

critically ill infants due to a decreased side effect profile in comparison to heparin [2, 4].

The 2012 American College of Chest Physicians' (ACCP) guideline for antithrombotic therapy in infants and children currently recommends an initial enoxaparin treatment dose of 1.5 mg/kg/dose every 12 h for patients less than 2 months of age and 1 mg/kg/dose every 12 h for those older than 2 months to target antifactor Xa levels ranging from 0.5 to 1.0 units/mL [5]. The impact of gestational age and weight on the enoxaparin dosing requirement needed to achieve a therapeutic antifactor Xa level is not addressed in the ACCP guideline, and subsequent studies have reported that infants typically require a higher initial dose to reach therapeutic antifactor Xa levels than what is currently recommended [2, 4, 6–10]. Based on this literature and anecdotal experience suggesting higher dosing is needed in those less than 1 year of age, the Cincinnati Children's Hospital Medical Center institutional enoxaparin clinical guidelines recommend an initial dose of 1.5 mg/kg/dose every 12 h for patients less than 1 year of age and 1 mg/kg/dose every 12 h for those 1 year or older.

Despite utilizing higher dosing than what is recommended by the ACCP guidelines for patients over 2 months of age, it was observed that frequent enoxaparin dose increases were necessary to achieve an antifactor Xa level within range of 0.5–1.0 units/mL. The primary aim of this study was to determine the optimal initial enoxaparin dose to utilize in infants admitted to the NICU.

Materials and Methods

Patient Selection

This study was conducted as a retrospective observational study of infants less than 12 months of age who were admitted to the NICU and received therapeutic enoxaparin between January 1, 2016, and June 30, 2021. Infants were excluded if they received enoxaparin prior to admission, received renal replacement therapy, had an acute kidney injury defined by serum creatinine greater than 1.5x their baseline after starting enoxaparin or change in greater than 0.5 mg/dL within 7 days from the start of enoxaparin therapy, received enoxaparin for thromboprophylaxis, or had no appropriate levels recorded defined as either no level, a level drawn earlier than 3.75 h or later than 6.25 h after the dose (shown in Fig. 1).

Antifactor Xa Levels

The levels were drawn per our institutional protocol guidelines that recommended drawing from a fresh venipuncture to ensure there is no contamination from any heparin left in IV line tubing. The protocol also recommends if you must draw from an IV line tubing, to then waste a portion of blood prior to drawing the laboratory sample and to obtain a simultaneous aPTT level identify any contamination. During the study period, antifactor Xa levels were run using the chromogenic antifactor Xa assay, which measures the concentration of anticoagulants that inhibit factor Xa [11]. Of note, we allowed a 10% deviation on either side of the 0.5–1.0 units/mL range to be considered therapeutic.

Outcome Variables

The primary outcome evaluated was the difference between the initial enoxaparin dose (mg/kg) compared to the enoxaparin dose in which the patient first achieved a therapeutic antifactor Xa level of 0.5–1.0 units/mL. Secondary outcomes assessed were the number of dose changes required to achieve a therapeutic antifactor Xa level, time to achieve a therapeutic antifactor Xa level, incidence of severe thrombocytopenia defined as a count of less than 50,000 platelets/μL during enoxaparin therapy, and incidence of bleeding found through patient chart review utilizing consistent terminology.

Statistical Analysis

Data analysis was performed using Minitab® Statistical Software. Descriptive statistics were computed for baseline and clinical characteristics. Medians and interquartile ranges were compared via Mann-Whitney U tests based on the distribution of the data for the primary outcome. Single regression analyses were utilized to examine the relationship between gestational age and weight in determining the appropriate therapeutic dose. Two-sided p values ≤ 0.05 were considered statistically significant.

