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The Impact of Antithrombin III Use in Achieving Anticoagulant Goals in Pediatric Patients

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OBJECTIVES To determine the percentage of patients with >10% reduction in heparin infusion rate within 48 hours of antithrombin III (ATIII) administration. Secondary objectives include the achievement of therapeutic anticoagulation and determining the days of subtherapeutic infusion prior to supplementation.

METHODS Retrospective chart review of 12 patients younger than 18 years of age who received ATIII concentrate supplementation while on continuous heparin infusion. Specific indications for heparin infusion therapy included extracorporeal membrane oxygenation (ECMO), treatment of thrombus, and post implantation of ventricular assist device(s).

RESULTS From time of heparin initiation to ATIII supplementation, patients spent a mean 4.9 ± 2.6 days of subtherapeutic infusion and required uptitration from a mean of 15.3 ± 4.4 units/kg/hr to a mean rate of 40.7 ± 9.5 units/kg/hr. 58.3% of the patients (n = 7) had a ≥10% reduction from the baseline heparin infusion rate within 48 hours of ATIII administration. Those patients considered responders (≥10% reduction from baseline rate) had a slightly higher mean baseline antithrombin level (76.3% ± 22.0% vs. 58.6% ± 2.7% in non-responders, p = 0.1) and were administered comparable doses of ATIII. ATIII supplementation did appear to increase the time of therapeutic anticoagulation within the 48 hours.

CONCLUSIONS Administration of ATIII is associated with >10% decrease in heparin requirements in more than half of the patients identified. In those patients deemed non-responders, there was a trend towards lower baseline antithrombin serum levels. Further studies are warranted to determine if the lack of response in some patients is due to inadequate dosing of ATIII or any patient-related factors.

ABBREVIATIONS ACT, activated clotting time; aPTT, activated partial thromboplastin time; ATIII, Antithrombin III; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; FFP, fresh frozen plasma; PRBC, packed red blood cell; VAD, ventricular assist device

KEYWORDS antithrombin III; ATIII; extracorporeal membrane oxygenation; heparin; pediatrics

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Introduction

Heparin resistance is a phenomenon characterized as an increase in the heparin dose response curve, clinically described as an inability to achieve therapeutic goals despite increasing infusion rates.[1,2] Antithrombin is a necessary cofactor for heparin's therapeutic activity, and inadequate levels are thought to play a role in heparin resistance. Reduced antithrombin concentrations can be a result of genetic deficiency, hepatic dysfunction, malnutrition, nephrotic syndrome, and the use of heparin products.[2] Children up to 16 years of age possess a lower concentration of antithrombin levels compared to adults (67%–80% of adult values), decreasing relative activity and function.[3] Various other factors not related to antithrombin may also contribute to heparin resistance, but these are not fully understood. These factors include coadministration with intravenous nitroglycerin, low molecular weight heparin usage, and aprotinin.[1,2,4] Other laboratory parameters impacting heparin resistance include elevated platelet counts, low serum albumin, and increased factor VIII activity.[2,5] The normal reference range for serum antithrombin levels is 80% to 120%.

Administration of antithrombin (ATIII) via exogenous ATIII, fresh frozen plasma (FFP), or packed red blood cells (PRBCs), has been used in patients to normalize antithrombin levels in an attempt to overcome heparin resistance.[6,7] The 2 Food and Drug Administration (FDA)-approved ATIII concentrates are either plasma-derived or recombinant. Both products are indicated for surgical prophylaxis of thrombosis in adults, but not for pediatrics.[8] These products do come with risks, specifically the concern for bleeding and disturbances in normal neonatal antithrombin concentrations. Specific dosing schemes and target levels have yet to be established for pediatric patients.[3,8] The financial impact of routine ATIII use should also be considered, as its use can be associated with significant monetary burden

and resource utilization.

