CLINICAL INVESTIGATION

Utility of Anti-Xa Monitoring in Children Receiving Enoxaparin for Therapeutic Anticoagulation

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Although enoxaparin is used to treat thromboembolism in children, current treatment guidelines are largely extrapolated from adults. The objectives of this study were to determine: i) correlation between enoxaparin dose and anti-factor Xa (anti-Xa) level, ii) intra-patient variability, and iii) whether dose or anti-Xa level is a predictor of outcomes. A retrospective chart review was conducted on all hospitalized patients receiving enoxaparin in a tertiary care pediatric institution. Simple linear regression, coefficient of variation (CV), and Student's t-test were used to analyze the objectives. Eighty treatment courses with interpretable anti-Xa levels were analyzed. Mean patient age was 6.5 years. Mean enoxaparin dose was 1.10 mg/kg q12h. Correlation between initial dosing and anti-Xa level was poor; $R^2 = 0.0307$ and 0.0237 for patients > 2 months with and without cardiac or renal diseases, respectively. Four out of seven patients ≤ 2 months of age compared to 4/32 patients > 2 months had a CV > 40%. Similarly, 4/12 cardiac patients compared to 4/27 non-cardiac patients had a CV > 40%. Neither dose nor anti-Xa level predicted treatment success or adverse reactions ($P > .05$). These results suggest a need to reexamine the use of anti-Xa levels for guiding enoxaparin therapy. Further prospective studies are warranted to clarify whether routine or selective anti-Xa monitoring should be recommended in pediatric patients.

KEYWORDS: Anti-factor Xa, low molecular weight heparin, enoxaparin

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INTRODUCTION

Low molecular weight heparins (LMWHs) are commonly used in the treatment of thromboembolism in children because of their many potential advantages over other antithrombotic agents, including predictable pharmacokinetics, subcutaneous administration, minimal monitoring, and a decreased risk of heparin-induced thrombocytopenia and osteoporosis.[1-3] Regular monitoring of anti-factor Xa (anti-Xa) activity is generally recommended in children.[2,4,5] However, there are limited pharmacokinetic studies published in the literature assessing LMWH

ABBREVIATIONS: anti-Xa, anti-factor Xa; CV, coefficient of variation; LMWH, low molecular weight heparin; SC, subcutaneously

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dosing and anti-Xa monitoring in children.[6-8] These studies have shown that a wide scatter of LMWH doses is required to achieve the commonly accepted anti-Xa therapeutic range of 0.5–1 U/mL. Infants ≤ 2 months of age have demonstrated increased dosage requirements as compared to older children because of their larger volume of distribution, increased clearance, and decreased anti-thrombin production.[1,2] A previous study by our investigative group found that pediatric patients ≤ 2 months of age or those with cardiac conditions or renal insufficiency were more likely to require dosage adjustments of enoxaparin to achieve the proposed therapeutic range.[9] However, no studies to date have demonstrated a correlation between the therapeutic range and clinical outcomes in children. Therefore, the objectives of this study were to determine: 1) the correlation between enoxaparin dosing and anti-Xa levels; 2) the intra-individual variability in anti-Xa levels with repeated measurements, following the same dose, in subgroups of patients according to their age, cardiac status, renal function, or the presence of malignancy; and 3) if the enoxaparin dose or its respective anti-Xa level is a good predictor of treatment success or adverse reactions.

METHODOLOGY

Patient population

The health care records of all hospitalized pediatric patients treated with enoxaparin from March 2000 to July 2003 at Children's and Women's Health Centre of British Columbia were reviewed retrospectively. Patients treated with enoxaparin were identified through the pharmacy database. Exclusion criteria were ≥ 19 years or health records not available for review.

Data collection

Data including patient demographics, concurrent medical conditions, concomitant medications, indications for enoxaparin, dose and duration of enoxaparin, anti-Xa levels, treatment outcomes, and adverse events were collected if available.

