Continuous Antithrombin III Administration in Pediatric Veno-Arterial Extracorporeal Membrane Oxygenation

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The purpose of this retrospective case-control study is to determine the effect of continuous antithrombin III (ATIII) infusion on extracorporeal membrane oxygenation (ECMO) coagulation. All ECMO patients within the pediatric intensive care unit from January 2012 to July 2014 were included. Comparison was made between those who received continuous infusion ATIII through a standardized replacement protocol with historic controls receiving intermittent ATIII doses. Patients receiving the continuous infusion ATIII protocol spent more time in goal ACT range (71.9% vs 52.2%, $p < 0.0001$). Mean daily ATIII activity was also increased in study group (77.3% versus 68.6%, $p = 0.04$). No statistical differences in number of heparin dose changes per day (3 versus 3.22, $p = 0.90$) were present between the 2 groups. Only 28% of the historic controls receiving intermittent ATIII doses achieved normal ATIII activity as compared with 80% of study patients ($p = 0.24$). Maximum heparin dose was also lower in continuous infusion protocol group ($p < 0.01$). Compared with nonprotocolized intermittent dosing, the use of a continuous infusion ATIII protocol demonstrated increased time within goal ACT range at a lower heparin dose, no increase in hemostatic complications, and trends toward fewer heparin changes and lower blood product usage.

ABBREVIATIONS ATIII, antithrombin III; ACT, activated clotting times; CTCAE, Common Terminology Criteria for Adverse Events; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; VA, veno-arterial

KEYWORDS anticoagulation; antithrombin; critical care; ECMO; pediatrics

J Pediatr Pharmacol Ther 2017;22(4):266–271

DOI: 10.5863/1551-6776-22.4.266

Introduction

The use of extracorporeal membrane oxygenation (ECMO) in pediatric patients necessitates the maintenance of hemostatic balance to minimize both the risk of hemorrhage and significant thrombotic complications. Extracorporeal circuits introduce a pro-inflammatory surface that initiates the coagulation cascade resulting in thrombosis.¹ As a result, the routine usage of anticoagulation therapy including continuous unfractionated heparin infusion is essential.

Management of heparin is complicated by acquired deficiency of antithrombin III (ATIII) and normal ATIII deficiency of the newborn. ATIII plays a vital role in anticoagulation by increasing the deactivation of thrombin, factor Xa, and factor IXa. In the presence of heparin, a conformational change is induced in the antithrombin structure, which leads to augmented enzymatic activity with an increase up 100-fold.² Acquired deficiency of ATIII is common in young patients, cardiopulmonary bypass, sepsis, and prolonged heparin therapy. ATIII deficiency manifests as heparin resistance, often leading to frequent and significant dose increases and difficulty in achieve therapeutic anticoagulation.²

There has been an increase in the administration of ATIII as an adjunct to ECMO anticoagulation. ATIII use

has increased in pediatric patients from 5% of institutions in 2004 to 52% of institutions in 2011, with a 2013 survey demonstrating almost 87% of institutions providing ECMO services utilizing ATIII.^{3,4} Despite this increased use, there is limited data for pediatric ATIII use in ECMO. The research thus far has demonstrated that dosing needs are higher than previously expected to obtain target levels of 80% to 120% and that intermittent dosing of ATIII is effective in reducing heparin needs but not in achieving therapeutic levels.^{5,6} Perry et al⁷ performed the only study to date that sought to describe clinical outcomes. They demonstrated a reduction in blood product usage with ATIII use in diaphragmatic hernia patients on ECMO. The aim of this study is to assess the effectiveness of an ECMO continuous ATIII infusion protocol as compared to intermittent dosing of ATIII in regards to outcomes of anticoagulation, including: stability of anticoagulation, need for heparin dose adjustments, achievement of targeted ATIII levels, and bleeding and thrombotic complications.

