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ORIGINAL ARTICLE

Efficacy and safety of antithrombin supplementation in neonates and infants on a continuous heparin infusion

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Abstract

Background: Antithrombin (AT) is a natural anticoagulant and potent inhibitor of several coagulation proteins, including activated factor X (FXa) and FIIa. The therapeutic activity of heparin depends on the presence of AT. Levels of plasma AT are low in neonates and young infants compared to those in adults. Exogenous AT supplementation is postulated to enhance the activity of heparin and facilitate attainment of therapeutic anticoagulation in infants.

Objectives: To describe the efficacy and safety of AT administration in infants on a continuous heparin infusion.

Methods: Retrospective cohort study of 50 infants who received AT while on a heparin infusion. The primary efficacy outcome was attainment of therapeutic anticoagulation within 48 hours after AT administration. Secondary outcomes included the percent of partial thromboplastin time (PTT) levels and/or antifactor Xa (anti-FXa) activity within the therapeutic window, attainment of the target AT activity level, the incidence and severity of bleeding, and all-cause in-hospital mortality. A secondary analysis investigated the relationship between simultaneously measured PTT levels and anti-FXa activity used for heparin monitoring.

Results: AT supplementation resulted in achievement of at least one therapeutic PTT level or anti-FXa activity in 90% of AT courses, though not sustained. PTT was within the therapeutic window more often than anti-FXa activity. When measured simultaneously, therapeutic anti-FXa levels were associated with supratherapeutic PTT levels.

Conclusion: AT supplementation in infants on a continuous heparin infusion may transiently improve the therapeutic effect of heparin, but this is largely dependent on the laboratory parameters used for monitoring.

KEYWORDS
antifactor Xa activity, antithrombin, hemorrhage, heparin, infant, newborn, partial thromboplastin time

Essentials

- Heparin requires antithrombin (AT), and levels of AT are decreased in neonates.
- This is a retrospective cohort study of infants supplemented with AT while on a heparin infusion.
- In the majority of patients, AT administration led to therapeutic anticoagulation.
- Partial thromboplastin time and antifactor Xa correlated poorly with each other.

1 | INTRODUCTION

Antithrombin (AT) is a natural anticoagulant and potent inhibitor of several coagulation proteins. Most notably, AT irreversibly binds to and inhibits up to 80% of activated factor II (FIIa) and largely inhibits FXa [1]. Heparins, both unfractionated and low molecular weight, accelerate and potentiate the interaction between AT and FIIa and FXa through a conformational change in the AT molecule [2,3]. The relationship between AT and heparin is bidirectional, where the presence of heparin enhances the effect of AT and the presence of AT enhances the effect of heparin.

Plasma AT concentrations are low in full-term neonates at birth (approximately 50%), and these concentrations are even lower in sick premature neonates (less than 30%) and reach adult levels (80%-120%) around 6 to 12 months of age [4,5]. The developmental differences in plasma AT activity levels are an important consideration when treating a neonate with heparin, as the antithrombotic activity of heparin depends on the presence of AT as a cofactor. Inadequate AT activity levels, due to either congenital or acquired deficiencies, may contribute to heparin resistance and an inability to achieve therapeutic effect, measured by the partial thromboplastin time (PTT) levels or antifactor Xa (anti-FXa) activity. As a result, AT supplementation is often considered in the neonatal population to enhance the activity of heparin in the setting of insufficient therapeutic effect despite increasing the dose of unfractionated heparin or low molecular weight heparin.

Antithrombin (human) is indicated in adult patients with hereditary antithrombin deficiency for the prevention of perioperative and peripartum thromboembolism and the prevention and treatment of thromboembolism [6]. The manufacturer provides guidance for a loading dose, dose adjustment, and maintenance dose, with respective target AT activity levels. Heparin is included as a drug-drug interaction, with notation to consider reducing the heparin dose during concomitant therapy to minimize or prevent bleeding. To date, the safety and efficacy of antithrombin (human) in the pediatric population have not been established.