Dosing and monitoring guidelines

Based on the current guidelines published in the literature and endorsed at our institution, appropriate enoxaparin dosing for the treatment of thromboembolic disease was defined as 1.5 mg/kg/dose ± 20% for any patients ≤ 2 months of age, or 1 mg/kg/dose ± 20% for any patients > 2 months of age, given subcutaneously every 12 hours. Anti-Xa activity was measured using the Berichrom chromogenic assay. The assay was performed on a CA 540 (Toa-Sysmex) coagulation analyzer, with an overall coefficient of variation of 6.66% (n = 45) for the period of July 2001 to July 2003. Traditionally, the recommendation is for anti-Xa levels to be drawn at 4 hours post dose.[1] However, due to the logistics of blood sampling in pediatric patients and in view of the variability in published half-life values for enoxaparin, we considered anti-Xa monitoring to be appropriate if the level was measured anytime between 3 and 6 hours post dose (at peak activity) and after at least the second dose of the current dosing regimen (approximating steady state).[9] Therapeutic anti-Xa level was defined as 0.5–1 U/mL ± 10%.[1,9]

Statistical analysis

Using simple linear regression methods, the correlation between enoxaparin treatment doses and their respective appropriately measured anti-Xa levels was determined in the following scenarios: i) initial dosing (including appropriate and inappropriate dosing based on the current guidelines); and ii) in patients with or without cardiac or renal diseases.

Coefficient of variation (CV), calculated as the standard deviation (SD) divided by the mean (X) × 100%, was used to characterize intra-individual variability in anti-Xa levels. Patients were then grouped into those with small or large intra-individual variability in anti-Xa levels, defined as CV < 10% or > 40%, respectively. Intra-individual variation was further analyzed in subgroups of patients according to their age, cardiac status, renal function, and the presence of malignancy.

Comparisons of enoxaparin dosing or anti-Xa levels and clinical outcomes were analyzed using Student's t-test. Treatment success was defined as radiographic resolution or improvement in the thrombus. The final enoxaparin dose or its respective anti-Xa level associated with treatment success was compared to that

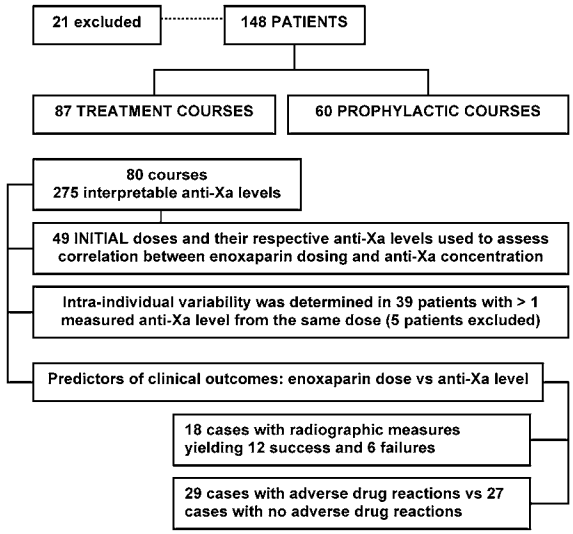

Figure 1. Flowchart for data analysis.

associated with treatment failure, defined as no radiographic change or as progression of the thrombus. The highest dose used or its respective anti-Xa level measured within 2 weeks before the documented adverse reactions (including redness or painful injection sites, bruises, hematoma, and/or gastrointestinal bleed) was compared with the highest dose or its respective level measured in patients without documented adverse reactions.

RESULTS

Health records of 148 patients were reviewed; 21 were excluded: 3 patients were greater than 19 years of age; 9 patients did not actually receive any enoxaparin doses; 9 health records were unavailable for review. A flow chart of data analysis is presented in Figure 1. The mean age (± SD) of the patients was 6.5 ± 6.5 years. There were a total of 87 treatment and 60 prophylactic courses. Analysis was performed on the 80 treatment courses with interpretable anti-Xa levels. Fifty-six percent (154/275) of anti-Xa levels were drawn at 4 hours post dose. The mean dose used was 1.1 ± 0.38 mg/kg (range: 0.38–2.36) administered SC q12h.

Correlation between enoxaparin dosing and anti-Xa level

Only 62% (30/49) of the initial doses based on the current guidelines achieved the predefined therapeutic range of 0.5–1 anti-Xa U/mL ± 10%. Patients ≤ 2 months of age were dosed appropriately at 1.5 mg/kg SC q12h based on current guidelines. Thus, regression analysis with a single x-variable would not yield meaningful results. When regression analysis was performed for patients > 2 months of age, based on both appropriate and inappropriate dosing, the correlation between initial dosing and anti-Xa levels was weak, irrespective of concomitant diseases; $R^2 = 0.0307$ and 0.0267 (with or without either cardiac or renal diseases, respectively) (Figure 2). The correlation between initial dosing and anti-Xa levels was weak regardless of the sampling time; $R^2 =$ 0.052, 0.0478, 0.0038, 0.416, for < 4 hours, at 4 hours, 4 hours to 6 hours, and 6 hours to 9 hours, respectively.

