Effect of Exogenous Antithrombin Administration on Anti-Xa Levels in Infants Treated With Enoxaparin

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OBJECTIVES Determine the effect of exogenous antithrombin III administration on low molecular weight heparin anti-Xa levels in the context of enoxaparin dosing in infants.

METHODS A retrospective chart review of infants receiving concomitant antithrombin III and enoxaparin. The primary objective of this study was to determine the median change in anti-Xa level with antithrombin III supplementation. Secondary objectives were to analyze the median change in antithrombin III levels after administration of exogenous antithrombin III, the dosing of antithrombin III, and the dose of enoxaparin throughout therapy. For a safety analysis, any bleeding events were recorded.

RESULTS The study included 17 patients who received a total of 33 doses of antithrombin III. The median change in anti-Xa levels in infants receiving exogenous antithrombin III was 0.2 units/mL ($p < 0.001$). The median dose of antithrombin III was 50 units/kg and was administered when patients were receiving a median enoxaparin dose of 1.71 mg/kg. The median increase in antithrombin III levels was 16.5% ($p < 0.001$).

CONCLUSIONS These results demonstrated that administration of exogenous antithrombin III to infants who were being treated with enoxaparin results in a significant increase in anti-Xa levels. At this time, there is insufficient evidence to recommend routine administration of antithrombin III to infants on enoxaparin. However, antithrombin III supplementation could be considered a potential option for patients who are unable to adequately achieve therapeutic anti-Xa levels with enoxaparin alone.

ABBREVIATIONS ATIII, antithrombin; IQR, interquartile range; LMWH, low molecular weight heparin; SCr, serum creatinine; UOP, urine output

KEYWORDS anti-Xa; anticoagulation; antithrombin; enoxaparin; infant

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Introduction

Newborns possess an immature and underdeveloped coagulation system compared to adults. In terms of procoagulants, they have a decreased amount of fibrinogen, factors VIII, IX, XI, and XII, and high molecular weight kininogen, which leads to an increased activated partial thromboplastin time compared to adults. In terms of anticoagulation, newborns also have a decreased amount of antithrombin (ATIII), alpha 2 macroglobulin, heparin cofactor II, protein C, and protein S, which in term infants reach adult values around 6 months of age.¹ When specifically assessing antithrombin, a healthy term newborn on day 1 of life has 63% of adult values (Table 1).² When compared to term infants, development of the coagulation system is further delayed in prematurity. One study evaluating coagulation factors and inhibitors of coagulation in the blood found there was a significant difference between preterm and term infants in antithrombin, protein C, and protein S among others.¹

These alterations in the infant coagulation system,

combined with factors that affect the critically ill infant (e.g., central venous catheters), place these patients at a higher risk of clotting than older pediatric patients.^{3–4} Factors that lead to an increased risk of thromboembolism in infants include decreased fibrinolysis, critical illness, possible congenital thrombophilia, and congenital heart disease.⁴ It has been reported that symptomatic neonatal thrombosis is reported in 5.1 per 100,000 births.⁵ The rate of clotting is on the rise with advances in medical techniques that are keeping critically ill children alive longer, which can lead to an increase in complications.⁴

Enoxaparin, a low molecular weight heparin (LMWH), acts as an anticoagulant by enhancing the inhibition rate of clotting by antithrombin, which interferes with normal hemostasis resulting in the inhibition of factor Xa (Figure 1).⁶ This mechanism is similar to that of unfractionated heparin. It has been shown that patients receiving exogenous antithrombin while treated with unfractionated heparin achieve therapeutic anti-Xa goals more quickly than patients not receiving antithrombin.⁷ Because neonates are naturally deficient in

Table 1. Normal Antithrombin Ranges for Healthy Full Term Infants

Day of Life	Serum ATIII Range (% of Adult Values)
1	63 (39–87)
5	67 (41–93)
30	78 (48–108)
90	97 (73–121)
180	104 (84–124)

ATIII, antithrombin III

antithrombin, exogenous antithrombin III administration with both unfractionated and LMWH has become common practice at some institutions despite the lack of evidence to support its use.⁸

The goal LMWH anti-Xa level for treatment of a venous clot is 0.5 to 1 international units/mL.⁶ It has been shown that neonates require significantly larger enoxaparin doses than older pediatric patients with doses of 1.7 mg/kg every 12 hours recommended for patients less than 2 months of age.⁹ This larger dosing requirement is likely due to a combination of an increased volume of distribution and the variable coagulation present in the neonates.⁷ This compares to 1.5 mg/kg every 12 hours as recommended by the American College of Chest Physicians guidelines for the management of venous thromboembolism in children.⁶ Despite this elevated starting dose, neonates, particularly preterm infants, appear to have a more difficult time achieving therapeutic anti-Xa levels.

