Antithrombin concentrate use in children on extracorporeal membrane oxygenation (ECMO), a retrospective cohort study

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Abstract

Objective: To describe whether receipt of any AT concentrate improves laboratory and clinical outcomes in children undergoing ECMO for respiratory failure during their hospitalization compared to those who did not receive AT.

Patients: 64 pediatric patients at a single, tertiary-care institution who underwent ECMO for respiratory failure between January 2007 and September 2011

Methods: This is a retrospective cohort study studying whether exposure to any AT concentrate improves outcomes in children on ECMO for respiratory failure compared to similar children who never received AT concentrate during their ECMO course. Subjects who received at least one dose of AT during their ECMO course were categorized to the AT cohort ("AT+"), whereas subjects who did not receive any AT were categorized to the comparison cohort ("No AT" cohort).

Results: Thirty patients received at least one dose of AT during their ECMO course and 34 patients did not receive any. The median age at admission, duration of ECMO or first AT level did not differ significantly between the two cohorts. The mean plasma AT level in those who had never received AT was 42.2% compared to 66% in the AT+ cohort. However, few levels reached the targeted AT level of 120% and those that did fell back to deficient levels within 6.8h. Heparin infusion rates decreased by an average of 10.2 units/kg/h for at least 12h following an AT dose in the AT+ cohort. No statistical differences were noted in the number of ECMO circuit changes, *in vivo* clots or hemorrhages, transfusion requirements, hospital or intensive care unit length of stay, or in-hospital mortality.

Conclusions: Intermittent, on-demand dosing of AT concentrate in pediatric patients on ECMO for respiratory failure increased AT levels, but not typically to the targeted level. However, in this retrospective study, no differences were noted in the measured clinical endpoints. A prospective, randomized study of this intervention may require different dosing strategies; such a study is warranted given the unproven efficacy of this costly product across institutions.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-saving technology which supports children during periods of reversible heart or lung failure. However, many complications, particularly hematological complications, adversely affect the outcomes of children on ECMO.[1-3] The non-biological surfaces of the ECMO circuit activate platelets and clotting factors which lead to fibrin deposition and thrombosis. A continuous infusion of heparin is typically used to counteract this tendency. In addition, critically-ill children often have multiple other risk factors for thrombosis or hemorrhage, such as indwelling catheters and systemic inflammation. Studies have reported a risk of thromboembolic or hemorrhagic complications as high as 60% in ECMO patients.[4] Central nervous system hemorrhage alone is reported in 10.9% of neonates and 3.1% of children on ECMO in a large registry.[5] Of children who died while on ECMO, 86% had signs of thrombosis or hemorrhage on autopsy.[6] In addition, clots form in the ECMO circuit and contribute to oxygenator failure, consumptive coagulopathy, embolic disease and death.[2,7]

Antithrombin (AT), a 58-kD serine protease inhibitor synthesized in the liver, irreversibly inactivates many endogenous activated clotting factors, including clotting factor Xa and thrombin.[8,9] Heparin, the commonly used anticoagulant, functions by potentiating AT's anticoagulant activity 1000- to 5000-fold.[10,11] Acquired AT deficiency can result from low production (e.g., liver disease), consumption (e.g., disseminated intravascular coagulation), increased losses (e.g., protein-losing enteropathy, nephrotic syndrome, chylothoraces) or by drug-induced mechanisms (e.g., L-asparaginase, heparin). Term neonates typically do not reach adult AT levels until 6 months of age.[12] AT concentrate has been available commercially in the United States since 1991.

Optimizing hemostasis is crucial in ECMO care. The extracorporeal circuit activates clotting factors and platelets, leading to a tendency to clot. A continuous infusion of heparin is given to offset this tendency. Heparin resistance, a state where unusually high doses of unfractionated heparin are needed to achieve therapeutic activated partial thromboplastin times (aPTT), Factor Xa levels, or activated clotting times, is well described in patients needing an extracorporeal circuit. As heparin mediates its anticoagulation property by potentiating AT, AT insufficiency is hypothesized to contribute to heparin resistance. Studies of adult patients undergoing cardiopulmonary bypass found that administration of AT concentrate increases sensitivity to heparin.[13-17] In addition, pediatric ECMO patients are frequently neonates, therefore AT synthesis by the liver has not reached adult levels contributing to a relative deficiency.[12] These factors have led some ECMO centers to administer AT concentrate to patients on ECMO to increase AT levels and increase sensitivity to heparin.