Materials and Methods

This study was approved by the University of Minnesota Institutional Review Board. A new continuous infusion recombinant ATIII (ATryn, rEVO biologics, Fram-

Table 1. Initial dose and daily titration for patients on continuous antithrombin during extracorporeal membrane oxygenation

Initial Dosing	
No Known Baseline ATIII Activity	4 units/kg/hr
Known ATIII Activity	
ATIII ≤40%	Loading dose 25 units/kg, followed by 6 units/kg/h
ATIII 41%–60%	4 units/kg/hr
ATIII >60%	2 units/kg/hr
Dosing Adjustments based on daily ATIII Level	
ATIII <50%	Loading dose 25 units/kg and increase dose by 2 units/kg/hr
ATIII 50%–59%	Increase dose by 2 units/kg/hr
ATIII 60%–79%	Increase dose by 1 unit/kg/hr
ATIII 80%–100%	No change
ATIII 100–119%	Decrease dose by 1 unit/kg/hr
ATIII >120%	Decrease dose by 2 units/kg/hr

ATIII, antithrombin III; ECMO, extracorporeal membrane oxygenation

* Initial 2 continuous infusion patients received dose adjustment by percentage based increase; however, actual dose administered was equivalent to dose adjustment per protocol above.

ingham, MA) protocol was implemented in August 2013 for all patients receiving veno-arterial (VA) ECMO in the Pediatric Intensive Care Unit. Patients who received continuous recombinant ATIII from August 2013 to July 2014 were included in this retrospective evaluation. A comparative group comprised an equivalent number of patients who received ECMO from January 2012 to July 2013, a time in which intermittent dosing of human pooled ATIII (Thrombate, Grifols Therapeutics, Inc, Research Triangle Park, NC) per physician discretion was used. Patients were identified through the University of Minnesota Masonic Children's Hospital ECMO database. Patients were excluded if they remained on ECMO < 24 hours, did not receive anticoagulation, or did not receive heparin per institutional guidelines. For patients with extended ECMO duration that was interrupted by surgical procedure including cardiac by-pass, only the initial ECMO period prior to surgery was evaluated for clinical effect, the entire ECMO duration was analyzed for bleeding events.

Protocol Development. The continuous ATIII infusion protocol was developed at the University of Minnesota Masonic Children's Hospital in 2013 (Table 1). Since dosing recommendations are not provided for acquired ATIII deficiency, the protocol was developed using manufacturer recommendations for hereditary deficiency. Dose tiers were created using ranges of ATIII activity to minimize bedside calculations. The starting dose was calculated to target the estimated need for activity at the upper end of the goal ATIII activity range of 80% to 100% according to the surgical replacement recommendations. Additionally, titration parameters were designed to closely mimic dose adjustments as suggested by the manufacturer for hereditary deficiency.

The protocol was managed by the bedside ECMO specialist with oversight by the pediatric critical care pharmacist. When the initial protocol was implemented, there were significant issues with percentage-based dose adjustments, which led us to modify our protocol to allow for more straightforward dosing and titration by the bedside nurse.

Loading doses were included in the dosing protocol for all patients with known ATIII activity under 40%. The manufacturer supports the drug administration over 15 minutes for all loading doses; however, due to concern of rapid ATIII binding to heparin complexes theoretically increasing the risk for bleeding, all ATIII boluses were administered over 2 to 4 hours depending on the current heparin dose.

ECMO Circuit. During the study period, there were no significant changes in the type or brand of ECMO equipment. The ECMO circuit utilized at our institution is a carmeda coated circuit, with a Maquet Quadrox-iD (MAQUET Cardiovascular, LLC, Wayne, NJ) pediatric diffusion membrane oxygenator and a Medtronic Affinity AP40 (Medtronic, Minneapolis, MN) centrifugal pump.