The paucity of data on the benefit of supplemental antithrombin III during enoxaparin administration in infants leaves opportunity to further evaluate supplementation. By evaluating specific changes in anti-Xa levels after the administration of exogenous antithrombin III, we will be able to assess the value of supplementation of antithrombin when administered with enoxaparin.

Materials and Methods

Inclusion and Exclusion. This institutional review board–approved, retrospective, observational review was conducted on subjects admitted from October 1, 2010, to August 1, 2016, who received concomitant enoxaparin and antithrombin III. Patients were included if they were admitted to the institution in the specified time frame, received enoxaparin for treatment of a thrombus, received supplemental doses of antithrombin III, and were less than 1 year of age at the time of supplement administration. Patients were excluded if they had a predisposition to bleeding or thrombus formation prior to the dose of antithrombin III, if they experienced renal dysfunction within 24 hours prior to the antithrombin III dose, if anti-Xa levels were not collected or if they were inappropriately collected, or if the patients received both a supplemental dose of

Figure 1. The mechanism of action of low molecular weight heparin (LMWH) relies on the enhancement of the inhibition of factor Xa by antithrombin III

LMWH, low molecular weight heparin.

antithrombin III and a dose increase in enoxaparin simultaneously. Predisposition to bleeding or thrombus formation was defined as any factor deficiency, protein C or S deficiency, von Willebrand disease, hemophilia, disseminated intravascular coagulopathy, or profound thrombocytopenia, defined as $<50 \times 10^3$ cells/ μ L. Renal dysfunction was defined as serum creatinine (SCr) ≥ 1.5 baseline or urine output (UOP) ≤ 0.5 mL/kg/hr.⁸ Anti-Xa levels were verified as appropriately obtained if they were drawn between 3.5 and 6.5 hours after the previous dose of enoxaparin. In order to limit confounding factors that may lead to an increase in anti-Xa levels, patients were excluded if the dose of enoxaparin was increased and a supplemental dose of antithrombin III was given.

Outcomes. The primary outcome was to assess the median increase in anti-Xa levels in patients less than 1 year of age who received exogenous antithrombin III concurrently with enoxaparin. Secondary outcomes include an evaluation of the dose and duration of antithrombin III therapy, an assessment of the median increase in antithrombin levels after antithrombin III administration, and an evaluation of enoxaparin dosing throughout therapy. In order to assess safety, reporting of any bleeding events that occurred in association with therapy, defined as major bleeding, clinically relevant non-major bleeding, and minor bleeding, was recorded.¹⁰

Patient Demographics. Demographic information collected at the time of supplemental antithrombin III dose for patients included postnatal, gestational, and postmenstrual ages, and weight. Total and weight based (i.e., mg/kg) dosing information for enoxaparin were collected at the initiation of enoxaparin, at the time

Figure 2. Distribution of screened patients.

ATIII, antithrombin III.

of antithrombin III dose, and at the end of therapy or discharge. The number of dose changes in enoxaparin through the course of thrombus treatment was also included. Antithrombin III dosing information included the total and unit/kg dosing and number of supplemental doses of antithrombin III the patient received throughout the enoxaparin treatment course. Recording of anti-Xa and serum antithrombin concentrations included the level immediately prior to the supplemental dose of antithrombin III and a follow-up level within 72 hours of the supplement. A complete blood count, SCr, and UOP were recorded at baseline when enoxaparin was started, before the antithrombin III dose, and following the antithrombin III dose.

Statistical Analysis. Comparison of the median change in anti-Xa levels and the median change of serum antithrombin levels were assessed using a related sample Wilcoxon signed rank test. P values less than 0.05 were considered significant. All other parameters were assessed using descriptive statistics.