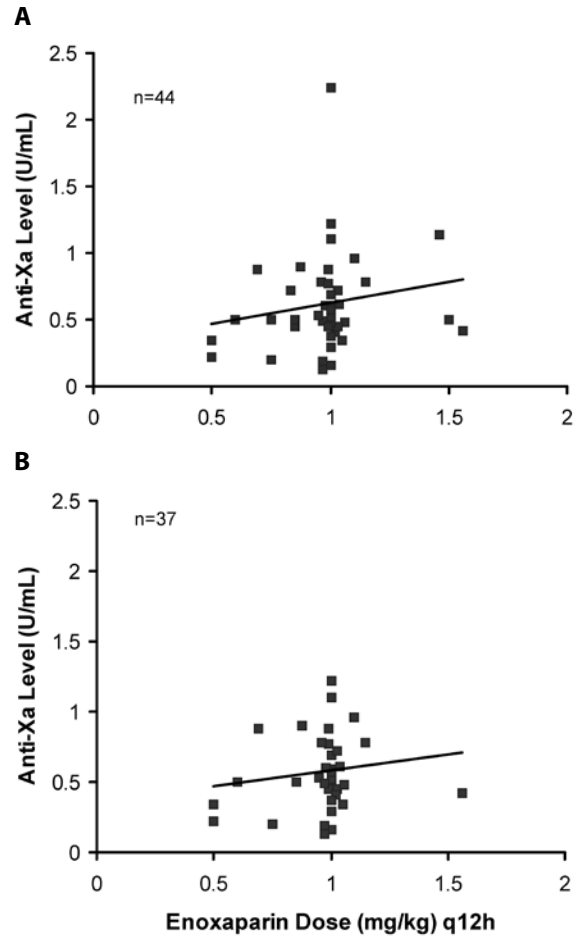

Figure 2. Correlation between initial enoxaparin dose and anti-Xa level in (A) all patients > 2 months of age, $R^2 = 0.0307$; (B) patients > 2 months of age with no cardiac or renal disease, $R^2 = 0.0237$.

Evaluation of intra-individual variability (Table 1)

Thirty-nine patients had more than one

Table 1. Intra-individual variations

Patients (n = 34)	CV < 10% (n = 3)	CV > 40% (n = 8)
Age ≤ 2 mo (n = 4)	0	4
Age > 2 mo (n = 30)	3	4
Cardiac patients (n = 9)	0	4*
Non-cardiac patients (n = 25)	3	4†
Non-cancer patients (n = 24)	0	8‡
Cancer patients (n = 10)	1	0

CV = coefficient of variation
**2 patients were also ≤ 2 months of age, 1 had concurrent obesity, 1 had concurrent renal impairment*
†1 patient was also ≤ 2 months of age
‡6 patients also had concurrent cardiac conditions and/or were ≤ 2 months of age

anti-Xa level measured with the same dose and were included in the analysis of intra-individual variability. Five patients were excluded: 3 whose levels were not drawn at the appropriate times and 2 with outlier anti-Xa levels > 4 U/mL. Intra-individual variations in anti-Xa levels were found to be wide. The number of assays performed for each dose ranged from 2 to 7. Six patients had only 2 assays performed. Of these, 4 had a CV > 40% while 2 had a CV of 10%–40%. Younger patients or patients with cardiac conditions, such as congenital heart diseases, were found to have greater variability (Table 1). The 4 cardiac patients with a CV > 40% were either ≤ 2 months of age or had concurrent obesity or renal impairment; hence, these factors may also have contributed to the wide intra-individual variability. There were only 2 renal patients with more than 2 interpretable anti-Xa levels; hence, it remains inconclusive whether renal patients have a large intra-individual variation based on this limited sample. However, substantial intra-individual variation was demonstrated in one patient with concurrent congenital heart disease and renal impairment requiring dialysis (Figure 3). In addition, the presence or absence of malignancy was unlikely the sole cause of the wide variability.

