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Original Article

Double-Blind, Randomized, Placebo-Controlled Trial Comparing the Effects of Antithrombin Versus Placebo on the Coagulation System in Infants with Low Antithrombin Undergoing Congenital Cardiac Surgery

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Objectives: To determine whether precardiopulmonary bypass (CPB) normalization of antithrombin levels in infants to 100% improves heparin sensitivity and anticoagulation during CPB and has beneficial effects into the postoperative period.

Design: Randomized, double-blinded, placebo-controlled prospective study.

Setting: Multicenter study performed in 2 academic hospitals.

Participants: The study comprised 40 infants younger than 7 months with preoperative antithrombin levels <70% undergoing CPB surgery.

Interventions: Antithrombin levels were increased with exogenous antithrombin to 100% functional level intraoperatively before surgical incision.

Measurements and Main Results: Demographics, clinical variables, and blood samples were collected up to postoperative day 4. Higher first post-heparin activated clotting times (sec) were observed in the antithrombin group despite similar initial heparin dosing. There was an increase in heparin sensitivity in the antithrombin group. There was significantly lower 24-hour chest tube output (mL/kg) in the antithrombin group and lower overall blood product unit exposures in the antithrombin group as a whole. Functional antithrombin levels (%) were significantly higher in the treatment group versus placebo group until postoperative day 2. D-dimer was significantly lower in the antithrombin group than in the placebo group on postoperative day 4.

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Conclusion: Supplementation of antithrombin in infants with low antithrombin levels improves heparin sensitivity and anticoagulation during CPB without increased rates of bleeding or adverse events. Beneficial effects may be seen into the postoperative period, reflected by significantly less postoperative bleeding and exposure to blood products and reduced generation of D-dimers.

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Key Words: antithrombin; congenital heart disease; cardiopulmonary bypass; pediatric anticoagulation; heparin

ANTITHROMBIN (AT) SERVES as the cofactor for much of the anticoagulant activity of heparin,¹ which is the most commonly used medication for anticoagulation during cardiopulmonary bypass (CPB) and the prevention of thrombosis² in the perioperative period. Antithrombin is the body's own natural anticoagulant and is present in lower levels in neonates and young infants and in children who develop thrombus.³ Infants and children with congenital cardiac disease, particularly those with single ventricle physiology, are known to be at risk for low AT levels.^{4,5}

Heparin works by augmenting AT's anticoagulant effects,⁶ thus low levels of AT decrease the efficacy of heparin.^{7,8} Heparin's effectiveness also is influenced by various other factors such as hemodilution, body temperature, and age. This is particularly true in small children in whom the initiation of CPB results in a 50% decrease in circulating coagulation factors and AT levels and a 60% reduction in platelet counts.⁹ Effective intraoperative anticoagulation prevents the activation of the coagulation system and a consumptive coagulopathy during CPB. The authors believe that there may be an underappreciation of the importance of effective anticoagulation during CPB as an critical step in the prevention of post-CPB bleeding. Therefore the authors hypothesized that pre-CPB normalization of AT levels to 100% of normal adult activity, using plasma-derived AT, would improve anticoagulation during CPB through increased heparin sensitivity and this in turn would decrease consumption of coagulation factors during CPB and improve hemostasis post protamine administration after CPB.

Postoperatively, the incidence of thrombosis in single ventricle patients ranges from 5% to 33% and leads to significant morbidity and mortality.^{10,11} Patients undergoing surgery with longer CPB times and those with worse cardiac function and low levels of AT are more likely to develop postoperative thrombus.² Therefore, once hemostasis has been achieved, it then becomes equally important to prevent the formation of thrombus in the immediate postoperative period. AT has unique antithrombotic properties; therefore higher AT levels could attenuate microthrombosis formation in the postoperative period, as measured using fibrin degradation products.