Site Specific Information. The antithrombin III product used in our institution is Thrombate III. The dose of antithrombin III that is most commonly utilized at the study institution is a standard 50 unit/kg bolus, which was largely reflected in this study. In previous assessments of this dose within the study institution, it had been determined that this bolus dose roughly correlates to the calculated dose based on percent increase needed to reach a goal antithrombin level of 100% adult levels. At the study institution, enoxaparin doses in the neonatal intensive care unit are administered as a dilution of 20 mg/mL for doses less than 10 mg.

Results

Within the specified timeframe, a total of 1739 infants

received enoxaparin. Of these, 23 patients received a supplemental antithrombin III dose. A total of 5 patients were excluded because they received a supplemental antithrombin III dose and an increase in their enoxaparin dose simultaneously. One patient was excluded for profound thrombocytopenia. All anti-Xa levels were drawn within the appropriate time, so no levels were excluded. This resulted in inclusion of 17 patients representing 33 individual antithrombin III doses (Figure 2).

Of the 17 included patients, 9 (53%) were male. The average gestational age at birth was 30.27 ± 5.67 weeks. Twelve patients were considered premature defined as a gestational age ≤ 36 weeks. The supplemental antithrombin III doses were administered at an average postmenstrual age of 46.32 ± 10.59 weeks. The average hemoglobin and hematocrit were 11.27 ± 2.01 g/dL and $33.8 \pm 5.88\%$, respectively. The average platelet count at baseline was $218.93 \pm 107.64 \times 10^3$ cells/ μ L. The average SCr was 0.31 ± 0.06 mg/dL and

Table 2. Patient Demographics*

Characteristic	Result
Male (%)	53
Postnatal age (wk)	16.16 ± 10.41
Gestational age at birth (wk)	30.27 ± 5.67
Postmenstrual age (wk)	46.32 ± 10.59
Hemoglobin (g/dL)	11.27 ± 2.01
Hematocrit (%)	33.8 ± 5.88
Platelets (10^3 cells/ μ L)	218.93 ± 107.64
SCr (mg/dL)	0.31 ± 0.06
UOP (mL/kg/hr)	3.46 ± 1.30

SCr, serum creatinine; UOP, urine output

* Data presented as mean $\pm$ SD unless otherwise noted.

Table 3. Median Anti-Xa Level Response to Exogenous ATIII Administration*

Anti-Xa level (units/mL)		Change in Anti-Xa Level (units/mL)	p Value†
Predose	Postdose		
0.43 (0.32–0.59)	0.55 (0.47–0.83)	0.2 (0.08–0.32)	< 0.001

* Data presented as median and interquartile range.

† P value determined by Wilcoxon signed rank test.

the average UOP was 3.46 ± 1.30 mL/kg/hr (Table 2).

In assessing the primary outcome, the preantithrombin III dose (predose) anti-Xa levels and postantithrombin III dose (postdose) anti-Xa levels were compared. The median predose anti-Xa level was 0.43 units/mL (interquartile range [IQR], 0.32–0.59) and the median postdose anti-Xa level was 0.55 units/mL (IQR, 0.47–0.83). This resulted in a statistically significant median change of 0.2 units/mL (IQR, 0.08–0.32) ($p < 0.001$) (Table 3). Ten of the 33 supplemental antithrombin doses were given with a predose anti-Xa level within the therapeutic range (0.5–1 international units/mL), most of which were repeat supplemental doses.

The dosing of antithrombin III used in 27 of the 33 doses was 50 units/kg (IQR, 50–50), with a median patient weight of 3.15 kg (IQR, 2.07–4.68). Patients received a median of 2 doses of supplemental antithrombin III throughout enoxaparin therapy. When evaluating the effect of the antithrombin III dose, the predose and postdose antithrombin levels were compared. Postdose levels were only available for 16 patients. Of these 16 patients, the median predose antithrombin level was 55% (IQR, 2.5–68.25) and the median postlevel was 75.5% (IQR, 60–88.75). This resulted in a significant median change of 16.5% (IQR, 9.25–26.25) ($p < 0.001$) (Table 4). The median predose serum antithrombin level is lower than would be anticipated for the mean age for this study group; however, since most patients were premature a decreased level is anticipated.

