

# Clinical and Hematological Outcomes of Aminocaproic Acid Use During Pediatric Cardiac ECMO

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**Abstract:** Bleeding and thrombosis-related complications are common in pediatric cardiac patients supported by extracorporeal membrane oxygenation (ECMO) and are associated with morbidity and mortality. The purpose of this study was to evaluate the utility of aminocaproic acid (ACA), an antifibrinolytic agent, as it pertains to bleeding in pediatric cardiac patients on ECMO. This included a retrospective cohort study of pediatric cardiac patients receiving ACA while supported on ECMO between 2013 and 2017. For each patient, data were collected in three time intervals: the 24 hours before ACA initiation, and then 0–24 and 24–48 hours following ACA initiation. For each time frame, bleeding, component transfusion, and laboratory data were collected and analyzed. A total of 62 patients were included, representing 42% of our cardiac ECMO patients during the time period. ACA was initiated at  $16.3 \pm 8.7$  hours following initiation of ECMO. The mean bleeding rate before ACA was 10.57 mL/kg/h, which reduced to 7.8 mL/kg/h in the 24-hour period after initiation of ACA

and a further decrease to 3.65 mL/kg/h during the 24- to 48-hour time period following ACA initiation. ACA administration was associated with reduction in bleeding ( $p < .001$ ) and packed red blood cell transfusions ( $p = .02$ ), administration of fresh frozen plasma ( $p < .001$ ), platelets ( $p = .017$ ), cryoprecipitate ( $p = .05$ ), factor VII ( $p = .002$ ), and Cell Saver ( $p = .005$ ). Hemoglobin and platelet count were stable, whereas prothrombin time (PT), partial thromboplastin time, and international normalized ratio (INR) showed significant reduction over the time course. ACA administration was not associated with specific adverse effects. A clinically significant reduction in bleeding amount, red blood cell transfusions, and other hematologic interventions occurred following ACA administration for pediatric patients on ECMO. Wider consideration for ACA use as a part of a multipronged strategy to manage bleeding during ECMO should be considered. **Keywords:** ECMO, antifibrinolytic therapy, bleeding, pediatric, cardiac, complications, outcome. *J Extra Corpor Technol. 2021;53:40-5*

Bleeding and clotting-related complications add significant morbidity to pediatric cardiac patients supported on extracorporeal membrane oxygenation (ECMO) (1,2). Bleeding and clotting complications also impact ECMO survival (1). A significant challenge in addressing these complications stems from the challenge of balancing adequate anticoagulation for the circuit while simultaneously preventing life-threatening hemorrhage. Such bleeding can be from the surgical site/cannulation site for ECMO in

addition to multiple suture lines if the child has undergone cardiac surgery. The potential for bleeding is compounded by coagulopathy in the form of acquired platelet dysfunction and fibrinolysis (3). Fibrinolysis contributes to bleeding by breaking down fibrin and fibrinogen, thereby destabilizing clots. In addition, fibrinolysis cleaves glycoprotein Ib and IIb/IIIa receptors on platelets, which reduces platelet adhesion and aggregation, further contributing to bleeding (4).

Antifibrinolytic agents such as  $\epsilon$ -aminocaproic acid (ACA), aprotinin, and tranexamic acid (TXA) are commonly used as therapy for post-bypass fibrinolysis (5). ACA is the most commonly used antifibrinolytic agent in the United States, whereas TXA is commonly used in other countries. ACA is a synthetic inhibitor of plasminogen activation and works by attaching to the lysine-binding site of plasminogen and subsequently displacing plasminogen

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from fibrin (4). It has long been used to control excessive bleeding post-cardiopulmonary bypass (6–8). The 2018 Extracorporeal Life Support Organization (ELSO) Guidelines for Pediatric Cardiac Failure suggests the use of anti-fibrinolytic agents such as ACA in addition to blood products and coagulation factor therapy to reduce significant bleeding. The guidelines, however, do admit that “at present, data to support routine use of antifibrinolytic therapy during extracorporeal life support is lacking” (2).

The aim of this study was to assess the effects of ACA use on bleeding in pediatric cardiac patients on ECMO. We also assessed the need for blood product utilizations and changes in coagulation laboratory findings with ACA therapy. Our primary hypothesis for the study is that the use of ACA in pediatric cardiac patients supported on ECMO is associated with reduction in bleeding and secondarily associated with reduction in transfusion requirements. We anticipate that the results of this study will add to the available evidence to guide utilization in pediatric ECMO.