While there is literature published that focused on ATIII use in pediatric patients on extracorporeal membrane oxygenation (ECMO), the findings overall are relatively inconclusive as to whether or not it impacts overall heparin requirements.[9–12] One retrospective, case control study in neonates younger than 4 weeks of age undergoing ECMO found that neonates with congenital diaphragmatic hernia (CDH) had a decrease in FFP, PRBCs, and platelet transfusions in the first 3 days on ECMO. For non-CDH neonates, only PRBC exposure was reduced.[9] An observational study evaluating 35 ECMO courses in pediatric patients younger than 18 years of age found a proportional correlation between antithrombin and anti-Xa levels, but only a minimal impact on heparin infusion rates.[10] Another observational study of 19 controls and 21 ATIII-treated pediatric patients on ECMO found no difference in heparin rates and increased circuit failure in ATIII-treated patients.[11] Lastly, a retrospective cohort study of 40 patients requiring ECMO (45 deployments) aged 0 to 18 years showed that daily antithrombin supplementation did not enhance coagulation–anticoagulation balance or circuit life.[12] One relevant non-ECMO study focused on ATIII supplementation in patients younger than 1 year of age anticoagulated for thrombus treatment and found no impact on anti-Xa levels and associated increase in bleeding events.[13]

ATIII use in pediatrics has risen substantially over the last decade despite a lack of literature supporting the use in the setting of heparin resistance. With frequent use of ATIII supplementation to augment heparin therapy in pediatric patients on ECMO, after implantation of paracorporeal ventricular assist devices (VADs), and for those receiving treatment for vascular thrombus at our institution, we sought to determine the overall impact of its use on heparin infusions. The objective of this study was to determine the percentage of patients with >10% reduction in heparin infusion rate within 48 hours of ATIII administration. Secondary objectives include the achievement of therapeutic anticoagulation with ATIII administration, and determining the mean number of days of subtherapeutic infusion prior to supplementation.

Materials and Methods

An institutional review board–approved retrospective chart review was performed on patients who were admitted at our institution between July 1, 2011, and July 1, 2014, and who received ATIII while on continuous heparin infusion for the indications of ECMO, post VAD implantation, or for the treatment of a vascular thrombosis. The study included patients treated in the 24-bed pediatric intensive care unit, 23-bed congenital heart intensive care unit, and 60-bed Level III Neonatal Intensive Care Unit at the University of Florida Health Shands Children's Hospital. Patients with either a known congenital antithrombin deficiency, age >18 years, or those who were initiated on continuous heparin infusion at an outside facility were excluded from the study.

Data collection included patient demographics, diagnosis, use of ECMO, VAD, type of anticoagulation monitoring used, type of ATIII used, serum ATIII levels if available, heparin infusion rate at the time of ATIII and for 48 hours prior to and after initiating ATIII, and occurrence of any adverse event after ATIII administration (e.g., drug reaction, bleeding, mortality, use of blood products). The baseline heparin rate was defined as the rate at the exact time of ATIII administration. To determine net changes in infusion rates, the lowest rate within the first 48 hours post ATIII was used. The duration of 48 hours was chosen as it would be unlikely for any significant pharmacological action of ATIII beyond this period based on the half-life elimination time (12–18 hours). Responders were defined as those patients who experienced a >10% reduction from the baseline rate while non-responders did not show any change or had a decrease of <10%. A cut off of 10% was used to define responders as any reduction <10% was not felt to be clinically significant. Demographics, indications, baseline antithrombin levels, ATIII dosages, and heparin rates were then compared between responders and non-responders.

Due to prescriber differences in the monitoring of heparin, therapeutic anticoagulation was defined as the individual patient's prescriber-defined goal. This included monitoring of activated clotting time (ACT), activated partial thromboplastin time (aPTT), and heparin anti-Xa levels or a combination of these tests.