Studies investigating AT administration in pediatric patients have found evidence of minimal benefit and possible harm. In a retrospective observational study of neonates and infants receiving enoxaparin with and without AT for the treatment of thrombosis, bleeding events occurred more frequently in patients who received AT [7]. Despite these findings, the use of AT supplementation to attain a therapeutic heparin infusion in pediatric patients has increased [8]. The purpose of this study was to describe the use of AT supplementation at Boston Children's Hospital (BCH), specifically investigating the efficacy and safety of AT supplementation in neonates and infants on a continuous heparin infusion.

2 | METHODS

2.1 | Study design and population

This study included a retrospective cohort of infants 12 months of age and younger admitted to BCH from January 1, 2016, to October 1, 2022, who received at least one dose of AT while on a heparin infusion that was continued for at least 48 hours after AT treatment. AT supplementation during extracorporeal membrane oxygenation or continuous renal replacement therapy were excluded from the study. Eligible patients and AT doses were identified using an internal reporting system, and patient data were collected in January 2023 via chart review. The study was deemed exempt by the BCH Institutional Review Board, and a waiver of consent/assent was obtained.

2.2 | Study definitions and data collection time points

A heparin course was defined as the period a patient was on a heparin infusion. If the heparin infusion was stopped for more than 48 hours and then resumed, it was considered a new heparin course that could be included in the study separate from the first. Some patients received AT at multiple time points during one heparin course. AT doses given more than 48 hours apart from each other were analyzed as separate treatments. However, if more than one AT dose was given within a 48-hour period, they were considered part of the same treatment (Supplementary Figure). Obtaining blood samples before and after AT supplementation was at the clinician's discretion. All measured PTT levels, anti-FXa activity, and AT activity were retrospectively collected from before through 48 hours after the AT treatment (Supplementary Figure).

2.3 | Primary and secondary outcomes

The primary outcome was attainment of therapeutic anticoagulation anytime within 48 hours after AT treatment, defined as at least one occurrence of a PTT level between 60 and 85 seconds and/or an anti-

FXa activity between 0.35 to 0.7 units/mL. In accordance with our hospital protocol for systemic heparin adjustment, heparin infusion rates were modified at the clinician's discretion based on PTT level, anti-FXa activity, or both.

Secondary outcomes included the percent of PTT levels and/or anti-FXa activity within the therapeutic window in the 48 hours after AT treatment, attainment of the calculated target AT activity level within 6 hours after a single AT dose, the incidence and severity of bleeding, and all-cause in-hospital mortality. The target AT activity level was determined by entering the AT dose, baseline AT activity level, and body weight into the dosing equation provided in the package labeling. Achievement of the target AT activity level was defined as a value within 80% to 120% of the calculated target AT activity level. Incidence and severity of bleeding were determined via nursing documentation and diagnostic imaging studies over three 24-hour time periods: the 24 hours prior to the AT treatment and the 24 and 48 hours after AT treatment (Supplementary Figure). Bleeding severity was assessed via the Neonatal Bleeding Assessment Tool (NeoBAT) in neonates and infants with a postmenstrual age less than or equal to 44 weeks [9] or the International Society on Thrombosis and Haemostasis (ISTH) criteria for pediatric safety endpoints in infants with a postmenstrual age greater than 44 weeks [10]. Similar severity bleeding categories between the NeoBAT and ISTH criteria were combined to simplify analysis. Moderate and clinically relevant nonmajor (CRNM) bleeding were combined and severe and major bleeding were combined according to the NeoBAT and ISTH criteria, respectively. The highest bleeding score within a 24-hour period was recorded.

2.4 | Comparison of PTT levels and anti-FXa activity as monitoring parameters for heparin infusions

In a secondary analysis, we investigated the relationship between simultaneously measured PTT levels and anti-FXa activity used to assess the therapeutic efficacy of heparin. To assess the incidence and severity of bleeding associated with each paired measurement, we assigned the highest severity bleeding score in the 24-hour period in which the samples were collected to each pair.

