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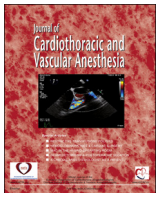

Original Article

Supplemental Antithrombin Is Effective in Achieving Adequate Anticoagulation in Infants and Children With an Inadequate Response to Heparin

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Objective: To demonstrate that supplemental antithrombin (AT) is effective in establishing adequate anticoagulation in infants and children with initially inadequate responses to heparin.

Design: Following institutional review board approval, a retrospective chart review was conducted on pediatric patients receiving AT during cardiac surgery requiring cardiopulmonary bypass.

Setting: A single institutional review in a hospital setting.

Participants: Thirty-one pediatric patients with age ranging from 1 day to 36 months (median 12 weeks) receiving AT during the study period.

Interventions: As this was a retrospective chart review, no active interventions on patients were performed.

Measurements and Main Results: Data collected included: patient age, sex, weight, activated clotting time (ACT) values, as well as heparin and AT doses. Primary outcomes were the increase in the ACT from pre- to post-AT and the number of patients who achieved an ACT >480 seconds. The paired t-test was used to compare pre- and post-AT ACT. Mean dose of AT was 50 U/kg (standard deviation 6). Following administration of AT, 30 pediatric patients achieved an ACT of >480 seconds. The post-AT ACT was significantly higher than the pre-AT by a mean of 327 seconds ($p < 0.0001$); 96% of patients achieved an adequate ACT to initiate cardiopulmonary bypass. No adverse events attributable to AT were recorded.

Conclusion: AT was effective in achieving adequate anticoagulation in a small cohort of infants and children undergoing cardiac surgery who initially were poorly responsive to heparin. Further research to examine the utility of AT in improving clinical outcomes is warranted.

Key Words: antithrombin; anticoagulation; cardiopulmonary bypass; pediatrics; ACT; activated clotting time; heparin

Cardiopulmonary bypass (CPB) and cardiovascular surgery initiate diffuse activation of coagulation through contact of the blood with the artificial surfaces of the pump oxygenator and surgical activation of the tissue factor pathway. Heparin, the standard anticoagulant for CPB, works by catalyzing the anticoagulation effect of endogenous antithrombin III (AT), multiplying its effect approximately 1,000-fold.[1] Clinicians have observed for decades that not all patients respond to conventional doses of heparin in the same manner, with 10% to 30% of patients not achieving a target level of anticoagulation as measured by the activated clotting time (ACT).[2,3] Studies in adult cardiac surgical patients have shown that heparin responsiveness is at least partially related to plasma AT concentration.[4] Several studies have demonstrated that supplemental AT is effective in increasing the anticoagulant response to heparin in adult patients and this use is recommended now in published guidelines.[1,5–8] Treatment of diminished heparin responsiveness appears to decrease deleterious activation of coagulation and inflammatory cascades during bypass.[9]

Infants and children undergoing cardiac surgery are subject to the same diffuse activations of coagulation, inflammation,

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and fibrinolysis as adults,[10] and also have decreased concentrations of pro- and anticoagulant proteins, as well as structural differences between juvenile and adult forms, producing a response to bypass and anticoagulation that is fundamentally different from adults. Antithrombin concentrations in term neonates are reduced to approximately 40% relative to adults and do not reach adult levels until 6 months of age.[11] Infants with congenital heart disease, particularly cyanotic types, may have further alterations in coagulation,[12] and hemodilution-induced decreases in coagulant factors are magnified in this population. Given these issues, it is not surprising that the anticoagulant response to standard doses of heparin in infants and children is both more variable and less likely to be adequate than in adults.[13] It has been shown that as many as 28% of infants do not achieve an adequate ACT following standard heparin dosing.[14] Despite this, infants and children commonly are anticoagulated with heparin dosing and monitoring procedures designed for adults. While it may seem obvious that supplementation of AT may improve anticoagulation in infants and children undergoing cardiac surgery with bypass, there are no published data regarding the efficacy of AT in this population. The purpose of this study was to determine whether AT supplementation in pediatric patients undergoing cardiac surgery with an initially inadequate heparin response was effective in improving anticoagulation.