To better describe ATIII prescribing patterns, all ATIII dosages were collected, including the quantity of doses and the cumulative patient exposures. This was then converted to weight-based dosing, reflected as units per kilogram. A hospital formulary change was made in 2012, thus the study period included the use of both Thombate III (Thrombate III, Grifols Therapeutic, Inc, Research Triangle Park, NC) and ATryn (ATryn, RVO Biologics, Inc, Framingham, MA) product administration. Baseline antithrombin levels as well as the timing of laboratory reporting were used to determine whether or not the laboratory value had resulted and was available to the prescriber at the time of entering the first ATIII dose. Turnaround times for antithrombin serum laboratory testing were anticipated to be roughly 3 to 5 days until March 2014 when in-hospital testing began. Although we do not have a written policy, our usual institutional practice has been to supplement ATIII, if the serum antithrombin levels are <80% and if the patient is requiring large doses of heparin infusion. FFP has been used to replace ATIII in previous studies; however, it is associated with transfusion-related complication and its reported efficacy is limited.[6]

To describe safety, blood transfusion requirements of

FFP and PRBC were collected for both the 48 hours pre and post the first ATIII dose. Documented infusion site reactions were also collected following the administration of the first ATIII dose. For overall bleeding events, documentation was collected throughout the ATIII therapy course until 7 days post the last dose of ATIII, if applicable. Overall length of stay, survival to discharge, and cause of death were also included.

Basic descriptive statistics were utilized for patient characteristics to compare the non-responder and responder groups. Pearson's correlation test was used to compare the indications for anticoagulation, gender, and the availability of the baseline antithrombin level at the time of prescribing of ATIII. The Student's t-test analysis was used for the remaining variables. Statistical analysis was performed using Excel and JMP software, (SAS Institute Inc, Cary, NC). Unless otherwise noted, data are presented as mean ± SD. A p value of ≤ 0.05 was considered as statistically significant.

Results

During the study period, 12 patients received supplemented ATIII while on continuous heparin infusions, and all 12 patients met criteria based on the 3 included indications (Table 1). The age overall was 5 ± 5.4 years, with a weight of 15.5 ± 11.5 kg. The overall baseline serum antithrombin level was 68.9% ± 18.7% with the supplementation dose being 44.8 ± 10.5 units/kg. One patient received Thrombate III while the remaining receiving ATryn. All but 2 patients received more than 1 dose of ATIII bolus supplementation, with the median quantity of doses being 2. Each patient was only included once for analysis.

Heparin continuous infusion was initiated at a dose of 15.3 ± 4.4 units/kg/hr, with a rate at time of ATIII supplementation being 40.7 ± 9.5 units/kg/hour. Prior to ATIII supplementation, 8 out of the 12 patients had reached a therapeutic goal at some point during treatment, which was defined as 2 consecutive values within their individually defined goal ACT, aPTT, or anti-Xa range. Patients spent 4.9 ± 2.6 days subtherapeutic prior to ATIII prescribing, defined as >50% of the daily monitoring values outside of the individually defined goal range. Time from heparin initiation to ATIII prescribing was a median of 11 days (range 1–38 days). For study purposes, only data after the first administration of ATIII were collected.

Seven out of 12 patients (58.3%) had >10% reduction from their baseline heparin rate during the first 48 hours (Table 2). Two of the 7 responders became supratherapeutic after ATIII administration necessitating continuous heparin infusions to be held for 4 hours and 6 hours. These 2 patients were excluded in the mean percentage change from baseline in the responders versus non-responders comparison due to a lowest rate post supplementation being 0 units/kg/hr. The overall mean percent change from baseline to the lowest rate in the first 48 hours post ATIII for the 10 patients included for analysis was a 10.3% decrease. Four of the 7 responders (57.1%) reached the 10% reduction in the first 24 hours, with the remaining 3 (42.9%) during the 48-hour period (Figure 1).