2.5 | Statistical analysis

For this descriptive study, we employed standard statistics including mean, standard deviation, median, range, and percentages. We used a mixed-effects nonlinear model to characterize the decline of AT activity levels following a single dose administration, allowing the half-life of the fitted exponential curve to vary randomly among AT doses. McNemar's test for paired dichotomies was used to test whether the likelihood of bleeding changed after AT administration. All data of interest were available for analysis. SAS software (version 9.4, Cary, NC) was used for all statistical computations.

3 | RESULTS

3.1 | Cohort characteristics and medication details

Fifty patients with 55 heparin courses were included in the study. Forty-six patients had a single heparin course, 3 had two, and 1 had three heparin courses during their hospital admission. Among the 55 heparin courses, 50 had one AT treatment, 4 had two, and 1 had three (separated by >48 hours), for a total of 61 AT treatments while on a heparin drip. The majority of AT treatments (n = 49) consisted of a single AT dose, 11 consisted of two doses, and 1 consisted of four doses (given within a 48 hour time period), for a total of 75 AT doses (Figure 1). The demographic characteristics of the patients are provided in Table 1. The median gestational age at birth was 38 weeks (range, 28-41 weeks), with a median birth weight of 3.1 kg (range, 0.8-4.5 kg). The median postnatal age at the time of the first AT dose was 19 days (range, 3-341 days). The majority of heparin courses were indicated for thrombosis (49%) and postoperative cardiac surgery (40%) (Table 2). The median heparin infusion rate 2 hours prior to AT dosing was 32 units/kg/hour (range, 0-50 units/kg/hour). The median PTT level and anti-FXa activity prior to AT treatment was 62.1 (range, 33.2-200) and 0.1 (range, 0.10-0.32), respectively. The median baseline AT activity level was 37%, and the median calculated target AT activity level was 99%, with a range of 47% to 150% (Table 2).

3.2 | EFFICACY OUTCOMES

AT supplementation resulted in therapeutic anticoagulation in 90% (55/61) of AT treatments. Of these 55 treatments, 52 had both PTT and anti-FXa activity measured in the 48 hours posttreatment (not always in the same blood draw), one had only anti-FXa activity measured, and two only measured PTT levels. Assessment of which laboratory parameter became therapeutic when both were measured showed that 73% were therapeutic based only on PTT levels, 8% based only on anti-FXa activity, and 19% based on both PTT levels and anti-FXa activity (Table 3). Despite a high percentage of AT treatments that achieved at least one therapeutic level (by either PTT or anti-FXa measurement), the benefit of AT administration was not sustained. An average of only 39% of PTT levels or anti-FXa activities measured in the 48 hours after the final AT dose were consistently in the therapeutic window (Table 3). Out of the 75 individual AT doses, 41 had a measured AT activity level within 6 hours after the dose, with 61% achieving a level between 80% and 120% of the calculated target. AT activity levels decreased over the 48 hours post-AT administration, with a calculated average half-life of 49 hours (Figure 2).

3.3 | Safety outcomes

Bleeding severity increased after 13/61 (21%) of AT treatments (Table 3), with the majority of bleeding events progressing from none

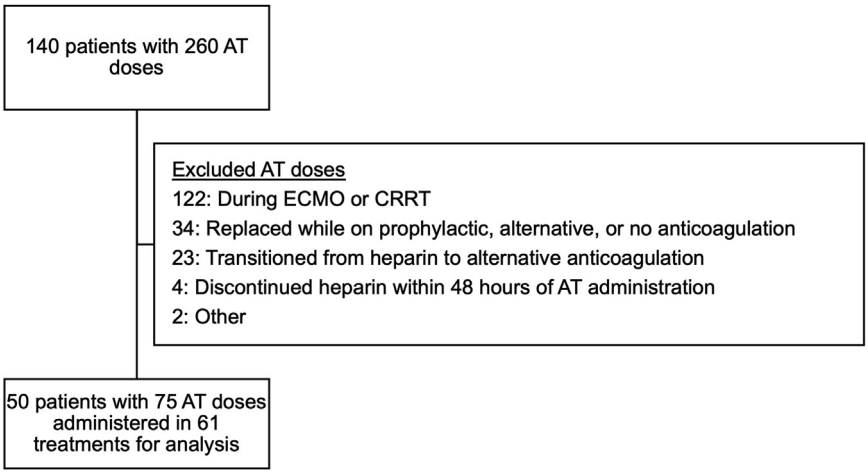

FIGURE 1 Flow diagram of study cohort. AT, antithrombin; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