Results

Baseline Characteristics

There were 56 infants who met inclusion and exclusion criteria (Fig. 1). Baseline characteristics are summarized in Table 1. The median birth weight was 2.4 (1.9) kg, and the median gestational age was 35 (9.1) weeks. There were 13 patients less than 28 weeks (extremely preterm), 6 patients who were between 28 to less than 32 weeks (very preterm), 15 patients who were between 32 to less than 37 weeks (moderate to late preterm), and 22 patients

Table 1. Patient demographics ($N = 56$)

Variables	Value
Sex, *n* (%)	
Male	28 (50)
Female	28 (50)
Days of life, days, median (IQR)	44.5 (68)
Race, *n* (%)	
Asian	3 (6)
African American	12 (21)
White	41 (73)
Birth weight category, *n* (%)	
Extremely low birth weight (<1 kg)	13 (23.2)
Very low birth weight (<1.5 kg)	8 (14.3)
Low birth weight (<2.5 kg)	11 (21.4)
Normal birth weight (≥2.5 kg)	23 (41.1)
Dosing weight at time of enoxaparin initiation, kg, mean (SD)	3.6 (1.3)
Gestational age, weeks, mean (SD)	33.6 (5.37)
Gestational age category, *n* (%)	
Extremely preterm (<28 weeks)	13 (23.2)
Very preterm (28 to <32 weeks)	6 (10.7)
Moderate to late preterm (32 to <37 weeks)	15 (26.8)
Term (≥37 weeks)	22 (39.3)
CGA at time of enoxaparin initiation, weeks, mean (SD)	42.3 (5.77)
Postnatal age at time of enoxaparin initiation, days, median (IQR)	44.5 (68)
Primary diagnosis for admission, *n* (%)	
Bowel obstruction/perforation	10 (17)
Congenital diaphragmatic hernia	6 (11)
Gastroschisis	5 (9)
Omphalocele	5 (9)
Pulmonary hypertension	5 (9)
Respiratory failure	6 (11)
Other	19 (34)
Enoxaparin indication, *n* (%)	
Central line-associated thrombosis	18 (32)
Venous thrombosis	15 (27)
Intracranial thrombosis	11 (20)
Loss of pulses*	8 (14)
Intracardiac thrombosis	3 (5)
Arterial thrombosis	1 (2)

IQR, interquartile range. *Loss of pulses involves those patients who develop loss of pulse due to arterial thrombus following cardiac catheterization.

greater than or equal to 37 weeks old (term). The median dosing weight at enoxaparin initiation was 3.3 (1.4) kg, and the median CGA at time of enoxaparin initiation was 41.5 (6) weeks. The oldest patient evaluated was 6 months of age. The most common primary diagnosis for admission was bowel obstruction or perforation in 10 infants (18%), and the most common indication for enoxaparin use was central-line associated thrombosis in 18 infants (32.1%). Antithrombin III (AT3) levels were obtained in 44 infants (79%) with a median antithrombin III (AT3) level of 67.5 (27.8).

Enoxaparin Dosing and Therapeutic Levels

The median enoxaparin dose at initiation was 1.5 (0) mg/kg/dose, and the median enoxaparin dose at the first therapeutic antifactor Xa level was 1.9 (0.7)

Table 2. Therapeutic enoxaparin dose by postnatal age

*Age, months	*n*/total (%)	Mean dose (SD), mg/kg
<1 month	20/56 (35)	2.02 (0.44)
1 to <2 months	12/56 (21)	2.23 (0.79)
2 to <3 months	11/56 (20)	1.96 (0.44)
3 to <4 months	5/56 (9)	1.92 (0.40)
4 to <5 months	6/56 (11)	1.52 (0.33)
5 to <6 months	1/56 (2)	1.82 (0)
≥6 months	1/56 (2)	1.80 (0)

*Age at the time of enoxaparin initiation.

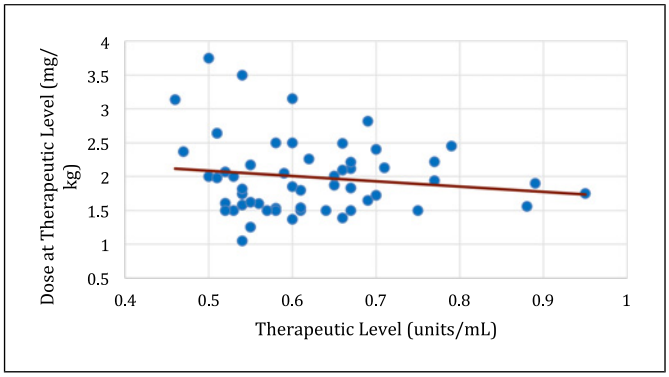

Fig. 2. Scatterplot displaying the enoxaparin dose and their associated therapeutic antifactor Xa level for all patients.