Those patients considered responders had a slightly higher mean baseline antithrombin level (76.3% ± 22.0% vs. 58.6% ± 2.7% in non-responders, p = 0.1) and were administered comparable doses of ATIII (46.4 ± 4.9 units/kg vs. 42.5 ± 16.0 units/kg in non-responders, p = 0.55). Neither values were statistically significant. No patients in the non-responder group had baseline antithrombin levels within the normal reference range (80%–120%). Two patients in the responder group had a normal baseline antithrombin level, and another patient was within 1% of the normal reference range. Baseline levels in the 2 patients with supratherapeutic heparin levels were 61% and 101%. Prescribing of ATIII with a baseline antithrombin level available to prescribers only occurred in 2 of the responder group patients,

Table 1. Baseline Demographics (N = 12)

Baseline Demographics	n (%)
Age	
0–6 mo	4 (33.3)
2–6 yr	4 (33.3)
7–11 yr	3 (25)
12–18 yr	1 (8.3)
Male	7 (58.3)
Heparin indication	
Ventricular assist device (Berlin EXCOR)	5 (41.7)
Thrombus	5 (41.7)
Extracorporeal membrane oxygenation	2 (16.7)
Primary diagnosis	
Congenital heart disease	2 (58.3)
Restrictive cardiomyopathy	2 (16.7)
Myocarditis	1 (8.3)
Neurofibromatosis	1 (8.3)
Miscellaneous	1 (8.3)
Monitoring	6 (50)
aPTT	5 (41.7)
Heparin anti-Xa	2 (16.7)
ACT	
Serum AT available at time of ATIII prescribing	7 (58.3)
ATIII product	
ATryn	11 (91.7)
Thrombate III	1 (8.3)

ACT, activated clotting time; aPTT, activated partial thromboplastin time; ATIII, antithrombin III

Table 2. Patient Characteristics of Responders to ATIII and Non-Responders

	Responders (n = 7)	Non-Responders (n = 5)	p value
Age, yr*	4.0 ± 4.4	6.4 ± 6.8	0.46
Weight, kg*	14.1 ± 10.8	17.6 ± 13.4	0.62
Baseline AT level (%)*	76.3 ± 22.0	58.6 ± 2.7	0.10
Availability of AT level at time of ATIII prescribing, no.	2	5	0.03
ATIII dose units/kg*	46.4 ± 4.9	42.5 ± 16.0	0.55
Indication, no.			0.5
Ventricular assist device	4	1	
Thrombus	2	3	
ECMO	1	1	
Days from start of heparin to ATIII*	17 ± 13.9	7.4 ± 5.4	0.18
Heparin rate at time of ATIII supplementation*	41.7 ± 9.03	39.3 ± 11.0	0.73
	Responders (n = 5)†	**Non-Responders (n = 5)**	
Change from baseline rate post ATIII (%)*	−23.8 ± 17.1	3.3 ± 5.1	0.04

ATIII, antithrombin III; ECMO, extracorporeal membrane oxygenation

* Mean ± SD.

† Patients excluded due to supratherapeutic anticoagulation requiring hold in therapy.

compared to all 5 in the non-responders. The majority of the patients in the responders group were on heparin for anticoagulation post VAD implantation, compared to the majority of non-responders anticoagulation for the treatment of a thrombus. There were no statistically significant differences observed between the 2 groups for any variables.

The average occurrence of therapeutic levels in the 12 hours pre-ATIII supplementation was 20.4% (Figure 2). For the 3- to 8-hour time frame post supplementation, the mean occurrence of therapeutic levels was 49.2%. Peak time in range was in the 24- to 36-hour period post supplementation with 60% of values therapeutic.