to minor bleeding (Supplementary Table). Moderate/CRNM or severe/major bleeding occurred after AT treatment in only 4 patients and included bloody urine and peritoneal drain output, postoperative bleeding of unknown origin, and a gastrointestinal bleed. Severe/major bleeding included a postoperative intraabdominal hemorrhage (Table 4). Thus, for patients included in this study, AT treatment had no effect on the change in bleeding severity ($p = 1$ by exact McNemar test). Importantly, 4 patients were excluded from the study due to discontinuation of the heparin infusion less than 48 hours after AT treatment. Due to the possibility that the infusion was discontinued due to a major bleed post AT administration, we reviewed these 4

TABLE 1 Cohort characteristics.

Characteristics	*n* (%) or median [range]
Sex, male	31 (62)
Race	-
White	21 (42)
Black/African American	3 (6)
Unknown	26 (52)
Ethnicity	-
Hispanic or Latino	5 (10)
Not Hispanic or Latino	28 (56)
Unknown	17 (34)
Gestational age at birth, weeks	38 [28-41]
Preterm < 37 weeks gestation	13 (26)
Term ≥ 37 weeks gestation	37 (74)
Weight at birth, kg	3.1 [0.8-4.5][a]
Low birth weight < 2.5 kg	10 (23)
Very low birth weight < 1.5 kg	0 (0)
Extremely low birth weight < 1 kg	1 (2)
Postnatal age at the time of the first AT dose, days	19 [3-341]
Length of stay, days	66 [9-230][b]

AT, antithrombin.
[a]Data available for 43 patients.
[b]Includes 51 hospital admissions.

TABLE 2 Medication and laboratory testing details.

	n or *n* (%) or median [range]
Patients	50
Heparin	-
Courses	55
Indication for heparin	-
Thrombosis	27 (49)
Postoperative cardiac surgery	22 (40)
Thrombosis and postoperative cardiac surgery	5 (9)
Postoperative noncardiac surgery	1 (2)
Infusion rate	-
2 hours before AT supplementation	32 [0-50]
24 hours after AT supplementation	32 [0-54]
48 hours after AT supplementation	32 [0-54]
Antithrombin	-
Treatments	61
Doses	75
Baseline activity level, (%)	37 [18-61]
Target activity level, (%)	99 [47-150]
Dose, units per kg	41 [9-84]
Laboratory Tests	
Pre-AT PTT level (seconds)	62.1 [33.2-200]
Pre-AT anti-FXa level (units/mL)	0.1 [0.1-0.32]

AT, antithrombin; FXa, activated factor X; PTT, partial thromboplastin time.

TABLE 3 Efficacy and safety outcomes.

Outcomes	*n* (%) or mean ± SD
Primary outcome	
Attainment of therapeutic anticoagulation after AT administration	55/61 (90)
PTT only	38/52 (73)
Anti-FXa only	4/52 (8)
PTT and anti-FXa	10/52 (19)
Secondary outcomes	
Average percent of samples in therapeutic window after AT course	-
PTT only	31% ± 22
Anti-FXa only	9% ± 20
PTT or anti-FXa	39% ± 25
PTT and anti-FXa	0% ± 2
Attainment of target AT activity level within 6 hours of dosing	25/41 (61)
AT courses with an increase in bleeding after AT administration	13/61 (21)
All-cause in-hospital mortality	9/50 (18)

AT, antithrombin; FXa, Factor Xa; PTT, partial thromboplastin time.