mg/kg/dose ($z = -12.7$, $p < 0.0001$). Looking at the data by age, the median dose required for a therapeutic antifactor Xa level in extremely preterm infants was 1.9 (0.6) mg/kg/dose. For very preterm and moderate to late preterm infants, the median dose required was 2.1 (0.7) mg/kg/dose and 1.74 (0.7) mg/kg/dose, respectively. Lastly, for term infants, the dose required for a therapeutic level was 1.9 (0.6) mg/kg/dose. The majority of patients were less than 4 months of age (86%) and had a therapeutic enoxaparin dose ranging from 1.92 to 2.23 mg/kg/dose, shown in Table 2. A scatterplot of the dose and associated therapeutic antifactor Xa level for all patients is shown in Figure 2. The median number of dose changes was 1 (2) to achieve a therapeutic antifactor Xa level, and the median time to achieve a therapeutic level was 1.7 (2.2) days. Using single regression analyses, there was no correlation found between gestational age, weight, CGA at the time of enoxaparin initiation, dosing weight at the time of enoxaparin initiation, and the enoxaparin dose required to achieve a therapeutic antifactor Xa level (Fig. 3). The mean therapeutic enoxaparin dose between preterm and term infants was not significantly different at 1.98 ± 0.6 mg/kg/dose versus 2.02 ± 0.5 mg/kg/dose, respectively, $p = 0.81$ (Fig. 4).

Adverse Effects

Two infants (3.6%) experienced severe thrombocytopenia, and seven infants (12.5%) had a bleeding event during enoxaparin treatment. Of the 7 patients who experienced bleeding events, six had enoxaparin held until the event was resolved, and one died following a pulmonary hemorrhage. The deceased patient did not experience supratherapeutic antifactor Xa levels and had other complications that attributed to their death. Only 2 of the seven patients who experienced a bleeding event were less than 32 weeks of gestational age (25.4 and 29.3 weeks). Table 3 shows the bleeding events with the enoxaparin dose the patient received, along with the most recent antifactor Xa level surrounding the event. No patients who had a bleeding event had an antifactor Xa level above the therapeutic threshold of 0.5–1.0 units/mL.

Discussion

In this study, we retrospectively evaluated the enoxaparin dose required to achieve a therapeutic antifactor Xa level in infants admitted to the NICU. The results of this study show that infants less than 4 months old admitted to the NICU required upwards of 2 mg/kg/dose every 12 h to promptly achieve a therapeutic antifactor Xa level, and that gestational age and birth weight do not appear to correlate with the need for a higher dose. The oldest patient during this study time period was 6 months of age; thus, we were unable to evaluate those older than 6 months.

Our results are consistent with previous retrospective studies that evaluated enoxaparin dosing in the NICU patient population. A study by Bohnhoff and colleagues [7] examined enoxaparin treatment dosing in 26 patients who developed venous thromboses in the NICU. Eight patients (31%) did not receive enoxaparin due to having contraindications to anticoagulation (i.e., hemorrhage, liver failure, or a recent operation). Patients were initially treated with a median enoxaparin dose of 1.5 mg/kg/dose for a goal antifactor Xa level of 0.5–1.0 units/mL. The results of this study showed that 94% of patients required higher enoxaparin doses with a median of 2.1 mg/kg/dose to