Enoxaparin dose vs anti-Xa level as predictors of clinical outcomes

Treatment outcomes were documented by radiographic measures in 18 cases: success (12) and failure (6). Neither the final dose nor the final anti-Xa level was found to be a good predictor of treatment success (Table 2, Figure 4). In none of the unsuccessful cases was there progression to pulmonary embolism. Similarly, neither the dose nor the anti-Xa level was found to be a good predictor of adverse reactions (Table 3, Figure 5). Most patients experienced more than 1 reaction: red, inflamed, and/or painful injection site (6); bruising (10); minor bleed (8); hematoma (8); and gastrointestinal bleed (1). One patient with a hemorrhagic abscess required surgical drainage. Although reported as an adverse effect of enoxaparin injection, a red or painful injection site would not be expected to correlate with the dose or anti-Xa level. However, the severity of the other adverse reactions, from bruising to hematoma, also was not related to the dose or anti-Xa level.

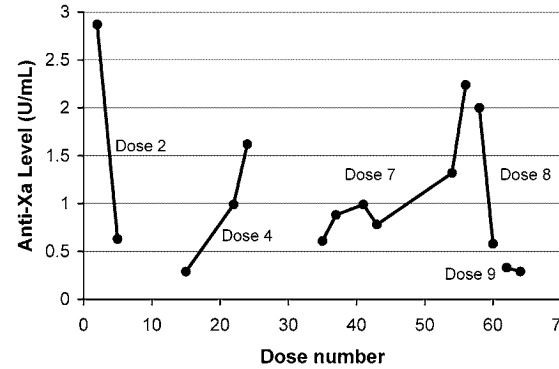

Figure 3. Intra-individual variation for a 2-year-old patient with concurrent congenital heart disease and renal impairment requiring dialysis. Dose # = the number of doses the patient has received during the treatment course. Doses 2 to 9 = the different doses used (Dose 2 = 0.50 mg/kg; Dose 4 = 0.50 mg/kg; Dose 7 = 0.89 mg/kg; Dose 8 = 1 mg/kg; Dose 9 = 0.55 mg/kg); Doses 1, 3, 5, 6 either had no anti-Xa levels measured or no interpretable levels.

DISCUSSION

In this study, a poor correlation between initial enoxaparin dosing and anti-Xa level was demonstrated for patients > 2 months of age, irrespective of concomitant diseases. Due to the retrospective nature of this study, we could not control for a wide range of doses. Consequently, in the case of patients ≤ 2 months, who all received the same initial dose, regression analysis was not performed. Although a linear relationship between enoxaparin dose and anti-Xa level was found in an in-vitro evaluation of pooled plasma specimens from

Table 2. Comparison of enoxaparin dose, anti-Xa level to treatment outcomes

	Treatment Outcomes	
	Success* (n = 12)	Failure† (n = 6)
Mean final dose (mg/kg q12h)	1.15	1.10
Median final dose (mg/kg q12h)	0.97	1.02
Range (mg/kg q12h)	0.50–2.36	0.97–1.33
Mean final anti-Xa level (U/mL)	0.69	0.74
Median final anti-Xa level (U/mL)	0.55	0.71
Range (U/mL)	0.13–2.00	0.53–0.96

P > .05 for all comparisons
**radiographic resolution of or improvement in the thrombus*
†No radiographic change, or progression of the thrombus