## METHODS

The Institutional Review Board at Children’s Healthcare of Atlanta approved the retrospective cohort study. We maintain an institutional database of patients supported on ECMO. We reviewed the ECMO database as well as the electronic medical records to identify patients who received ACA while on ECMO. Patients younger than 18 years at the time of ECMO initiation and supported in the cardiac intensive care unit were reviewed. Patients were included in the study if ACA use was documented on ECMO and data of interest (detailed in the following text) were available for the patient. Patients with incomplete data regarding ACA use, dose, and duration of therapy were excluded from the study. For each patient, three time periods were established for data collection: up to 24 hours before ACA initiation, the first 24 hours after ACA initiation (0–24 hours), and the second 24 hours after ACA initiation (24–48 hours). Data collected during each time period was broadly categorized into information regarding bleeding, interventions, laboratory values, and outcomes. Our standard ECMO circuit during the study period consisted of Class 6 bypass tubing (Medtronic, Minneapolis, MN) for the circuit along with an adult or pediatric Quadrox-i Oxygenator (Maquet, Rastatt, Germany). The circuit also included an arterial filter (Medtronic) as well as a capacitance chamber in the form of Better Bladder™ (Circulatory Technologies, Inc., New York, NY). Most of the circuits included a centrifugal pump (Sorin Revolution®, Milan, Italy). A minority of patients (less than 5 kg) were supported with an S5 roller pump (Century, Mesa, AZ). ECMO circuits were primed with packed red blood

cells immediately before use. Our standard anticoagulation protocol involved use of unfractionated heparin, with target anti-Xa levels between .3 and .7 IU/mL as well as bedside activated clotting time (ACT) (active clotting time) measurements using point-of-care i-STAT device (Abbott Laboratories, Abbott Park, IL) with a Kaolin ACT cartridge. The ACT targets were adjusted based on patient anti-Xa levels as well as clinical scenario of bleeding or clotting, and the targets were adjusted daily if needed. ECMO transfusion guidelines were to keep fibrinogen >250 mg/dL, platelets >100,000/mL, and hematocrit >30%. Bleeding data were quantified by totaling the amount of bleeding (in mL) from surgical (cannulation) site and chest tube output as applicable. Transfusion volume for blood products during the same periods was tabulated. These values were averaged over the number of hours and by patient weight in kilograms, yielding values in mL/kg/h.

The hematologic and coagulation laboratory values obtained are as listed: hemoglobin, platelet count, prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), ACT fibrinogen, D-dimer, and antithrombin assay. Thromboelastography (TEG)<sup>®</sup> (Haemonetics, Braintree, MA) result values, including values with and without heparinase, were collected when available. TEG5000 (Haemonetics) was used to perform the measurements.

Data on the various interventions to manage coagulation and bleeding were also obtained; this included packed red blood cells (pRBCs), Cell Saver (blood obtained from the operative field during cardiac surgery), fresh frozen plasma (FFP), platelets, cryoprecipitate, albumin 5%, albumin 25%, antithrombin 3, and recombinant factor VII. Administration of any additional antifibrinolytic agents such as tranexamic acid was also noted. Heparin administration was documented as well.

Data were described using mean (with SD) and frequency as appropriate. Data comparison using Student *t* test for continuous data and chi-square test for categorical data was performed. We used ANOVA for assessing differences in repeated measures.  $p < .05$  was considered significant.

## RESULTS

During the study period of January 2013–October 2017, 146 patients were supported with ECMO in the cardiac intensive care unit. Of these, 62 patients (42.46%) received ACA while on ECMO. Gender distribution was 38 (61.3%) males and 24 (38.7%) females.

The median age at ECMO initiation was 19 days and mean of 901.95 days (+1,745.45), with a range of 2–6,137 days. The median height was 52 cm (range 37–198 cm), with a mean of 72.39 cm (SD ± 39.8), whereas

the median weight was 3.6 kg (range 2.2–94.8 kg), with a mean of 11.8 kg (SD  $\pm$  19.0).

The median duration of ECMO support was 6 days (range 1–21 days), with a mean of 7.11 days (+4.66). The most frequent indication for ECMO was cardiac failure following heart surgery, comprising 77.4% of patients. The second most common indication was other causes of cardiac failure such as cardiomyopathy, representing 11.9% of patients. Among patients with congenital heart disease, hypoplastic left heart syndrome was the commonest diagnosis (17/62, 27%). Other common diagnoses were total anomalous pulmonary venous return (4), aortic stenosis (4), truncus arteriosus (4), atrioventricular septal defect (4), and tricuspid valve stenosis/atresia (4). ECMO was initiated as ECPR in 19/62 (30%) patients, whereas the rest were elective cannulations.