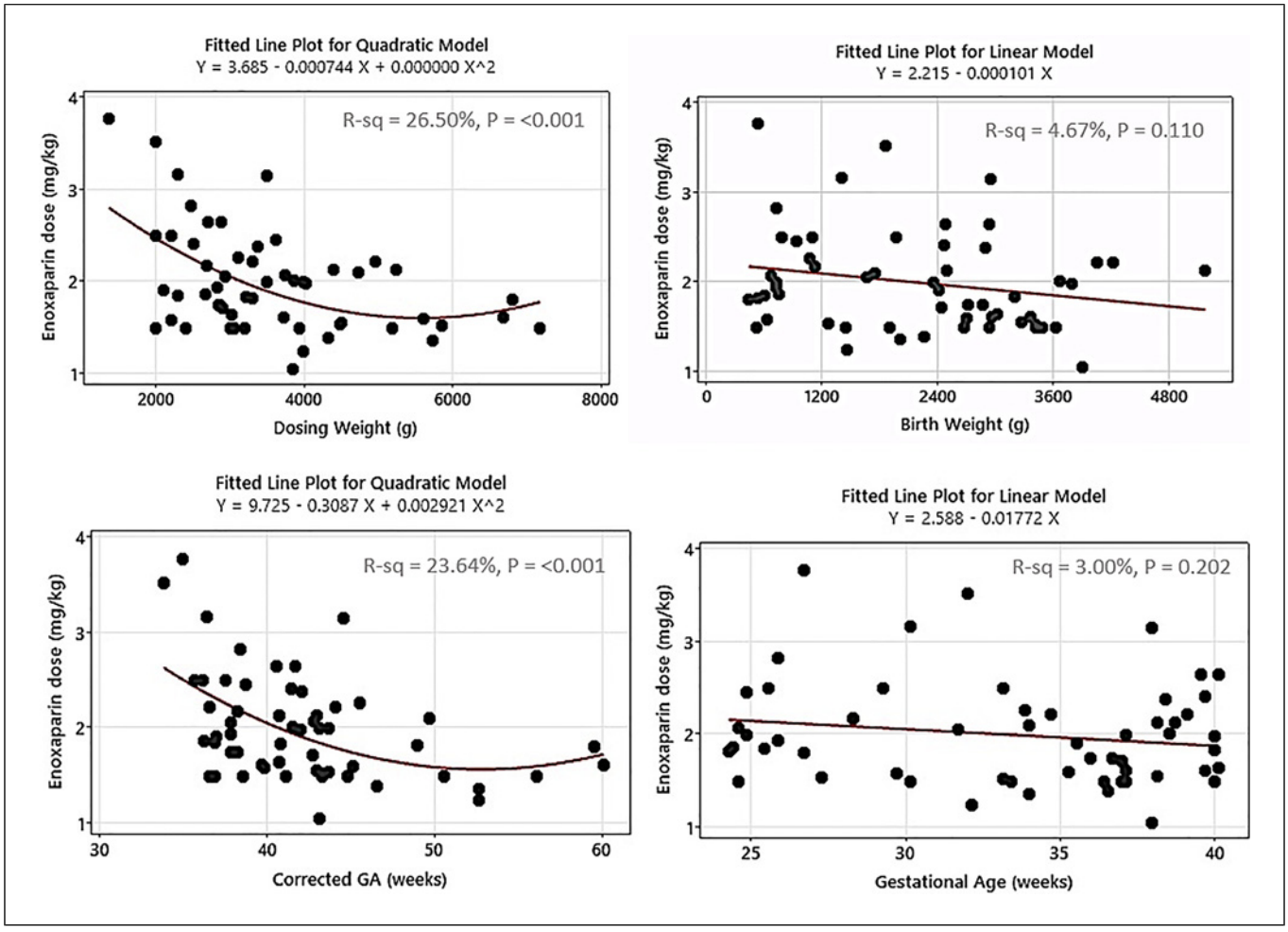

Fig. 3. Single regression analyses analyzing weight and gestational age (GA) with the enoxaparin dose required to achieve a therapeutic antifactor Xa level.