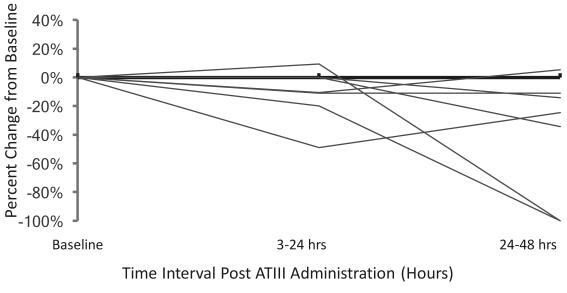
Regarding safety, there were no documented infusion reactions to either ATIII product (Table 3). Six of the patients required administration of PRBCs, and 3 of those patients received FFP in the 48 hours prior to supplementation. Post ATIII, 2 patients received PRBCs and 2 FFP in the first 48 hours. Withdrawal of care occurred in 2 patients due to intracranial hemorrhaging, with only 1 occurring within 7 days of ATIII administration. However, this hemorrhaging was documented prior to ATIII administration and was not deemed related to the drug supplementation. Another patient had bleeding documented 3 days post ATIII; however, it was directly related to undergoing an orthotopic heart transplant and was thus not included.

Discussion

With the use of off-label ATIII in pediatrics rising substantially over the last decade, it is crucial to determine whether or not antithrombin supplementation is indeed efficacious in the setting of heparin resistance. The financial implications of this high cost therapy and unclear safety in the pediatric patient population necessitate further examination of these practices. ATIII should be used only after due consideration in select patients due to the paucity of studies establishing its efficacy in improving anticoagulation. The majority of the pediatric literature published thus far focus on the use of ATIII supplementation in the setting of ECMO, and has found inconclusive results.[9–11]

Average heparin infusion rate at the time of anticoagulation initiation was 15.3 units/kg/hr, while the average heparin infusion rate prior to prescribing ATIII was 40.7 unit/kg/hr. Some patients exceeded the hard-maximum guardrail (50 units/kg/hr) in the smart pump infusion library at our hospital requiring infusion outside of the heparin guardrails. Both increasing the hard limit for heparin on the drug library infusion pump guardrails and administering a high-risk medication outside of the library pose substantial patient safety risks.

Figure 1. Association of ATIII with heparin requirement.



ATIII, antithrombin III.

Table 3. Safety

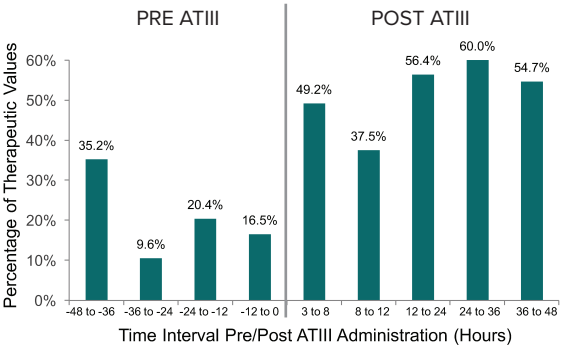
Safety	Outcome
Documented infusion reaction, no. (%)	0 (0)
Documented bleeding event, no. (%)	1 (8.3)
Administration of PRBCs, no. (%)	
48 hr pre-ATIII	6 (50)
48 hr post-ATIII	2 (16.7)
Administration of fresh frozen plasma, no. (%)	
48 hr pre-ATIII	3 (25)
48 hr post-ATIII	2 (16.7)
Survival to discharge, no. (%)	7 (58.3)
Cause of death, no. (%)	
Intracranial hemorrhage	2 (16.7)
Multiorgan failure	2 (16.7)
Cardiac arrest	1 (8.3)
Length of stay, days	
Median (range)	90 (9–295)

ATIII, antithrombin III; PRBC, packed red blood cell

Overall, 7 out of the 12 patients (58.3%) met the primary endpoint of having a >10% reduction from baseline heparin infusion rate after ATIII supplementation. There were no statistically significant differences between the responders and non-responders, except for the percent change from the baseline heparin infusion rate at time of ATIII administration. There did appear to be a trend towards lower baseline antithrombin levels in the non-responders group. All of the non-responder patients had baseline serum antithrombin levels ≤62% (range 55–62), and thus all considered abnormal (reference range 80%–120%).[2] The responders group contained 2 patients with normal baseline antithrombin levels (101%, 112%), and 2 patients within 10% of the normal reference range (74.4%, 79%). This can likely be explained by the fact that serum antithrombin laboratory samples were not conducted in-hospital until the spring of 2014, yielding a range of 1 hour to 5 days between the lab receiving the blood sample and reporting the value. Thus, 5 of the 7 responders received ATIII supplementation prior to the laboratory value resulting, compared to none in the non-responders group.