Methods

Patient Selection

This randomized, double-blinded, placebo-controlled prospective study in infants aged birth to <7 months undergoing CPB surgery with preoperative AT levels <70% at 2 academic centers (Duke and Vanderbilt Children Medical centers) took place after the authors received Institutional Review Board

approval and written informed consent from a legal guardian for each patient. One cohort was given AT (Thrombate III; Grifols USA, Los Angeles, CA) intraoperatively via intravenous administration over a 5-minute period, shortly after anesthesia induction, to normalize AT functional assay to 100% of normal adult values. The other cohort received placebo. This use of AT (ie, in this manner in pediatric cardiac surgery) is off-label. The patients were randomly assigned to one of the cohorts by the investigational drug pharmacy (at each institution using a computer program. After randomization, the investigational drug pharmacy provided a standardized 5 mL syringe of clear liquid containing the study drug, either placebo or AT, to the study team for administration. Prior preliminary data have shown that few children older than 7 months have AT levels <70%. The following formula found in the product insert was used to calculate the AT dose: $[(100\% - \text{patient's baseline AT level } \%) \times \text{weight (kg)}] / 1.4$. Exclusion criteria included weight <2.5 kg, suspected hereditary AT deficiency, extracorporeal membrane oxygenation (ECMO) at time of the surgery, history of documented thrombosis, history of intracranial hemorrhage, <37 weeks estimated gestational age at the time of surgery, prior AT supplementation, and any therapeutic anticoagulation. Blood was drawn at 7 different time points, each time 2.5 mL, for a total of 17.5 mL from each patient. The study was registered at clinicaltrials.gov (NCT02103114) by EJ on April 3, 2014, before any study enrollment.

Anticoagulation Management

The heparin management strategy was standardized at both institutions for this study. Both institutions used the Medtronic Hemostasis Management System (HMS) Plus machine (Medtronic, Inc., Minneapolis, MN), with an initial targeted minimum heparin concentration of 4.1 U/mL, and a minimum activated clotting time (ACT) of 480 seconds was required before initiation of CPB. The AT or placebo was administered after induction and after the baseline (T1) blood draw. The first sample for the HMS and ACT machines was drawn roughly 30 minutes after the study drug administration. The post-heparin ACT was drawn 5 minutes after the heparin dose. If the ACT value was <480 seconds, an additional 200 U/kg of heparin was administered. All ACT values were determined using the point-of-care ACT machines, the Hemochron Jr. (ITC, Edison, NJ), at both institutions.

During CPB, ACT values were determined every 30 to 45 minutes. If the ACT was <480 seconds, heparin 150 U/kg was administered. During CPB, measurement with the HMS

machine was performed every 45 to 90 minutes to maintain a heparin concentration of at least 3.4 U/mL. In addition, all patients received aminocaproic acid for antifibrinolysis (50–75 mg/kg load, 50–75 mg/kg/h infusion, 0.5–0.75 mg/100 mL CPB circuit volume). Both ACT and HMS values were used as part of the anticoagulation management because this is the current standard of care. All patients received 1 U of red blood cells in the CPB circuit prime; 1 U of fresh frozen plasma (FFP) was added to the CPB prime, based on a clinical decision or any existing standard-of-care protocols. CPB circuit volume, including cardioplegia, hemofilter, and modified ultrafiltration circuit, was estimated to be roughly 350 mL at both centers. Hematocrit values during CPB were maintained >25%. All patients at both institutions underwent modified ultrafiltration (MUF) at the termination of CPB but before protamine administration. The protamine dose was determined using the HMS machine, which estimates how much protamine should be administered to reverse the current heparin level. Both institutions followed similar blood transfusion practices. On CPB platelet and fibrinogen values and, in some cases, rotational thromboelastometry were used to guide blood product ordering and transfusions in the early post-CPB period to guide blood product ordering and transfusions. Platelet transfusions were given if the platelet count was $<150 \times 10^9/L$; cryoprecipitate was given if the fibrinogen value was <150 mg/dL; and packed red blood cells or leftover MUF circuit blood were transfused to maintain a hematocrit $<30\%$ for all patients and $>40\%$ in patients with cyanotic lesions in the post-CPB period.