Anticoagulation. ATIII infusion was started upon ECMO cannulation in all case cohort patients. In control patients, ATIII was administered as a bolus dose per the discretion of the managing physician as no established parameter for ATIII replacement existed at that time. The control patients did have goals for ATIII activity of >80%, but there was not standardized measurement of ATIII levels. Heparin dosing was given per our institutional policy. Patients received a 25 to 100 units/kg heparin bolus at initiation of ECMO with circuit prime. The timing of initiating heparin infusion after cannulation was at the discretion of the medical team. Heparin infusion

Table 2. Patient Demographics

	Continuous Antithrombin (n = 7)	Controls (n = 7)	p value
Age, mo, median (range)	3.0 (1.0–216.0)	0.7 (0.03–8.0)	0.13
Male, n (%)	4 (57.1%)	5 (71.4%)	0.31
Weight, kg (range)	5.7 (2.8–97.0)	3.6 (2.5–9.7)	0.31
ECMO duration, days (range)	5.8 (3.0–19.0)	2.9 (2.2–19.0)	0.07
Indication for ECMO			NS
Cardiac, n (%)	5 (71.4%)	7 (100%)	
Respiratory, n (%)	2 (28.6%)	0 (0%)	

ECMO, extracorporeal membrane oxygenation; NS, not significant

was ordered per institutional protocol titrated to the goal activated clotting times (ACT) range, with ranges of 150 to 170 seconds typical for significant bleeding, 160 to 180 seconds for moderate bleeding, and 180 to 200 seconds for minimal bleeding. Heparin infusion was managed by the pediatric ECMO team at bedside with hourly ACTs and titrated per protocol to achieve goal ACT. With implementation of the continuous ATIII protocol, routine daily monitoring of ATIII activity (measured as a percent of normal [100%]) was utilized by pharmacy and the ECMO specialist to adjust therapy. ATIII levels at our institution are processed once daily (11:00 am), thus evaluation of the morning ATIII activity was primarily used to adjust therapy, with additional ATIII levels being considered when there were concerns about being in goal range. The morning ATIII level was drawn with standard morning labs at 5:00 am.

Data Collection. Data were abstracted from the electronic medical record at the University of Minnesota Masonic Children's Hospital. Data points collected included age, sex, weight, diagnosis, duration of ECMO, ACT levels, ATIII activity, bleeding complications, thrombotic complications, blood product requirements, and heparin dosing. Time spent in range was averaged as a value of total minutes within range compared with total minutes of ECMO duration while receiving heparin. Goal ATIII levels were defined as above 80% activity. Bleeding and thrombotic complications were assessed by chart review and categorized by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 through the National Cancer Institute.⁸ All events were classified, but only Grade 3 and higher were analyzed. Transfusion data were separated by type of blood product (packed red blood cells, fresh frozen plasma, and platelets) and then normalized by weight and ECMO duration prior to analysis. There were no changes in guidelines for blood product administration during the time period of the study. Goals for blood product administration included hemodynamic stability, hemoglobin of 10 mg/dL, and platelets of 100,000/mcL. Cryoprecipitate was transfused to maintain fibrinogen greater than 150 mg/dL, and fresh frozen plasma was administered to keep International Normalized Ratio

(INR) less than 1.8. No other blood products or clotting factors were utilized in the patients analyzed.

Data Analysis. Categorical variables were summarized as frequencies with percentages. Continuous variables were summarized as means with standard deviations or medians with ranges. Comparisons of patient characteristics were conducted using chi-square, or Fisher tests on categorical variables, and Wilcoxon-Mann Whitney tests on both normally and non-normally distributed continuous variables. A value of $p \leq 0.05$ was considered statistically significant, and all tests of significance were 2-tailed.

Results

Eighteen patients were evaluated for inclusion in this study. Fourteen patients were included in the final data analysis, 7 from each patient group. One patient was excluded for heparin protocol violation, 2 patients were excluded for ECMO duration of less than 24 hours, and 1 patient was excluded for no heparin administered during the ECMO run. Patient characteristics are described in Table 2. Demographics were not statistically different between the 2 groups although the historical control group represented a younger demographic and shorter ECMO duration as compared with the continuous infusion group.