The dosing of ATIII was relatively comparable between responder and non-responder groups, with the responders receiving a slightly larger dose in units per kilogram (while not statistically significant). Although neither ATIII product is FDA-approved in the pediatric population, the prescribing information recommends supplementation based off weight and baseline antithrombin activity.[14,15] Thus, the amount of ATIII supplementation is directly related to the overall degree of deficiency. At this study site facility, prescribing of ATIII has been historically based on administering

Figure 2. Percentage of therapeutic anticoagulation post ATIII administration.



ATIII, antithrombin III

an amount either rounded to the nearest vial size or on a units/kilogram basis at the discretion of the prescriber. This was especially true in the cases when the prescriber did not have a baseline antithrombin level at the time of prescribing ATIII. Had the prescribing been consistent with the package insert recommendations for adults with an antithrombin deficiency, then those patients with lower baseline antithrombin levels would have received significantly larger ATIII doses. Follow-up antithrombin levels were not consistently obtained post supplementation, so it is unclear whether or not the supplementation dosages did indeed restore serum concentrations to normal levels. While there was not a statistically significant difference between the 2 groups for baseline antithrombin levels, the overall limited sample size and trend towards lower levels in the non-responders group dose raise the hypothesis that these patients may not have responded because they did not receive large enough ATIII doses.

To better determine the impact on achieving therapeutic anticoagulation, all anti-Xa, aPTT, and ACTs laboratory values were obtained for the 48 hours pre and post ATIII supplementation. Because our study site does not use strict protocols for heparin titration, the determination of therapeutic achievement was based on each individual patient's defined titration parameter and goal range. While the inconsistencies in laboratory parameters may seem like a limitation, each patient had a clearly defined laboratory parameter and goal range with all heparin titrations based on these values. Based on the percentages in Figure 2, it did appear as though ATIII increased the percentage of time in therapeutic range. The time frame with the highest percentage of therapeutic values was 24 to 36 hours post ATIII administration. This seems relatively inconsistent with the half-life of ATryn (received by 11 out of 12 patients) being 11.6 hours.[14] Further studies are warranted to determine whether or not supplementation does indeed cause a statistically significant improvement in therapeutic anticoagulation. Of the 2 patients with bleeding, 1 was directly related to surgery and the other a progres-

sion of a previously discovered intracranial bleed. The overall survival to discharge was 58.3%.

The primary limitation of this study is the small sample size. While there was a physician-approved heparin titration protocol utilizing anti-Xa at the study site, there was still a lack of standardization in labs to adjust heparin infusion rates. The delayed turnaround time for serum antithrombin concentrations also differed significantly between those patients deemed non-responders and responders. While the 3 indications for using heparin anticoagulation helps with the clinical applicability of the variability within the pediatric intensive care setting, it is unclear based on this study whether the differing disease states would have an impact on the overall response to ATIII supplementation. Lastly, dosing of ATIII was inconsistent with the manufacturer recommendation for adults with antithrombin deficiency.

Conclusion

Administration of ATIII is associated with >10% decrease in heparin requirements in more than half of the patients identified. In those patients deemed non-responders, there was a trend towards lower baseline antithrombin serum levels with relatively similar ATIII doses. ATIII supplementation appeared to increase the amount of time patients were in therapeutic range. Further studies are warranted to determine if the lack of response in some patients is due to inadequate dosing of ATIII or any patient-related factors.

ARTICLE INFORMATION

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