Outcome Variables

Demographics, laboratory values, hemostatic agents, blood products administered, operating room times, 24-hour chest tube output, rates of chest exploration for bleeding, ECMO within 24 hours, time to extubation, and occurrence of postoperative thrombosis documented on echocardiogram or ultrasound performed for clinical indications or as part of routine care were recorded for this study.

Blood samples (AT functional assay, calibrated automated thrombogram, D dimer, anti-factor Xa assay levels) were drawn at baseline 30 min after receiving the study drug and prior to going on CPB, 30min after CPB initiation, immediately before CPB termination, on arrival in the intensive care unit (ICU), on postoperative day (POD) 2 and 4. Except for the point-of-care ACT, rotational thromboelastometry, and HMS machine measurements, all other blood tests were performed at a single laboratory. Heparin sensitivity was calculated as the ACT increase in seconds at 5 minutes after heparin bolus divided by the heparin/kilogram dose.^{12,13}

Statistics

The power calculation was computed based on a 2-sample *t* test with equal variance for a range of effect sizes, which is the ratio of the absolute mean difference between 2 treatment groups over the pooled standard deviation (SD) of the outcome

measure. Using the Hashimoto et al.¹ article and the mean and SD of the fibrinopeptide A data of the control and AT groups for CPB at 60 minutes, the estimated effect size was 1.39. Given this effect size, it was calculated that 10 patients per group were needed to reach 84% power. Using 20 patients per group, this study has the advantage to detect a smaller effect size (0.92) with 80% power than the one estimated from fibrinopeptide A. For the descriptive statistics of demographic and perioperative characteristics and laboratory values, mean (SD) or median (interquartile range [IQR]) was computed for continuous variables and frequencies (percentage) for categorical variables. The difference between 2 treatment groups for each variable was evaluated. The primary outcome was the difference in calibrated automated thrombogram measurements of the AT group versus the placebo group at time point 5 (ie, arrival in the ICU). For the categorical variables, if the expected value of at least 1 cell was <5 , the Fisher exact test was used; otherwise, the chi-square test was applied. For continuous variables, the Shapiro-Wilk test was used to test the normality of the data first. If the normality was not satisfied, the Wilcoxon rank sum test was used to test the median difference of the variable between 2 groups; otherwise, a 2-sample *t* test was applied to test the mean difference. A *p* value of <0.05 was considered to be statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Over a 24-month period from June 2014 to June 2016, 223 patients were screened, 68 of whom met inclusion criteria; guardians for 40 of these patients provided consent for inclusion in the study and those patients were randomly assigned to a cohort, but 1 patient (in placebo group) was withdrawn from the study because of ECMO initiation in the operating room because of severe cardiac dysfunction.

Thirty percent of the 223 screened patients had AT levels $<70\%$; among neonates (birth plus 4 weeks), 89% had AT levels $<70\%$ (Table 1 provides demographic variables of study participants). Demographics between the 2 groups were similar, including the complexity of the cases as defined using Aristotle scores.¹⁴

Intraoperative variables are demonstrated in Table 2. Notable differences were observed between the 2 groups, including higher first post-heparin ACT (sec) results (median [IQR]) (661 [553–1,000] in the treatment group v 539 [485–703] in the placebo group; $p = 0.04$), despite similar initial heparin dosing as calculated using the HMS machine. No additional dosing of heparin was required to achieve an ACT >480 after the initial heparin dose in either group. One patient in each group received a portion of their CPB pump prime unit of FFP as part as clinical volume management before CPB. The total heparin dose per kilogram (U/kg) in the AT group was 1,201 (1,050–1,424) versus 1,444 (1,146–1,828) (median [IQR]) in the placebo group ($p = 0.04$). There was an increase in the heparin sensitivity (secs/U heparin/kg) in the AT group of 0.99 (0.84–1.53) (median [IQR]) versus 0.72 (0.65–1.04) ($p = 0.004$) in the placebo group.