Study endpoints are detailed in Table 3. Patients who received continuous infusion recombinant ATIII were found to be within the goal treatment ACT range for 72% of time as compared with the historical control group, which spent 54% of time within goal treatment, ACT range ($p < 0.0001$). Patients receiving continuous recombinant ATIII achieved significantly higher ATIII activity levels (77.3% vs 68.6%, $p = 0.04$). Patients receiving continuous antithrombin achieved goal ATIII activity (defined as $>80\%$ activity) 71% of the time as compared with 28% of the time for historical patients; however, this was not statistically significant. The maximum heparin dose utilized in the ATIII group was statistically significantly lower ($p < 0.01$) than the control group. There was a statistically significant difference in the average daily amount of ATIII given between the groups with the case

Table 3. Study Endpoints

	Continuous Antithrombin (<i>n</i> = 7)	Controls (<i>n</i> = 7)	p value
Percent Time in Goal ACT Range	71.9%	54.2%	≤ 0.0001
ATIII activity, median (CI)	78 (73.5–81.0)	70 (51.6–88.4)	0.04
Achieved therapeutic ATIII, <i>n</i> (%)	5 (71.4%)	2 (28.5%)	0.29
No. ATIII levels/day ECMO, mean (range)	1.5 (1–2.2)	1.25 (1–1.4)	0.47
No. heparin dose changes every 24 hr, median (CI)	2 (2.4–3.6)	3 (2.4–4.0)	0.08
Maximum heparin dose, units/kg/hr, median (CI)	32 (28.5–36.2)	36 (36.8–42.5)	≤ 0.01
ATIII administered units/kg/day, median (CI)	98.0 (41.0–155.0)	271 (11.2–43.0)	0.05

ATIII, antithrombin III; ACT, activated clotting times; CI, confidence interval; ECMO, extracorporeal membrane oxygenation

cohort receiving more (*p* = 0.05).

There was no difference in hemostatic complications between the 2 groups (Table 4). Additionally, there was not any difference in blood product usage between the ATIII infusion group and the controls when adjusted for weight and duration of ECMO (Table 5). Cryoprecipitate use was excluded from analysis due to minimal use in both groups.

Discussion

This study sought to provide support for the use of a continuous ATIII replacement protocol in pediatric VA ECMO to provide stability of ATIII levels and markers of anticoagulation. There is limited data demonstrating the clinical effectiveness of ATIII repletion in pediatric ECMO, but its use has increased over the past decade.³ Best practices for the use of ATIII in pediatric ECMO have not been established and a number of questions remain.

The decision regarding when to initiate replacement remains controversial. Three centers have reported initiating antithrombin when activity fell below 80% and was combined with heparin resistance (heparin doses greater than 40 units/kg/hr), with one center additionally administering when activity fell below 80% and had thrombosis present in the circuit.^{5,6,11}

Optimal delivery of ATIII in ECMO is also still unclear. One study evaluating ATIII activity during ECMO demonstrated a median time to decrease ATIII level below 80% of 6.8 hours following replacement doses.⁶ Along with the inability to maintain ATIII levels after bolus doses for

prolonged periods of time, other studies demonstrate a need for immediate heparin dose decreases following intermittent ATIII replacement to keep ACT within goal range.^{6,12} Although our protocol only routinely checked ATIII levels once daily, the ATIII group was significantly closer to goal levels (>80%) than the control patients. The amount of ATIII given to the protocol patients was significantly higher, but prevented reacting to low levels of ATIII levels with the morning results and instead provided greater stability of the ATIII levels throughout the day and the ECMO course. This stability in the ATIII level likely contributed to the proportion of ACT values that were in range for the protocol group. However, we were unable to demonstrate a decreased frequency of heparin dose adjustments due to the ATIII stability in our small sample size.

Normal ATIII levels are known to vary by age. Studies of developmental hemostasis reveal that neonates have an immature anticoagulation cascade, and expected ATIII levels are lower than normal pediatric or adult activity. The average newborn is expected to have ATIII activity of approximately 50% to 60% with infants reaching pediatric and adult values of 80% to 100% by 3 to 6 months of age.^{13,14} Uniform goal antithrombin levels were selected to simplify the protocol adjustments even though the patient population studied ranged widely in age. It is unclear if the standard goal across age groups impacted the study results, but this provides another avenue of investigation.