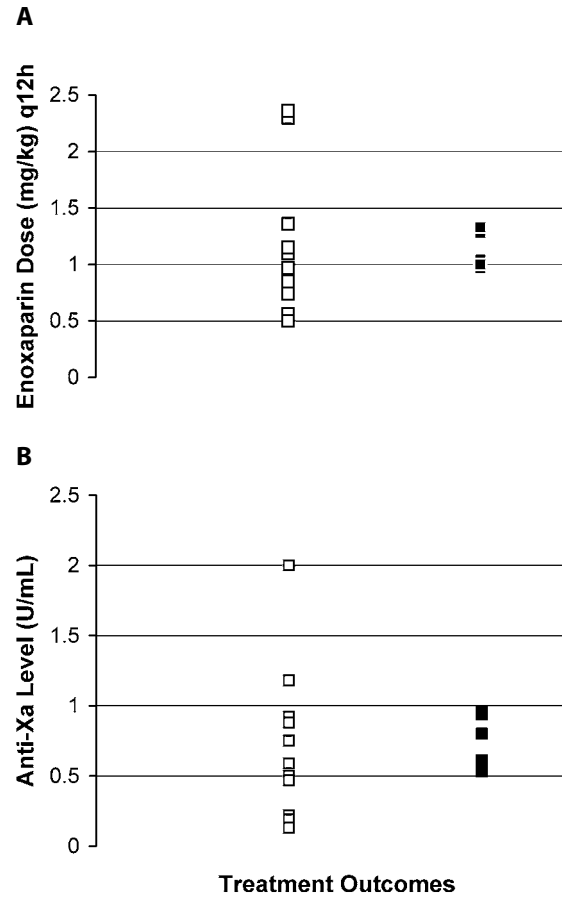

Figure 4. Comparison of dose (A), anti-Xa level (B) to treatment outcomes. Treatment success (□) = radiographic resolution of or improvement in the thrombus; Treatment failure (■) = no radiographic change, or progression of the thrombus.

both healthy children and adults, it is unlikely that these in-vitro data would be applicable to critically ill children due to the acuity of their illness and their immature anticoagulation system.[6] Additionally, in only 62% of the study patients did the initial dose result in an anti-Xa level in the target range, which is consistent with other reports in the literature.[6,7,10] Massicotte et al. found that only 50% (10/20) of their patients achieved a therapeutic anti-Xa level after a dosage of 1 mg/kg subcutaneously q12h.[6] Seven patients, 6 of whom were < 2 months of age, required an increase in LMWH dose while 3 required a decrease. Similarly, in another pharmacokinetic sub-study, only 3/6 patients achieved the target therapeutic range after an initial dose of 1 mg/kg.[7] Although a mean dose of 0.98 mg/kg was reported in their entire study involving a total of 25 patients, the enoxaparin dose ranged from 0.55–1.5 mg/kg. Likewise, no definite correlation between age and the final dose was shown in the study of Punzalan et al. In our study, not only was there poor correlation between initial doses and anti-Xa levels ($R^2 = 0.0074$, n = 49) but also weak correlation between all the treatment doses and their respective anti-Xa levels ($R^2 = 0.0121$, n = 275). Hence, it is apparent that anti-Xa level cannot be predicted from a fixed enoxaparin dose in any given patient. Similarly, the study by Dix et al. has shown that only 33% of patients were maintained in the therapeutic range all of the time and only 65% were in therapeutic range 70% of the time.[10]

With this poor correlation between dose and anti-Xa level, it is prudent to determine if intra-individual variations or certain patient characteristics may account for these fluctuations. Younger patients (≤ 2 months of age) and cardiac patients were found to have wide intra-individual variations. Although an altered hemostatic system has been reported in neonates,[1,4,6,11] intra-individual variability in anti-Xa levels has not been studied previously. Similarly, wide intra-individual variations have not been previously reported in cardiac patients. Two patients with anti-Xa levels > 4 U/mL were considered as outliers and were excluded from the analysis. One patient had heparin flush in the indwelling catheter where the sample was drawn but it was unclear why the anti-Xa level was elevated from a review of the health care record of the second patient. These patients distributed equally in each group and would not have altered the results even if included. Although the causes for these variations have not been delineated,

Table 3. Comparison of enoxaparin dose, anti-Xa level to adverse reactions

	Adverse Reactions	
	Yes (n = 29)	No (n = 27)
Mean dose (mg/kg q12h)	1.14	1.17
Median dose (mg/kg q12h)	1.04	1.10
Range (mg/kg q12h)	0.56–2.36	0.60–2.14
Mean anti-Xa level (U/mL)	0.84	0.85
Median anti-Xa level (U/mL)	0.77	0.85
Range (U/mL)	0.34–2.00	0.48–1.65