Table 1
Demographics Variables

	ATIII Group (n = 20)	Placebo Group (n = 19)	p Value
Age (d)	4 (3.0-8.5)	6 (3.0-13.0)	0.17 [*]
Sex (M:F)	14:6	13:6	0.92 [†]
Weight (kg)	3.4 ± 0.5	3.5 ± 0.6	0.79 [‡]
Aristotle score level			0.30 [§]
2 (includes Aristotle scores 6.0-7.9)	3 (15.0%)	1 (5.3%)	
3 (includes Aristotle scores 8.0-9.9)	7 (35.0%)	4 (21.1%)	
4 (includes Aristotle scores 10.0-15.0)	10 (50.0%)	14 (61.5%)	

NOTE. Data are presented as mean ± standard deviation, median (interquartile range), or number (%).

Abbreviations: ATIII, antithrombin III.

^{*} Wilcoxon rank sum test.

[†] Chi-square test.

[‡] Two-sample *t* test.

[§] Fisher exact test.

No differences were noted between the 2 groups with regard to FFP prime usage (79% *v* 63%) and with intraoperative transfusions of residual MUF circuit blood, packed red blood cells, platelets, or cryoprecipitate. Similarly, CPB and cross-clamp times were not statistically different, nor were the protamine administration-to-chest closure times (see Table 2). Unfortunately, the results from the calibrated automated thrombogram test, a thrombin generation laboratory test to examine whole blood thrombin generation, were deemed inconsistent and unreliable by the laboratory and could not be analyzed. Recombinant factor VIIa was dosed in 5 separate patients in each group

and a 3-factor prothrombin complex concentrate (Profilnine; Grifols USA) was dosed in 4 separate patients in each group. Of these doses, 1 patient in the AT group and 2 patients in the placebo group received both recombinant factor VIIa and 3-factor prothrombin complex concentrate.

Postoperative variables are presented in Table 3. A significantly lower 24-hour postoperative chest tube output (mL/kg) was observed in the AT group (17 [14-27] *v* 31 [15-58] (median [IQR]) in the placebo group; *p* = 0.04). There was an overall lower blood product unit exposure collectively in the AT cohort (6 *v* 19, *p* = 0.004). Six patients in the AT group were collectively exposed to 6 blood product units, whereas 11 patients in the placebo group were collectively exposed to 19 blood product units. When analyzed as total blood product volume transfused in 24 hours (mL/kg), there was no statistical difference (*p* = 0.06). Furthermore, the volume transfused (mL/kg) in 24 hours for the different blood product components was analyzed (Fig 1). Only the platelets transfused showed a statistical difference between the 2 groups. Because the study was not powered to detect a difference in postoperative transfusion volumes, these values should be considered in that light. Antifactor Xa levels were drawn to check for any residual heparin on arrival in the ICU, roughly 2 to 2.5 hours after protamine dosing. Antifactor Xa levels all were 0.1 mg, the lowest number the test could report.

Table 4 shows the laboratory results. Antithrombin levels (% functional assay) were significantly higher in the treatment group versus the placebo group at 30 minutes after study drug administration (99 ± 19 *v* 49 ± 16, *p* < 0.001); 30 minutes on CPB (83 ± 20 *v* 55 ± 27, *p* = 0.001); just before CPB