In a single, tertiary-care, pediatric center, 78% of patients who received AT were on ECMO.[18] In 2009, 50.6% of all ECMO patients in a large, inpatient database of 43 freestanding, tertiary-care pediatric centers in the United States received at least one dose of AT (Wong, et al., submitted manuscript). Despite the high prevalence of AT use in ECMO, the impact of AT use on clinical outcomes in critically-ill children is unclear. A meta-analysis of 20, randomized, controlled trials which enrolled 3,458 critically-ill patients, including 267 children, concluded that administration of AT concentrate did not decrease mortality, respiratory failure, days on mechanical ventilation, length of stay in the hospital or intensive care unit, or improve quality of life.[19] The analysis also found that subjects who received AT concentrate had a statistically significant 1.5-fold risk of bleeding compared to controls.[19] One controlled trial published only in abstract form in 1995 showed a decrease in markers of thrombin generation in 4 infants who received AT while on ECMO compared to 5 historical controls who did not receive AT.[20] No difference was observed in degree of fibrinolysis, heparin requirement, platelet utilization, clinical markers of end organ failure, or ECMO duration.[20] Small case series including 7-34 children who received AT concentrate while on ECMO do not report excessive bleeding complications.[21-24] Better powered efficacy studies and safety studies are lacking in ECMO.

This retrospective cohort study examines the effect AT dosing has on outcomes, including AT level, heparin dose, transfusion requirements, length of stay and mortality in 63 ECMO patients at a single pediatric center.

Study Question

In children undergoing ECMO for respiratory failure, does receipt of any AT concentrate improve laboratory and clinical outcomes during their hospitalization compared to those who did not receive AT?

Primary Endpoint

- AT level

Secondary Aims

- Unfractionated heparin dosing rate
- # of circuit changes
- # of identifiable *in vivo* clots
- # of identifiable *in vivo* hemorrhages
- Transfusion requirements
- Length of stay
- Mortality

Rationale for the study

Despite being routinely administered in ECMO centers in the U.S. and around the world, the efficacy and safety of AT use in pediatric patients is uncertain.

Methods

This retrospective cohort study was approved by Seattle Children's Hospital (SCH) Institutional Review Board. The study population included all patients admitted to Seattle Children's Hospital who underwent ECMO for respiratory failure between January 2007 and September 2011. This time frame was chosen because it included all patients who received AT and allowed for a sufficiently large comparison cohort who did not receive AT. Patients were identified through SCH ECMO service's patient list. Subjects who received at least one dose of AT during their ECMO course was categorized to the AT cohort ("AT+"), whereas subjects who did not receive any AT were categorized to the comparison cohort ("No AT" cohort).

Study Definitions

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Washington.[25] Age was defined as age of subject at time of ECMO initiation. Diagnosis was the listed primary diagnosis in the ECMO service's database. ECMO duration was defined as the number of hours between initiation and cessation of the ECMO pump. Circuit changes were only counted when the entire circuit, pump, and oxygenator where changed out together. Thromboembolic and hemorrhagic complications were included if they occurred between start of ECMO and 7 days following ECMO discontinuation or death, whichever occurred first. The presence and severity of these were determined by a single author (TW) by reviewing progress and procedure notes and radiological findings. Severity was graded on a scale of 1-5 based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Anything grade 3 ("Severe or medically significant but not immediately life-threatening; prolongation of hospitalization indicated; disabling") or above was considered "severe." The volume and type of each transfusion was recorded, as was the time and dose of every AT dose. Each record was also searched for administration of other hemostatic agents including thrombin glue, an antifibrinolytic agent (aminocaproic acid or tranexamic acid), desmopressin, activated clotting factor VII, or other clotting factor concentrate given during the ECMO course. From perfusion records, the hourly heparin infusion rate and activated clotting time goal were recorded. The following labs were abstracted from the

electronic medical record during each subject's ECMO course: ACT, antithrombin level, aPTT, prothrombin time (PT), fibrinogen level, and complete blood counts.