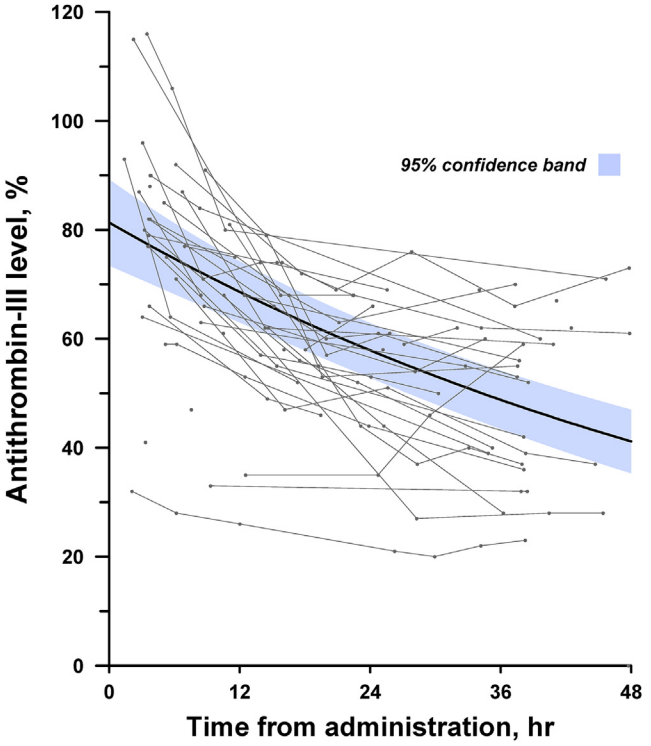

FIGURE 2 AT activity levels decline after administration of a single AT dose, with a calculated average half-life of 49 hours. AT, antithrombin.

charts in detail and found two cases in which heparin was discontinued due to bleeding episodes. Specifically, one patient developed frank blood from a chest tube and another bloody stools. Thus, the incidence of bleeding post-AT may be higher than that reported in this study.

In 32% of AT treatments, the heparin infusion rate was empirically decreased by the clinical team out of concern for increasing the risk of bleeding after AT administration. Upon statistical analysis, there was no correlation between decreasing the heparin infusion rate and bleeding severity, though there was a nonsignificant increase in minor bleeding if the heparin infusion rate was not empirically decreased. All-cause in-hospital mortality was 18%, with 1 death partially attributable to thrombosis progression (Table 3).

3.4 | Comparison of PTT levels and anti-FXa activity as monitoring parameters for heparin infusions

Out of the 250 simultaneously measured PTT levels and anti-FXa activity (from the same blood draw), only one pair was within the therapeutic range for both the PTT and anti-FXa (Figure 3). In the majority of paired samples, the anti-FXa activity was subtherapeutic, with a wide range of PTT levels. Other than the single pair mentioned, all other samples with a therapeutic anti-FXa activity had a simultaneously measured supratherapeutic PTT level (Figure 3). Three patients had an episode of moderate bleeding with a total of seven paired PTT levels and anti-FXa activity available during those episodes (Table 4). Of the seven paired samples obtained during an episode of moderate bleeding, 86% (6/7) occurred when the PTT level was supratherapeutic and the anti-FXa activity was subtherapeutic. Only one patient had an episode of severe bleeding. Only a PTT level was measured that day (no paired anti-FXa activity), so this data point was unable to be included in the analysis.

4 | DISCUSSION

Indications and dosing strategies for AT supplementation in pediatric patients are scarce. The 2018 American Society of Hematology guidelines for the treatment of pediatric venous thromboembolism recommend against empiric AT replacement in pediatric patients with deep vein thrombosis, cerebral sinovenous thrombosis, or pulmonary embolism [8]. In comparison, the panel suggests using AT replacement in pediatric patients with deep vein thrombosis, cerebral sinovenous thrombosis, or pulmonary embolism who clinically failed standard anticoagulation and have low AT activity levels, based on age-appropriate reference ranges [8]. These recommendations are based on little evidence of benefit and perhaps evidence of harm, emphasizing the need for more extensive research in pediatric patients.