Table 2
Intraoperative Variables

	ATIII Group (n = 20)	Placebo Group (n = 19)	p Value
ACT baseline (sec)	129 ± 22	120 ± 13	0.14 [*]
Pre-CPB heparin dose determined with HMS machine (U/kg)	510 (484-578)	606 (485-673)	0.11 [†]
ACT post-heparin (sec)	661 (554-1,000)	539 (485-703)	0.04 [†]
Heparin dosing (total) (U/kg)	1,201 (1,050-1,424)	1,444 (1,146-1,828)	0.04 [†]
Heparin sensitivity [ACT (sec)/heparin (U/kg)]	0.99 (0.84-1.53)	0.72 (0.65-1.04)	0.004 [†]
Blood prime (n)	20 (100%)	19 (100%)	ND
FFP prime (n)	15 (78.9%)	12 (63.2%)	0.28 [‡]
Total CPB time (min)	186 ± 60	213 ± 66	0.19 [*]
Total cross-clamp time (min)	87.4 ± 54	101.4 ± 32	0.33 [*]
Protamine dose determined using HMS machine (mg/kg)	9.8 (9.1-10.1)	10.0 (6.5-10.7)	0.55 [†]
Protamine-to-chest closure time (min)	107 (65-123)	89 (60-155)	0.76 [†]
Post-protamine but intraoperative MUF PRBC tf (mL/kg)	21.4 (6.3-32.3)	6.7 (0-29.3)	0.21 [†]
Post-protamine but intraoperative PRBC tf (mL/kg)	0 (0-19.5)	0 (0-37.2)	0.66 [†]
Post-protamine but intraoperative FFP tf (mL/kg)	0 (0-0)	0 (0-3.9)	0.38 [†]
Post-protamine but intraoperative platelet tf (mL/kg)	7.6 (0-22.7)	14.8 (0-22.5)	0.40 [†]
Post-protamine but intraoperative cryoprecipitate tf (mL/kg)	0 (0-7.0)	5.6 (0-10.6)	0.22 [†]

NOTE. Data are presented as mean ± standard deviation, median (interquartile range), or number (%).

Abbreviations: ACT, activated clotting time; ATIII, antithrombin III; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; HMS, hemostasis management system; MUF, modified ultrafiltration; ND, no difference; PRBC, packed red blood cell; tf, transfusion.

^{*} Two-sample *t* test.

[†] Wilcoxon rank sum test.

[‡] Chi-square test.

Table 3
Postoperative Variables

	ATIII Group (n = 20)	Placebo Group (n = 19)	p Value
Chest tube output (chest closure plus 24 h) (mL/kg)	17 (14-27)	31 (15-58)	0.04*
Total 24-h postoperative blood volume transfused (mL/kg)	0.0 (0.0-11.3)	5.2 (0.0-25.0)	0.06*
24-h postoperative red blood cell volume transfused (mL/kg)	3.9 (7.3)	10.1 (16.4)	0.2*
24-h postoperative FFP volume transfused (mL/kg)	0.8 (3.4)	2.8 (7.3)	0.27*
24-h postoperative cryoprecipitate volume transfused (mL/kg)	0 (0)	2.1 (5.4)	0.07*
24-h postoperative platelet unit volume transfused (mL/kg)	0 (0)	2.7 (5.6)	0.04*
Exposure to any blood products in 24 h postoperatively (n)	6	11	0.08†
Collective total 24-h postoperative blood product unit exposures in each group (n)	6	19	0.004‡
Antifactor Xa levels (UI/mL) on arrival in ICU	0.1 (0.0)	0.1 (0.0)	ND
ECMO within 24 h	0 (0%)	2 (10.5%)	0.23*
Chest exploration with 24 h	2 (10%)	3 (15%)	0.66*
Intracerebral bleed (POD1-7)	1 (5%)	3 (15%)	0.34*
Thrombotic events (POD1-7)	0	0	ND
Days to sternal closure	2 (1.0-4.0)	3 (0.0-4.0)	0.96§

NOTE. Data are presented as mean $\pm$ standard deviation, median (interquartile range), or number (%).

Abbreviations: ATIII, antithrombin III; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; HMS, hemostasis management system; ICU, intensive care unit; ND, no difference; POD, postoperative day.

* Wilcoxon rank sum test.

† Chi-square test.

‡ Fisher exact test.

§ Two-sample *t* test.

termination (median [IQR]) (78 [70-95] v 69 [35-89]; $p = 0.05$); and on arrival in the ICU (82 ± 18 v 63 ± 19 , $p = 0.003$). By POD 2 there was no difference in AT levels between the groups; this persisted through POD 4. D-dimer was significantly lower in the AT group than the placebo group on POD 4 (median [IQR]) (3.2 [(2.5-4.3] v 5.6 [4.3-8.4]; $p = 0.008$).

Discussion

This study demonstrates that supplementation of AT improves anticoagulation, defined by an increase in heparin sensitivity with higher ACT values and less total heparin

(U/kg) administered during CPB in infants without increased rates of bleeding or adverse events. This improved intraoperative anticoagulation may have beneficial effects into the acute postoperative period, reflected by less postoperative bleeding and blood product exposures in the first 24 hours in the AT group.