ECMO protocol

All patients were cannulated peripherally (internal jugular or femoral veins). Most patients were supported with a centrifugal pump (Revolution; Sorin Group, Arvada, CO) and either a heparin-bonded hollow-fiber oxygenator (Minimax; Medtronic Inc., Minneapolis, MN) or a polymethylpentene oxygenator (Quadrox-D; Maquet Cardiovascular, Wayne, NJ); however a few early in the study period where supported with a roller pump (Stockert SIII; Sorin Group). All patients received a continuous infusion of unfractionated heparin which was adjusted to keep the activated clotting times (ACT) within the physician-determined target range. ACTs are checked hourly as per protocol. AT concentrate (Thrombate III®, Grifols) was prescribed at the discretion of the attending critical care physician. However, a guideline has been in place at Seattle Children's since 2008 that AT can be given for AT antigen level <80% with either an unfractionated heparin (UFH) requirement of > 40 units/kg/hr or the presence of an extracorporeal thrombosis. The suggested AT dose is calculated to obtain an AT antigen target level of 120% (IU = [(120-AT level) x weight (kg)]/1.4) and the dose was rounded up to the nearest half vial. AT antigen levels were assayed by an immuno-turbidimetric method (Liatest® ATIII; Stago, Leiden, The Netherlands).

Statistical analysis

Description of continuous variables was summarized using a mean if the distribution was approximately normal and summarized using a median if the distribution was skewed. Means were compared using T-tests and medians were compared using Wilcoxon rank-sum test. Categorical outcomes were analyzed using the Fisher Exact test. Transfusion of blood products were compared between AT cohorts using multiple linear regression of log transformed volumes of components received, adjusted for age, first AT level and ECMO duration. Magnitude of increase in AT levels was evaluated using a linear mixed effects model, adjusted for age, first AT level and ECMO duration. The decrease in AT level following an AT dose was predicted using a second linear mixed effects model adjusted for age, as the other covariates were not found to affect model fit. R, version 2.12 (R Foundation for Statistical Computing; Vienna, Austria) was used to fit the linear mixed effects models and Stata 12 (StataCorp; College Station, TX) was used for other analyses. Statistical significance was defined as p-value ≤ 0.05.

Results

Subjects

During the 57-month study period, 64 unique patients underwent ECMO for respiratory failure over 64 admissions. The AT+ cohort contained 30 subjects (47%) who received a total of 77 AT doses (range 1-8 doses/patient) while the No AT cohort contained 34 subjects (53%). Chemical (meconium aspiration or near-drowning) and infectious (bacterial or viral) pneumonias were the most common diagnoses in both cohorts (Table 1). There were no statistically significant differences between the two cohorts for median age at time of admission, ECMO duration, and first AT level (Table 2).

AT concentrate increased AT level short term

When comparing all AT levels drawn within 12 hours (h) of a prior AT measurement, the AT level was 66% in the AT+ cohort compared to 42.2% in the No AT cohort [23.8% higher in AT+; 95% confidence interval (CI), 10.2 – 37.5%, p<0.001], adjusted for age, ECMO duration and first AT level. When limiting the comparison to only the first AT level drawn after an AT dose within 12h. of a prior measurement in the AT cohort to AT levels drawn within 12h of a prior measurement in the No AT cohort, AT levels was estimated to be 80.1% in the AT+ cohort compared to 41.7% in patients in the No AT cohort (38.4% higher in AT+; 95% CI, 36.1-45.2%, p<0.001).

Only 6 of 77 doses reached the targeted AT level of 120% (8%), whereas no AT level drawn from the No AT cohort reached 120%. Of the 28 doses after which the AT level was followed sufficiently, median time to fall to an AT level of 80% was 6.8h after receiving the dose (mean: 9.8h) (Figure 1). For every hour following an AT dose, average AT level dropped by 1.3 ± 0.34%, regardless of patient's age.

AT concentrate decreased UFH need short term

Within the AT+ cohort, mean UFH rate decreased from 42.7 u/kg/h for the 3h prior to an AT dose to a mean of 32.6 u/kg/hr for the 3h following the AT dose (a decrease of 10.1u/kg/hr; 95% CI for the decrease, 7.6-36.6; p<0.001). The UFH rate remained significantly lower 12h following administration (10.2 u/kg/h lower; 95% CI, 6.2-14.1; p=<0.001) (Table 3).