Methods

The study was approved by the Research Subjects Review Board of the University of Rochester (Rochester, NY), and patient consent was waived. The inpatient pharmacy supplied a list of all patients receiving supplemental AT (Thrombate III, Grifols, Los Angeles, CA) in the cardiac operating rooms from 01/2012- 08/2016. Patients older than 3 years of age were excluded from inclusion as the issues identified above primarily affect infants and small children. Medical records were reviewed and pertinent data were extracted including patient age, sex, weight, ACT values, heparin doses, and AT doses. Primary outcomes were the difference in the ACT from the pre-AT to post-AT and the number of patients who achieved an ACT of >480 seconds. An ACT of 480 is required within this institution for initiation of CPB. All ACT measurements were performed with a Hemachron Response ACT + machine by qualified perfusionists as per standard practice. The authors' institutional standard anticoagulation protocol is an initial dose of 400 U/kg, with an additional dose if an ACT of 480 seconds is not achieved. If an ACT of >480 seconds was not achieved after 2 doses of heparin, AT is administered. Assuming roughly 50% baseline AT activity, a goal of 120% activity is targeted.[15] This led to a calculated 50 U/kg dosing regimen.

Statistical Analysis

Statistical analysis was performed using the program SAS 9.4 (SAS Insitute, Cary, NC). Normally distributed continuous variables are reported as mean values and standard deviations. The paired t-test was used to compare the difference between the pre- and post-AT ACT. A p value of <0.05 was considered significant.

Results

During the study period, 404 pediatric patients aged 1 day to 36 months underwent cardiac surgery requiring CPB. Thirty-three pediatric patients received AT during the date range. Two patients were adolescents (ages 12 and 14 years) and were excluded. Thirty-one pediatric patients received AT during the study period, with age ranging from 1 day to 36 months and a median age of 12 weeks, were included in the study cohort. The average weight of the study population was 5.8 ± 3.1 kg, with a male-to-female ratio of 21:10.

All patients had received at least 2 doses of heparin prior to AT administration. The mean initial heparin dose was 407 U/kg, and the mean post-heparin ACT duration was 400.7 seconds. The mean second dose of heparin was 232 U/kg and the mean total dose of heparin per patient prior to dosing of AT was 639 U/kg, with resulting mean ACT duration of 423 seconds. Mean dose of AT per patient was 50 U/kg (standard deviation of 6 U/kg). Following administration of AT, 30 of 31 (96.7%) patients achieved an ACT of >480 seconds. As seen in Table 1, the post-AT ACT was significantly higher than the pre-AT ACT by a mean duration of 327 seconds (p value <0.0001). Figure 1 demonstrates each individual's ACT response to heparin and AT dosing. No patients received fresh frozen plasma (FFP), cryoprecipitate, or platelets intraoperatively.

One patient, aged 36 months, did not achieve a target ACT despite receiving 510 U/kg of heparin and 41.5 U/kg of AT, resulting in a final ACT of 414 seconds prior to CPB. One patient required an additional AT dose of 52 U/kg while on CPB to maintain an adequate ACT. No adverse events attributable to AT were recorded.

The average postoperative blood loss via chest tube output was found to be 32.5 mL/kg over 24 hours. Eleven patients

Table 1
Characteristics of Surgery

Types of Surgery		
TOF repair	9	(29%)
Arterial switch	6	(19%)
RV-to-PA conduit	5	(16%)
Aortic coarctation repair	3	(9%)
VSD repair	3	(9%)
AVC repair	3	(6%)
Norwood procedure	2	(5%)
Intraoperative Data	Mean ± SD	
Baseline ACT (seconds)	126.2 ± 22.6	
Initial heparin dose (IU/kg)	407 ± 13.8	
Post-first-dose heparin ACT (seconds)	400.7 ± 56.9	
Total heparin pre-AT (IU/kg)	639.2 ± 86.9	
Pre-AT ACT (seconds)	422.9 ± 45.6	
Post-AT ACT (seconds)	749.8 ± 213.3	

Abbreviations: ACT, activated clotting time; AT, antithrombin III; AVC, artioventricular canal; PA, pulmonary artery; RV, right ventricle; SD, standard deviation; TOF, Tetralogy of Fallot; VSD, ventricular septal defect.

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