ACA therapy was started after a mean of 16.3 hours (SD + 8.7 hours) post-ECMO initiation. ACA was started at a median loading dose of 100 mg/kg infused over 30–60 minutes. The range of loading dose used was from 42.2 to 102.9 mg/kg (mean 97.6 SD + 9.9). This was followed by a continuous infusion at a median rate of 33.3 mg/kg/h, with a mean of 31.5 SD + 5.0 mg/kg/h (range of 10–33.3 mg/kg/h). It is important to note that the indication for use of  $\epsilon$ -ACA was bleeding while on ECMO; however, the decision and

timing of initiation was the individual provider's decision. In general, it was used in the setting of significant bleeding not responsive to standard measures based on the provider's assessment. Similarly, cessation of ACA therapy was also a provider decision made. The indications for starting and stopping the therapy were not specifically noted in the records and were not ascertained.

### Bleeding

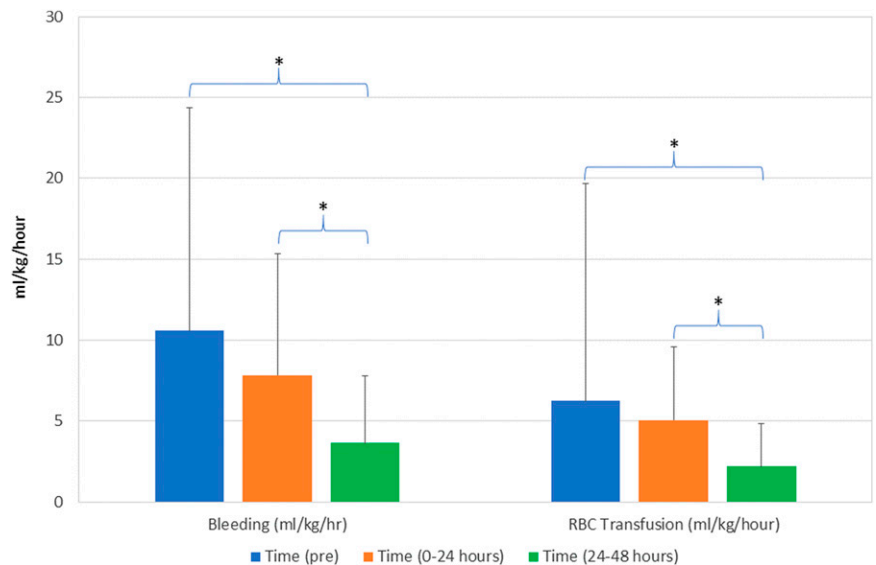
Bleeding was the most important outcome of interest. The bleeding documented from the chest tubes as well as any additional surgical site was quantified and charted. This was used to calculate the hourly bleeding rate (mL/kg/h). The mean bleeding before ACA initiation was 10.5 ( $\pm$ 13.8) mL/kg/h, decreasing to 7.8 ( $\pm$ 7.5) mL/kg/h for the 24 hours after initiation of ACA and to 3.65 ( $\pm$ 4.1) mL/kg/h for hours 24–48 ( $p$  = .0003, Table 1).

The need for red blood cell transfusion (RBC) also correspondingly decreased over time, with a mean rate of transfusion reducing from 6.24 ( $\pm$ 13.4) mL/kg/h to 2.18 ( $\pm$ 2.6) mL/kg/h ( $p$  = .022) by 24–48 hours post-initiation of ACA (Figure 1).

We assessed the utilization of blood products other than red blood cells with relation to starting ACA and are shown in Table 2. There was a statistically significant reduction in

**Table 1.** Relationship of bleeding and transfusion needs with ACA initiation.

	24 Hours Pre-ACA Mean (SD)	0–24 Hours Post-ACA Mean (SD)	24–48 Hours Post-ACA Mean (SD.)	Significance
Blood loss (mL/kg/h)	10.58 (+13.8)	7.83 (+7.51)	3.65 (+4.14)	$p$ = .00029
Red blood cell transfusion (mL/kg/h)	6.24 (+13.4)	5.06 (+4.54)	2.18 (+2.67)	$p$ = .0220



**Figure 1.** Bleeding and transfusion requirements pre- and post-ACA initiation.

**Table 2.** Use of blood component therapies pre- and post-ACA initiation.

Blood Products (mL/kg/hour)	24 Hours Pre-ACA (mean)	0–24 Hours Post-ACA (mean)	24–48 Hours Post-ACA (mean)	One-Factor ANOVA <i>p</i> Value
Fresh frozen plasma	2.39	1.69	.67	<b>.0008*</b>
Platelet transfusion	2.13	1.56	1.26	<b>.017*</b>
Cryoprecipitate	.60	.24	.07	<b>.05</b>
Albumin 5%	2.36	1.13	.48	.07
Albumin 25%	.11	.01	.03	.27
Antithrombin III	.02	.01	.02	.45
Cell saver	.88	.02	.01	<b>.004*</b>

Bold values represent statistically significant *p* values.