AT concentrate did not affect the number of circuit changes

The median number of circuit changes per ECMO day was 0 in the No AT cohort (mean 0.05) and 0.03 in the AT+ cohort (mean 0.08), p=0.18.

AT concentrate did not decrease *in vivo* hemostatic complications

No patient within our sample had more than one identifiable *in vivo* thrombosis during their ECMO course. Within the No AT cohort 14.7% versus 13.3% in the AT+ cohort had one clinically-evident, *in vivo* clot, p=1.0.

The maximum number of *in vivo* hemorrhages any subject had during their ECMO course was four. The median number of bleeds per ECMO day was 0 in both cohorts (mean was 0.07 bleeds/ECMO day in the No AT cohort and 0.09 in the AT+ cohort), p=0.42. A severe hemorrhagic complication was observed in 14.7% of subjects in the No AT cohort and 16.7% in the AT+ cohort, p=0.64.

Cerebrovascular lesions confirmed by imaging were diagnosed in 20.6% of those in the No AT cohort and 10% in the AT+ cohort, p=0.31. Lesions included both hemorrhagic lesions and infarcts.

AT concentrate did not affect transfusion requirements

Transfusions of red blood cells, platelets and fresh frozen plasma (FFP) are a surrogate marker for bleeding and bleeding potential among critically-ill patients. Among patients of the same age, ECMO duration, and first AT level, the need for red blood cells (RBCs), platelets, and fresh frozen plasma (FFP) did not differ significantly between the AT and No AT cohorts (Table 4).

Length of stay and mortality did not change with AT concentrate administration

The length of stay (LOS) in the hospital and pediatric intensive care unit (PICU) were similar between the two cohorts. Median PICU LOS was 24.5d in the No AT cohort and 21.5d in the AT+ cohort, p=0.63. Median hospital LOS was 32 days for the No AT cohort and 34.5d in the AT+ cohort, p=0.91.

Of subjects in the No AT cohort, 38.2% died during their ECMO hospitalization compared to 23.3% in the AT+ cohort, p=0.28.

Discussion

The use of intermittent dosing of AT concentrate in pediatric ECMO patients with respiratory failure increases the AT level and decreases UFH short term compared to similar patients who never received AT concentrate in this single-center, retrospective, cohort study. However, the number of circuit changes, volume of blood products received, number of *in vivo* thromboses, hospital and PICU length of stay, and in-hospital mortality did not significantly differ between the

two cohorts. The number of cerebral vascular accidents and *in vivo* bleeds were also not significantly different between cohorts.

The clinical impact of administering AT concentrate to children undergoing ECMO is uncertain. To our knowledge this is the first, large, controlled study published evaluating the effects of AT concentrate in pediatric patients undergoing ECMO for respiratory failure.

Our primary outcome was to determine whether AT concentrate increased AT levels. This was chosen because an increase in AT level is a direct, measurable outcome that has yet to be studied in this population. Secondary endpoints were chosen as they were clinically relevant. However, as they were secondary endpoints, the study was not powered sufficiently to allow us to draw inferential conclusions. We limited our study population to pediatric patients who had respiratory failure as the primary indication for needing ECMO. This population was chosen because their pathophysiology was thought to be the more consistent than patients undergoing ECMO for cardiac indications or for congenital diaphragmatic hernias. As such, these findings must be generalized to these other populations with caution. As this is not a randomized trial, residual confounding likely still exists. In particular, indication bias may have led PICU physicians to give AT concentrate to patients who were perceived as sicker or at higher risk of coagulopathy.