reach therapeutic antifactor Xa levels than what had been initiated, with the highest doses required in patients with a corrected gestation age of less than 37 weeks (2.5 vs. 1.8 mg/kg/day, $p < 0.01$). Similarly, our study found a need for higher dosing in infants, specifically those less than 4 months of age. In contrast to Bohnhoff and colleagues [7], our results did not find a correlation between CGA and the dose required to reach a therapeutic antifactor Xa level. Bohnhoff and colleagues [7] found no record of any adverse events due to enoxaparin therapy at either discharge or follow-up. Whereas in our study, we saw bleeding events ranging from minor bleeding occurrences such as bloody drainage and bruising to severe bleeding events such as pulmonary hemorrhage in 12.5% of patients as identified from patient chart review. Another study by Chandler and colleagues [8] evaluated 30 neonates less than 28 days of age who were treated with enoxaparin. The mean starting dose of enoxaparin was 1.53 ± 0.38 mg/kg/dose, and the mean number of dose adjustments required prior to achieving a therapeutic antifactor Xa was 1.7 ± 1.8. Fifty-three percent of patients did not achieve a therapeutic antifactor Xa level after the first dose, and cumulatively, 71% of the preterm or low birth weight neonates achieved subtherapeutic antifactor Xa levels after initial doses. These findings are consistent with our findings and results from other studies, which indicate a need for higher initial doses of enoxaparin in infants than what is currently recommended to minimize excessive dose adjustments [2–4, 7–10, 12–15].

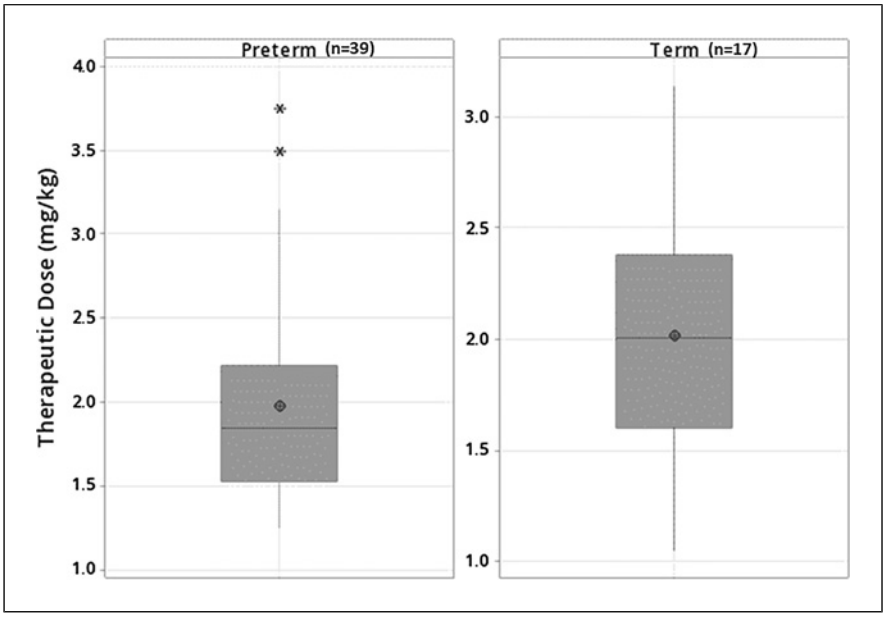

Fig. 4. Enoxaparin dose required to achieve a therapeutic enoxaparin antifactor Xa level in preterm and term infants.

Table 3. Bleeding events

Patient #	Gestational age, weeks	Bleeding event	Therapeutic enoxaparin dose, mg/kg
1	25.43	Bloody drainage, bruising, and petechiae	1.85
2	38	New area of hemorrhage on brain MRI	1.23
3	38	Punctate microhemorrhage on brain MRI	2.47
4	37.14	Mild subarachnoid/intraventricular hemorrhage	2.32
5	29.29	Parenchymal hemorrhage	2.5
6	38.14	Bloody stools	2.39
7	39.14	Pulmonary hemorrhage	2.03