AT is a glycoprotein produced in the parenchymal cells of the liver and is a member of the serine protease inhibitor family. It plays a critical role in preventing vascular thrombosis. AT inactivates activated coagulation factors (II, IX, X, XI, and XII) by binding to them, and it is this effect that heparin dramatically accelerates. Heparin has been shown to have variable effectiveness in infants for multiple reasons, including lower AT levels, lower dose response, and increased rate of clearance.^{15,16} Furthermore, previous studies have shown that FFP transfusions do not completely correct the effect of low AT plasma levels, and moreover, the large volume required is impractical in small children.¹⁷

AT derived from human plasma (Thrombate III, which has a biological half-life of 2.5 days, has been approved for use in the setting of hereditary AT deficiency and has been extensively used “off-label” in adult cardiac surgery patients requiring CPB with heparin resistance. Its administration in adults has been shown to be both efficacious and safe and to decrease levels of fibrin monomer and D-dimer production.^{18,19} In the adult population, Koster et al. concluded that the generation of fibrin, even in the presence of high heparin concentrations, is attributed to reduced AT concentrations or reduced inhibition of clot-bound thrombin.²⁰ Therefore, in addition to maintenance of higher heparin concentrations, monitoring and substitution of AT should be considered to ensure more efficient AT activity during CPB.²¹ It has been suggested that maintaining an AT level $>80\%$ could prevent coagulation system activation and the production of fibrin breakdown products.²²⁻²⁴

Fig 1. Box plot representation of the 24-hour blood product component transfusions. AT, antithrombin; cryo, cryoprecipitate; FFP, fresh frozen plasma; PRBC, packed red blood cell.

*Statistical significance of $p < 0.05$ (Wilcoxon rank sum).

Table 4
Study Laboratory Values

	Time Point	ATIII Group (n = 20)	Placebo Group (n = 19)	p Value
ATIII functional assay (%)	T1 (baseline)	54 ± 12	54 ± 13	0.98 [*]
ATIII functional assay (%)	T2 (30 min after study drug)	99 ± 19	49 ± 16	< 0.001 [*]
ATIII functional assay (%)	T3 (30 min on CPB)	83 ± 20	55 ± 27	0.001 [*]
ATIII functional assay (%)	T4 (just before CPB)	78 (70-95)	69 (35-89)	0.05 [†]
ATIII functional assay (%)	T5 (arrival in ICU)	82 ± 18	63 ± 19	0.003 [*]
ATIII functional assay (%)	T6 (POD 2)	58 ± 15	57 ± 14	0.84 [*]
ATIII functional assay (%)	T7 (POD 4)	71 ± 20	66 ± 17	0.48 [*]
D-dimer (μg/mL)	T1 (baseline)	1.1 (0.7-1.5)	0.9 (0.7-1.9)	0.86 [†]
D-dimer (μg/mL)	T5 (arrival in ICU)	0.6 (0.5-0.9)	1.0 (0.6-1.5)	0.23 [†]
D-dimer (μg/mL)	T6 (POD 2)	1.3 (0.9-2.0)	1.7 (1.0-2.9)	0.31 [†]
D-dimer (μg/mL)	T7 (POD 4)	3.2 (2.5-4.3)	5.6 (4.3-8.4)	0.008 [†]

NOTE. Data are presented as mean ± standard deviation or median (interquartile range).

Abbreviations: ATIII, antithrombin III; CPB, cardiopulmonary bypass; ICU, intensive care unit; POD, postoperative day.

^{*} Two-sample *t* test.

[†] Wilcoxon rank sum test.