In this study of 50 infants who received AT supplementation while on a continuous heparin infusion, AT treatment was efficacious in attaining therapeutic anticoagulation, though the response did not appear sustained. Guidelines for the timing and frequency of PTT level

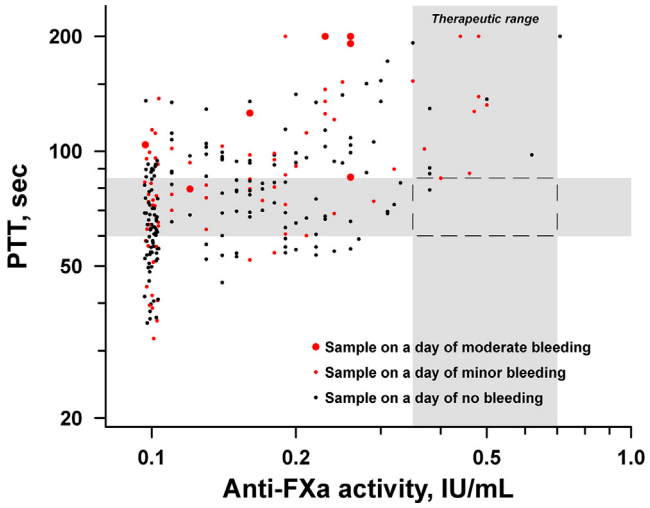

FIGURE 3 Relationship between simultaneously measured partial thromboplastin time levels and antifactor Xa (anti-FXa) activity and severity of bleeding in neonates and infants on a continuous heparin infusion.

or anti-FXa activity monitoring after AT administration are not available, resulting in variation in the timing of monitoring post AT supplementation. Thus, it is impossible to ascertain the true time spent in the therapeutic range after AT treatment.

While the definition of therapeutic anticoagulation varies, we found higher efficacy of AT supplementation in pediatric patients on heparin infusions than in prior studies. A retrospective cohort study in infants and young children on heparin for acute thrombosis reported attainment of targeted anti-FXa activity after the initial AT dose in 41% of subjects [11]. Similarly, in a separate study of patients less than 18 years of age, administration of AT while on heparin for extracorporeal membrane oxygenation, postventricular assist device implementation, or the treatment of a vascular thrombosis allowed for a decrease in heparin infusion rates by greater than 10% in 58% of patients [12]. The discrepancy between our findings and others is likely due to the fact that we included both PTT level and anti-FXa activity in the definition of therapeutic anticoagulation since monitoring preferences differ across units and institutions. From our study, the PTT more readily becomes therapeutic, which significantly increased our reported efficacy.

Due to heparin's utilization of AT, administration of both heparin and AT is thought to decrease the half-life of AT. In a retrospective population pharmacokinetics study, the calculated half-life of AT in patients less than 19 years of age (median age of 4 months) was found to be 22 hours with heparin and 27 hours without heparin [13]. In our study, the median age of the cohort was 19 days (range, 3-341 days), and postdose AT activity levels (measured per clinician discretion) were used to estimate an average half-life of 49 hours. It is unclear why the half-life was prolonged in our study compared to the previous report. However, this finding highlights the need for further research regarding AT pharmacokinetics in the neonatal population, as well as guidance for when to monitor postadministration AT activity levels.

Bleeding severity increased after 21% of AT treatments in our study, with the majority of patients increasing from none to minor bleeding. Prior studies reported a lower incidence of bleeding after AT supplementation, ranging from 10% to 17% [11,12]. The higher incidence of bleeding we observed might be due to the younger age of our study cohort and our use of both the NeoBAT and ISTH criteria to determine bleeding severity. Among the entire study population, bleeding was assessed in 41/61 (67%) of AT treatments using the ISTH criteria and in 20/61 (33%) using the NeoBAT criteria. Unlike other commonly used bleeding assessment tools, the NeoBAT provides specific examples of bleeding in each severity category, which allows for a more granular assessment of bleeding. Consequently, more bleeding events (especially minor bleeding) may have been

TABLE 4 Clinical details in patients with moderate to severe bleeding.