This was designed *a priori* as a cohort study. However, the AT exposure could have been analyzed in several different manners. For instance, instead of the “any versus none” cohort approach which we took, AT exposure could have been coded as a continuous variable such as units of AT received/kg/ECMO day. However, both of these exposures are dependent on the AT concentrate dosing strategy to allow for a sufficient increase in AT levels to demonstrate a difference. An alternative approach would be to examine outcomes as a measure of the patient’s AT level, such as mean AT level or number of days with an AT level >80%, without regard to whether they received AT concentrate or not. Therefore, if a trend demonstrated improved outcomes with higher levels of AT, administering AT concentrate to achieve higher levels could at least be justified. In an exploratory analysis, we compared 20 patients with the highest mean AT level to the 20 patients with the lowest mean AT level. Age was significantly lower and ECMO duration was surprisingly significantly shorter in the group of patients with the lowest mean AT level. Also, somewhat counter-intuitive, circuit changes were significantly less common in the group with the lowest mean AT. No significant difference was noted in mean UFH rate, transfusion requirement, number of clots and bleeds, ICU and hospital length of stay

or in-hospital mortality in the two groups. This could form the foundation of a future confirmatory study.

Based on our findings and study design, we conclude that intermittent, on-demand dosing of AT concentrate in pediatric patients on ECMO for respiratory failure increased AT levels, but not typically to the targeted level. When AT was measured for a sufficient amount of time, the majority of AT levels fell to <80% by 6.8h. The UFH rate remained lower than before the AT dose for > 12h. However, in this retrospective study, no differences were noted in the measured clinical endpoints. A prospective randomized study of this intervention may require different dosing strategies; such a study is warranted given the unproven efficacy of this costly product across institutions.

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Table 1: Cohort characteristics, n (%)

Characteristic	AT+ (n=30)	No AT (n=34)	Total (n=64)
Age at ECMO Initiation			
<1 month old (%)	23 (76.7)	20 (58.8)	43 (67.2)
1-2.9 months old (%)	2 (6.7)	2 (5.9)	4 (6.3)
3-11.0 months old (%)	1 (3.3)	3 (8.8)	4 (6.3)
1-9.9 years old (%)	1 (3.3)	4 (11.8)	5 (7.8)
10-17.9 years old (%)	3 (10)	4 (11.8)	7 (11.9)
≥ 18 years old (%)	0 (0)	1 (2.9)	1 (1.6)
Sex			
Female	21 (70)	22 (64.7)	43 (67.2)
Mortality			
In-hospital death	4 (23.3)	13 (38.2)	20 (31.3)
Principal Diagnosis Categories			
Chemical pneumonitis	12 (40)	10 (29.4)	22 (34.4)
Infectious pneumonia	10 (33.3)	12 (35.3)	22 (34.4)
Congenital pulmonary defect	2 (6.7)	3 (8.8)	5 (7.8)
Pulmonary hypertension	3 (10)	4 (11.8)	7 (10.9)
Pertussis with hyperleukocytosis	2 (6.7)	1 (2.9)	3 (4.7)
Other	1 (3.3)	4 (11.8)	5 (7.8)

Table 2: Cohort characteristics, median (range)

Characteristic	AT+ (n=30)	No AT (n=34)	*p*-value
Age at ECMO initiation, months	0.1 (0-188)	1.7 (0-250)	0.21
ECMO duration, hours	181 (71-613)	146 (44-1,468)	0.48
First AT level, %	50.5 (15-75)	54 (19-108)	0.76
Hospital LOS, days	34.5 (3-110)	32 (302)	0.91
ICU LOS, days	21.5 (3-63)	24.5 (5-125)	0.63

Table 3: Mean unfractionated heparin (UFH) rate in AT+ cohort 3, 6 and 12h after AT dose compared to prior to AT dose

	n	Mean UFH rate +/- SD (u/kg/h)	Difference	95% CI for difference	*p-value*
3h pre-AT	63	42.7 +/- 16.6	(Ref)	(Ref)	(Ref)
3h post-AT	63	32.6 +/- 16.0	-10.1	-7.6, -12.7	<0.001
6h post-AT	47	33.3 +/- 15.9	-10.7	-7.7, -13.6	<0.001
12h post-AT	29	34.7 +/- 14.8	-10.2	-6.2, -14.1	<0.001

Table 4: Additional volume received of specified blood component in AT+ cohort compared to No AT cohort, adjusted for age, ECMO duration, and first AT level, ml/kg.

Blood Product	Additional volume received (ml/kg)	95% CI	*p*-value
RBC	1.19	0.80, 1.77	0.4
Platelets	1.27	0.82, 1.98	0.3
FFP	0.86	0.39, 1.92	0.28

Figure 1: AT level (%) versus hours from AT concentrate administration.