There are published reports of increased bleeding with ATIII administration in critically ill adult patients.¹⁵

Table 4. Hemostatic Complications*

	Continuous Antithrombin (<i>n</i> = 7)	Historical Controls (<i>n</i> = 7)	p value
Vascular Grade 3 or higher	0	1	NS
Surgical Grade 3 or higher	0	1	NS
CNS Grade 3 or higher	2	2	NS
Transfusion Grade 3 or higher	5	6	NS
Any event Grade 3 or higher	6	7	NS

NS, not significant

*Evaluated per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Table 5. Blood Product Administration

	Continuous Antithrombin (n = 7)	Historical Controls (n = 7)	p value
Platelets, mL/kg/day*	25.2 (5.8–35.9)	32.0 (5.3–61.4)	0.77
Red blood cells, mL/kg/day*	42.0 (1.8–108.6)	51.4 (11.5–73.6)	0.65
Plasma, mL/kg/day*	27.1 (1.4–74.7)	35.0 (0–59.9)	0.77

* mean (range).

Other reports of intermittent ATIII administration during ECMO in adult and pediatric patients have not shown increases in bleeding or PRBC transfusion.^{6,11} The continuous infusion of ATIII used in this protocol was not correlated with an increase in bleeding or thrombotic complications or blood product usage. There was a decrease of more than 15% of blood product usage in the ATIII cohort, although small sample size precluded relevant analysis. A larger study could address this observation further.

Currently 2 antithrombin products are available in the United States. Pooled human antithrombin (Thrombate III, Grifols, Los Angeles, CA) is a plasma-derived product. Its advantages include a long half-life and potential for less frequent dosing.⁹ Several disadvantages include a short stability after reconstitution and theoretical potential for contamination and infusion reactions. Recombinant antithrombin (ATryn) is derived from the milk of genetically engineered goats.¹⁰ It has the advantages of a longer stability but has the theoretical potential for causing an immune response due to its recombinant nature. When considering which product to utilize for continuous infusion administration, a major factor was the stability of the product for administration, utilizing manufacturer data provided in package inserts, and the impact that the frequency of syringe change and product waste would have on overall cost. Ultimately recombinant antithrombin was selected, as it would allow for syringe change only once daily, decreasing nursing demands and drug waste.

Small sample size, a historical control cohort and a study population that included mostly post-cardiac surgery patients primarily limit this study. These factors may reduce the applicability of these findings to other institutions. While there was a difference noted in maximal heparin dosing, there were age disparities between the 2 groups that may have impacted this finding since neonates typically require larger doses of heparin to attain anticoagulation. An additional limitation is the limited frequency by which ATIII is routinely monitored in the study institution. Recent studies have found a decreased time to achieving therapeutic ATIII with activity levels measured more frequently.^{5,16} The ATIII levels in our patients on day 1 of ECMO may have been low without the team's knowledge; however, we accounted for this by assuming ATIII activity was 50% to 60% and dosed the initial ATIII bolus accordingly.^{11,17,18}

Future studies are indicated to prospectively study the ATIII effectiveness in changing clinical outcomes of anticoagulation including number of circuit changes, significant bleeding events, and blood product usage. Also imperative to the discussion of effectiveness would be establishing appropriate ATIII target levels. Lastly, a cost analysis would be helpful in understanding the overall benefit of using a therapy with such a considerable cost as ATIII.

Conclusions

Major complications during ECMO frequently result from bleeding or thrombotic events. This small, retrospective study comparing pediatric ECMO patients receiving continuous infusion ATIII through a standardized protocol with historic controls receiving intermittent ATIII doses demonstrated increased time within goal ACT range at a lower heparin dose, no increase in hemostatic complications, and trends toward fewer heparin changes and lower blood product usage. This experience suggests additional study of continuous infusion ATIII during ECMO may define practice changes that could improve patient safety and outcomes.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments Portions of this data were presented in poster format at the 23rd Annual Pediatric Pharmacy Advocacy Group Annual Meeting, May 2014 in Nashville, Tennessee. We would like to acknowledge Nicholas Brown, MD, for his contributions to data collection early in the design phase of this study.

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