P > .05 for all comparisons

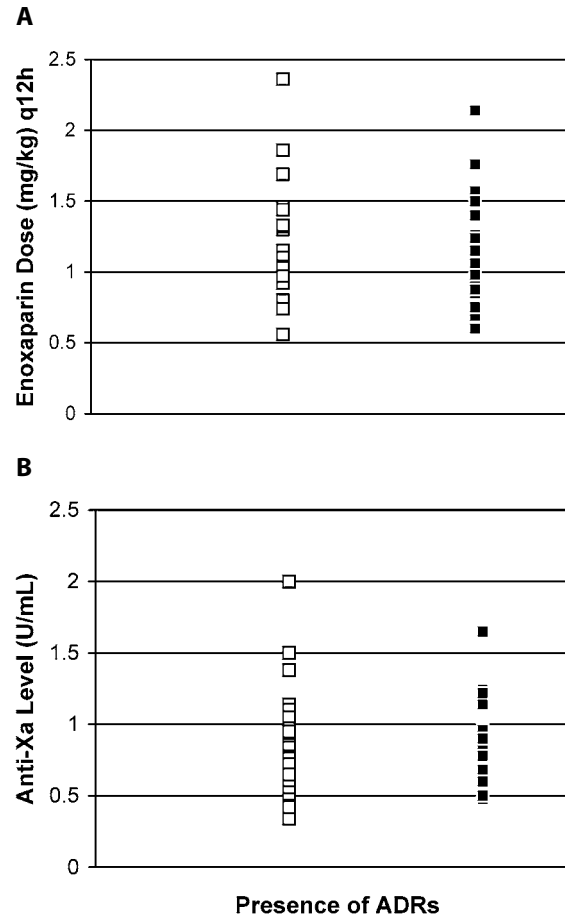

Figure 5. Comparison of dose (A), anti-Xa level (B) to adverse drug reactions (ADRs). ADR (□,n = 29); No ADR (■, n = 27).

further studies may clarify whether, in cardiac and renal patients, decreased clearance from reduced systemic perfusion, altered hemostatic states, or other mechanisms may be responsible.

The poor correlation between enoxaparin dose and anti-Xa level coupled with substantial intra-individual variations in certain subgroups of pediatric patients suggest that anti-Xa monitoring is indicated in these patients. The utility of anti-Xa monitoring to determine the safety or efficacy of LMWH therapy in adults has been questioned recently,[12] but has never been studied in children. Routine anti-Xa monitoring in adults, except in renal failure, obesity, and pregnancy, is not recommended.[4,12] The literature showed that: 1) there is considerable interpatient variation in anti-Xa levels, 2) patients with higher anti-Xa levels did not necessarily have a greater bleeding risk than those with lower levels, and 3) patients with lower anti-Xa levels did not have a greater risk for recurrent thromboembolism than those with higher levels.[12,13] Hence, unless there is a clear relationship between pharmacological response and therapeutic monitoring, the role of anti-Xa monitoring in children remains questionable as suggested by a clinical pharmacokinetic monitoring decision-making algorithm.[14] It remains unclear from this study whether anti-Xa level or enoxaparin dose is a reliable predictor of either efficacy or toxicity due to the limited sample size. We acknowledge that the resolution of thrombus also depends on other factors such as: was the initial thrombus occlusive or not; how soon did anticoagulation commence and when did it become therapeutic; and was the inciting cause still present? Hence, the end result may not just be correlated to the therapeutic level (dose or anti-Xa concentration) achieved. Thus, further prospective studies are warranted to clarify whether routine or selective monitoring should be recommended.

Several limitations of the study should be addressed, including the retrospective nature of the study, the small sample size, and the definition of treatment outcomes. As with any retrospective review, missing data or interpretation of data is of concern. The majority of patients received their enoxaparin doses while in the hospital; therefore, compliance was unlikely an issue. Also, the reliability of the timing of the anti-Xa level was based solely on the accuracy of the dosing time recorded by the nurse and the sampling time recorded by the laboratory. However, any discrepancy is unlikely of significance given the window of 3 to 6 hours allowed for anti-Xa level monitoring in this study. Other potentially confounding

factors include: variability in anti-Xa activities associated with different lots of enoxaparin[15] and error involved in administering very small doses that could result in significant variation in actual dose delivered if correct dilutional techniques are not used. Furthermore, adverse reactions may not have been documented or documentation may have been delayed. The highest dose or associated anti-Xa level drawn within 2 weeks of the documented event was assumed to have the greatest temporal association with the adverse reaction(s) and was used in the analysis. Only definitive treatment outcomes by radiographic measures were included in the analysis. In clinical practice, although patients may have improved clinically and as a consequence their treatment is considered a success, documentary evidence for success cannot be consistently retrieved from a chart review. Finally, these results pertain only to enoxaparin and may not be applicable to other LMWHs.

CONCLUSIONS

The correlation between enoxaparin dosing and anti-Xa level was poor with substantial intra-individual variations in patients ≤ 2 months of age or possibly those with cardiac conditions. Neither the dose nor anti-Xa level was a good predictor of clinical outcomes. These results suggest a need to reexamine the confidence with which we currently use anti-Xa levels for guiding enoxaparin therapy. Further prospective studies are warranted to clarify whether routine or selective anti-Xa monitoring should be recommended in pediatric patients.

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