The dosing of enoxaparin was evaluated at multiple points throughout therapy including the initiation of enoxaparin for each patient and at the time of each individual supplemental antithrombin dose. The median enoxaparin dose at the initiation of enoxaparin therapy was 1.03 mg/kg/dose (IQR, 1.01–1.45), with a median patient weight of 2.9 kg (IQR, 2.67–4.81). This would be an appropriate median initial dose considering the median age at the time of antithrombin III administration was 16.16 ± 10.41 weeks. The median enoxaparin dose at the time of the supplemental antithrombin III dose

was 1.71 mg/kg (IQR, 1.53–2.63). The median enoxaparin dose at the end of therapy or at discharge was 2.24 mg/kg at a weight of 3.28 kg (IQR, 3.01–5.89) (Table 5). With the supplemental antithrombin III doses, no major bleeding, clinically relevant non-major bleeding, or minor bleeding events occurred.

Discussion

Naturally low antithrombin levels in infants may be linked to the difficulty in achieving goal anti-Xa levels in this population.¹ The results of this study show that administration of exogenous antithrombin III to infants who were being treated with enoxaparin resulted in a significant increase in anti-Xa levels. Patients received a median of 2 supplemental antithrombin III doses in this study. At this time, there is insufficient information to routinely administer antithrombin III to all infants receiving enoxaparin. Antithrombin III supplementation could be considered a potential option for patients who are unable to adequately achieve therapeutic anti-Xa levels with enoxaparin alone. Limitations of this study include the small sample size, retrospective in nature, and that it was only performed at a single center. An additional limitation includes varied prescribing practices of supplemental antithrombin III and dosing when patients had therapeutic anti-Xa levels. In this study, the anti-Xa levels were assessed as a change from predose to postdose, regardless of the starting anti-Xa level or antithrombin level. This study was designed as an internal comparison rather than a cohort comparison to those who did not receive enoxaparin, thus this variance does not alter the study results. The secondary outcome of the change in antithrombin level was limited due to a lack of follow-up of antithrombin levels after dose administration for all patients. In this analysis, there was no comparison group of patients who received enoxaparin, but did not receive antithrombin III supplementation. Possible future studies could include a retrospective matched comparison or a prospective randomized trial with standardized level

Table 4. Median Antithrombin Level Response to Exogenous ATIII Administration**

ATIII Level (%)		Change in ATIII Level (%)	p Value
Predose	Postdose		
55 (42.5–68.25)	75.5 (60–88.75)	16.5 (9.25–26.25)	< 0.001†

* n = 16 due to a lack of post-ATIII dose antithrombin levels in all patients.

† Data presented as median and interquartile range.

‡ P value determined by Wilcoxon signed rank test.

Table 5. Enoxaparin Dosing Throughout Therapy

Enoxaparin Dosing (mg/kg)	Median (IQ Range)
Initial	1.03 (1.01–1.45)
At ATIII dose	1.71 (1.53–2.63)
Final	2.24 (1.64–2.60)

ATIII, antithrombin III

monitoring in addition to clinical outcome measures such as clot resolution.

A previously published retrospective chart review evaluated the time to goal anti-Xa levels between those being treated with enoxaparin and antithrombin III compared to enoxaparin alone. The study included patients who were < 1 year old and treated with enoxaparin for a thrombus. The review revealed that supplementation with antithrombin III during enoxaparin therapy in infants did not decrease time to therapeutic anti-Xa levels, and it increased overall cost and the risk of bleeding events. The study, however, did not evaluate the degree of effect exogenous antithrombin administration had on anti-Xa levels nor did it evaluate the duration of the effect after antithrombin administration had been discontinued.⁸ In comparison to this study, our study did not address time to therapeutic anti-Xa levels; however, a significant rise in anti-Xa levels was observed that could potentially decrease time to a therapeutic range. It was a goal of this study to evaluate the duration of the elevation of serum antithrombin III levels to address this weakness of the previous study; however, inconsistent postsupplement level availability was a limiting factor. In contrast to the previous study, our study also showed no recorded bleeding events with therapy.

In conclusion, antithrombin III supplementation could be considered a potential option for infants who are unable to adequately achieve therapeutic anti-Xa levels with enoxaparin alone. The goal of this supplementation would be for patients to achieve goal anti-Xa levels in a more efficient manner.

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