Bleeding severity	Postnatal age on day of bleed	Hospital location	Description of bleeding	Monitoring on day of bleed	
-	-	-	-	PTT	Anti-FXa activity
Moderate CRNM	14	NICU	Urine and peritoneal drain output bleeding	200 192 200 126 104	0.23 0.26 0.26 0.16 0.1
Moderate CRNM	32	CICU	Postoperative bleeding of unknown origin	80 108 80	0.12 UK UK
Moderate CRNM	342	CICU	Gastrointestinal bleed	86	0.26
Severe Major	35	NICU	Postoperative intraabdominal hemorrhage	200	UK

CICU, cardiovascular intensive care unit; CRNM, clinically relevant nonmajor; FXa, factor Xa; NICU, neonatal intensive care unit; PTT, partial thromboplastin time; UK, unknown.

accounted for in our study, in comparison to studies that utilized different, and perhaps less detailed, assessment tools.

Finally, the gold-standard laboratory test to monitor the efficacy of a heparin infusion remains controversial. Within our institution, both PTT levels and anti-FXa activity are used, and preferences vary between clinicians. Prior studies reported mixed results regarding the relationship between these laboratory monitoring parameters [14,15]. In our study, PTT levels and anti-FXa activity correlated poorly as therapeutic targets of heparin, with only 1/250 simultaneously measured samples falling within the therapeutic range for both parameters. In all but one paired sample, achievement of a therapeutic anti-FXa activity was associated with a supratherapeutic PTT level, potentially placing the infant at an increased risk of bleeding. A prior study in neonates and young infants on a heparin infusion reported major bleeding in 11% patients, defined as intracranial hemorrhage, gastrointestinal or genitourinary bleeding, and bleeding from a surgery site or any other site that required blood transfusion [16]. The median activated partial thromboplastin time (aPTT) level and anti-FXa activity in the nonbleeding versus bleeding groups at the time of major bleeding were 136 seconds versus greater than 180 seconds and 0.22 units/mL versus 0.48 units/mL, respectively [16]. Colleagues at our institution previously reported a significant increase in the risk of bleeding while on a heparin infusion when PTT levels exceeded 150 seconds, regardless of anti-FXa activity [14]. Further research is needed to investigate the relationship between AT supplementation, PTT levels, anti-FXa activity, and bleeding outcomes. Until then, it is reasonable to consider obtaining both values when monitoring the efficacy of a heparin infusion.

Despite the strengths, there are limitations to our study. The retrospective study design and reliance on chart review are subject to inherent limitations. The lack of a control cohort prevented us from comparing outcomes to patients on a heparin infusion who did not receive AT supplementation and so the benefit of AT supplementation compared to no AT supplementation is unclear and cannot be deduced from this study. Additionally, we defined therapeutic efficacy after AT supplementation as a single occurrence of a PTT level between 60 and 85 seconds and/or an anti-FXa activity between 0.35 and 0.7 units/mL. However, it may be more appropriate to use patient-specific goals that consider the unique hemostatic balance of the neonate (who has a developmentally normal prolongation of the PTT). Finally, our study design did not permit for detailed assessment of bleeding severity, as bleeding severity was determined retrospectively over 24-hour time periods.

5 | CONCLUSIONS

In summary, we found that AT supplementation in neonates and infants on a continuous heparin infusion may increase the therapeutic effect of heparin, but this is dependent on the laboratory parameter used for monitoring. PTT levels achieved therapeutic efficacy more often than the anti-FXa activity. The PTT and anti-FXa activity do not correlate as therapeutic targets of heparin, and permitting the PTT level to increase over a certain threshold in an attempt to achieve a therapeutic anti-FXa activity may increase the risk of bleeding. Further research and evidence-based guidelines are needed to provide recommendations regarding heparin infusion titrations, AT dosing, and laboratory monitoring of both AT activity levels and PTT levels and/or anti-FXa activity in order to achieve the goal of adequate anticoagulation with minimal bleeding risk.

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AUTHOR CONTRIBUTIONS

J.A, H.A.F, A.H, R.K, M.S-V, and P.D. contributed to the conception and design of the research study. Acquisition of data was performed by J.A. All authors contributed to the analysis of the results and preparation/revision of the manuscript. All authors have approved the final version for submission.

RELATIONSHIP DISCLOSURES

All authors, including Jennifer Alami, Henry A. Feldman, Alison Hanson, Riten Kumar, Martha Sola-Visner, and Patricia Davenport, have no relevant conflicts of interest to declare.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102336.