Contributing factors for the larger dose requirement in this population include differences in volume of distribution and clearance. Volume of distribution links the amount of drug administered to the measured plasma concentration [15]. Infants have a proportionally higher amount of body water per kilogram of body weight when compared to children and adults, and preterm infants have an even higher value when compared to term infants. As water-soluble drugs distribute into various fluid compartments, this leads to lower plasma concentrations of these drugs. Therefore, higher doses of enoxaparin may be required to reach sufficient drug levels in the blood to achieve a therapeutic response [2, 4]. Clearance of enoxaparin is traditionally higher in infants compared to older children and adults, which in turn, leads to requiring an increased dose [9]. Due to the differences in pharmacokinetic parameters in this patient population, close monitoring of antifactor Xa levels is recommended [7–10, 14]. Another factor that could be adding to the need for a higher dose may include the characteristically low levels of AT3 in infants. AT3 is a K-dependent protease that inhibits coagulation by lysing thrombin and factor Xa. Therefore, low levels of AT3 would increase the levels of these coagulation factors causing a more hypercoaguable state, which in turn would require a higher dose of the anticoagulant to overcome these factors. In this study, we evaluated the AT3 levels in our population and found the median to be 67.5%, which is within the typical range for infants but still lower than the normal levels in children and adults. Therefore, aligning with this concept could be a possible reason for why our patients required higher enoxaparin doses to achieve therapeutic antifactor Xa levels.

In our study, there were 7 patients (12.5%) who experienced a bleeding event during enoxaparin therapy. None of these bleeding events were correlated with antifactor Xa levels above the therapeutic threshold of 1.0 units/mL. These findings are higher than some of the previous studies that found varying bleeding complication rates ranging from 0 to 7% [4, 7, 13].

Our study found no difference between age and weight with the enoxaparin dose required to achieve therapeutic antifactor Xa levels. This may be due to the small sample size within our study. This study does show that infants less than 4 months of age who are admitted to the NICU require higher initial doses of enoxaparin than are recommended in the current guidelines.

Strengths of our study include completion at a level IV NICU with a large surgical population, which led to a wide variety of patients being included. Safety parameters and potential adverse events associated with enoxaparin use were evaluated. Lastly, this study adds to the limited data available on enoxaparin dosing in the infant population. Conclusions that can be drawn from our results are limited due to the retrospective nature of this study. Other limitations include being unable to determine exactly how the antifactor Xa levels were drawn, the lack of efficacy data in terms of time to clot resolution, and evaluation of only the first therapeutic antifactor Xa level; potential future subtherapeutic levels were not captured in our data. The results from this study could benefit critically ill infants by requiring fewer dose adjustments to reach a therapeutic antifactor Xa level. Reaching therapeutic antifactor Xa levels with fewer dose adjustments would result in less laboratory draws for the patient and help conserve blood. Each antifactor Xa assay costs approximately USD 200, so reducing the amount of levels drawn prior to achieving a therapeutic level would result in potential cost savings for the institution. Using the results of our study as an example, one to two dose changes were needed to achieve a therapeutic level; thus, by adjusting our initial dose, an estimated cost savings of USD 2,000–4,000 for 10 patients per year would be achieved. Additionally, reaching therapeutic antifactor Xa levels sooner may decrease the risk of adverse events related to the thrombosis.

At our institution, we have made changes to our low molecular weight heparin protocol based on the findings from this study. We increased the initial enoxaparin dosing recommendations for those less than 4 months to start at 2 mg/kg/dose every 12 h. We kept our dosing recommendations for those 4–12 months of age to be initiated on a dose of 1.5 mg/kg/dose every 12 h, due to the limited sample size in this age range.

In conclusion, our data add to the literature suggesting higher initial enoxaparin doses are needed in infants. Our data suggests that infants less than 4 months of age required 2 mg/kg/dose every 12 h of enoxaparin to achieve a therapeutic antifactor Xa levels. Due to small sample size for those 4–6 months of age, it is difficult to make recommendations for dosing; however, our data suggest that these patients may also require a higher initial dosing than is currently recommended. Further prospective studies are needed to confirm the safety parameters of an increased enoxaparin dose in this patient population.

Acknowledgments

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Statement of Ethics

The Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center (IRB No. 2021-0616) approved the study protocol. The need for informed consent was waived by the IRB at Cincinnati Children's Hospital Medical Center.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.N., T.H., and B.H. conceived the presented idea and wrote the manuscript with input from all authors; R.N. and S.D. collected the data; and R.N., T.H., S.D., and B.H. performed the analysis and interpreted the results.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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