Existing pediatric studies have shown improved anticoagulation and decreased thrombosis effects in patients with higher AT levels. In the study by Tzanetos et al., patients who developed thrombosis had lower preoperative levels of AT (48.3 ± 19 v 92.5 ± 26) and low preoperative cardiac function.² A study similar to the present study, but one that focused only on the intraoperative period, concluded that supplementation with AT during CPB in children suppressed the activation of the coagulation system.¹ This implies that significant subclinical activation of the coagulation system occurs in spite of adequate ACTs. This “resistance,” or “insensitivity,” to heparin during CPB leads to ongoing activation of the coagulation and fibrinolysis systems and may result in a consumptive coagulopathy, which may manifest with increased bleeding, the need for blood products, and prolonged intraoperative surgical times. Furthermore, low postoperative AT levels increase the risk of thrombosis in already vulnerable patients with indwelling central lines, shunts, low-flow cardiac output states post-CPB, and surgical stress.^{20,25-28}

The present study included patients up to 7 months old; however only neonates were enrolled because almost all patients >30 days old had AT levels >70% (see Table 1). In the children who were enrolled, the mean AT functional activity level was 54% (Table 4).

The decision to supplement AT to 100% was made based on the pediatric literature in nonsurgical pediatric patients with known AT deficiency and the few existing references to its use in CPB in children.²⁹⁻³² The optimal level of AT for adequate anticoagulation is unclear, and lower replacement targets may be reasonable and as effective. Conversely, because AT levels decrease significantly in the early postoperative period, replacement to higher levels intraoperatively¹³ or re-dosing in the ICU might show additional benefits. There is some theoretical concern that supplementing to >100% may lead to bleeding. In an adult study, replacement to 120% resulted in a statistically but not clinically significant increase in postoperative bleeding.¹⁸ These data might represent uniquely adult concerns of possible re-heparinization in the presence of increased AT levels,^{18,33} which were not observed in the present study and were

demonstrated by both groups experiencing clinically negligible residual heparin (antifactor Xa assay levels of 0.1 IU/mL, which is the lowest value the test can measure) on arrival in the ICU. The present study showed that replacing to 100% appeared to be protective, with significantly less bleeding and blood product exposure in the AT group. The authors hypothesized that AT supplementation allowed for better anticoagulation during CPB, with less activation of the coagulation cascade intraoperatively, allowing more of the patient’s own coagulation factors to be available when needed.

Previous AT studies have shown that normalizing AT levels leads to an increased heparin sensitivity and results in decreased production of markers of thrombin generation and fibrin breakdown¹³ (ie, prothrombin activation fragment 1.2,¹⁷ D-dimers,¹⁹ and fibrinopeptide A¹ levels) during the CPB period. Although it is disappointing that the authors’ calibrated automated thrombogram laboratory values were not usable and therefore were not able to demonstrate decreased thrombin activity as previous studies have shown, the study clearly shows an increase in heparin sensitivity in the AT group.

There are a number of limitations to the present study. First, even though this is the biggest randomized, prospective, blinded study in infants replacing AT, the study is relatively small with 40 patients. Using the HMS machine to define heparin dosing is imperfect, but the authors believe that it still is the most practical way to try to individualize heparin dosing.^{34,35} In adult patient groups and in the data in the present study, pre-CPB HMS machine values have not been shown to be correlated with baseline AT activity or post-heparin ACTs.³⁶ However, relying on weight-based dosing or ACTs alone has shown continued thrombin generation, a marker of inadequate anticoagulation, during CPB in children. The present study cannot be used to determine whether the “beneficial” effects, or what portion of the beneficial effects, were purely from the higher ACT values versus other AT effects; in other words, would the same effect have been observed if patients in the placebo group were given more heparin to increase the ACT? Second, there is such variation and complexity in each child’s surgical repair that the

risk of surgical bleeding in a small number of patients might bias the study. Every attempt was made to standardize practices in each institution, especially as they pertained to the coagulation management and blood transfusion practices, but all differences likely could not be adjusted for.

In conclusion, supplementation of AT improves heparin sensitivity and anticoagulation during CPB in young infants without increased rates of bleeding or adverse events. Furthermore, these results may show potential beneficial effects into the postoperative period, reflected by significantly less postoperative bleeding and exposure to blood products. Larger randomized controlled trials are needed to confirm the potential benefits of AT supplementation in infant cardiac surgery.

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