\*Significant *p* values

the use of FFP, cryoprecipitate, platelets, recombinant factor VII, and Cell Saver from the pre- to post-ACA initiation (all  $p < .05$ ). FFP, cryoprecipitate, and platelet use were significantly lower both at 24 and 48 hours than at pre-ACA. In addition, there was significant reduction for these products between 24 and 48 hours post-ACA therapy. During this time period, the mean hemoglobin and platelet count were not different, reflecting the adherence to our standard practice and maintenance of stable hemoglobin and platelet count. No significant difference in utilization was found for albumin 5%, albumin 25%, and antithrombin three within the study population over those time periods. TXA was used in four patients before the use of ACA; however, the usage was discontinued after starting ACA in all of these patients, whereas in one patient, TXA was added after initiation of ACA.

### Coagulation Studies

The coagulation studies were recorded over the various time frames and are shown in Table 3. PT decreased from 19.96 to 16.7 seconds from pre-ACA phase to 24–48 hours post-ACA initiation ( $p = .0241$ ). INR decreased from 1.54 to 1.34 ( $p = .00021$ ), whereas the PTT decreased from 119.0 to 78.18 seconds over the same time period ( $p < .0001$ ).

Thromboelastography parameters were measured daily. The indicator of fibrinolysis, TEG Ly30 did not change over time ( $p = .40$ ). Similarly, TEG R heparinase and TEG MA heparinase ( $p = .32$ ) did not change over time. D-dimer ( $p = .33$ ), activated clotting time (ACT,  $p = .23$ ), hemoglobin ( $p = .07$ ), platelet count ( $p = .16$ ), fibrinogen ( $p = .14$ ), and antithrombin assay ( $p = .47$ ) were found to have no statistically significant differences between time periods.

### Complications and Outcomes

There were 39 patients (62.9%) who underwent 48 surgical interventions during the time of ACA infusion. The majority of these interventions (42/48) were surgical chest explorations for bleeding. There were four additional procedures for cannula site adjustment and two fasciotomies for left lower extremity compartment syndrome in patients with left femoral cannulation.

Neurologic complications occurred in 20 patients (32.2%). Intracranial hemorrhage occurred in six patients (9.7%), seizures in four patients, intraventricular hemorrhage in three, anoxic or hypoxic brain injury in two, thrombotic stroke in two, and subdural hemorrhage in one. Brain death was declared in two patients. Neurologic complications

**Table 3.** Laboratory parameters pre- and post-ACA initiation.

	24 Hours Pre-ACA (mean)	0–24 Hours Post-ACA (mean)	24–48 Hours Post-ACA (mean)	<i>p</i> Value
Hemoglobin (mg/dL)	12.20	12.63	12.83	.074
Platelet count (count in thousand per microliter)	110.77	99.97	98.24	.16
Prothrombin time (seconds)	19.96	16.82	16.70	<b>.024</b>
INR	1.55	1.36	1.34	<b>.0002</b>
Partial thromboplastin time (seconds)	119.04	84.42	78.18	<b>&lt;.0001</b>
Fibrinogen (mg/dL)	225.52	244.03	256.98	.13
D-dimer	1,226.33	2,273.33	3,520.63	.32
Antithrombin assay	72.61	65.54	68.47	.47
TEG R heparinase (minutes)	8.84	8.42	7.86	.32
TEG MA heparinase (mm)	54.26	52.69	56.27	.31
TEG Ly30 heparinase (%)	.13	.12	.47	.40
Activated clotting time (seconds)	165.00	158.84	159.47	.23

Bold values represent statistically significant *p* values.

occurred before initiation of ACA in seven patients, seven during the first 48 hours of infusion time, whereas six were noted more than 48 hours after ACA initiation. We did not conduct time relationship analysis because of difficulty with ascertaining the exact timing of occurrence of these events rather than the timing of detection on imaging or on EEG.

Mechanical circuit complications occurred in 24/62 patients (38.7%). Most of these events were clots seen in the arterial filter, which is a standard part of our circuit. In all instances, this was addressed by cutting out the arterial filter. There was one instance of centrifugal pump change out related to a clot at the pin and one oxygenator change out related to functional performance. There were seven total circuit changes through the time period; common indications for circuit changes were observation of clots in more than two circuit locations/components. Circuit change for circuit disseminated intravascular coagulopathy was not reported. There was no time relationship between these events and the initiation of ACA was distributed over time.

Other complications included three episodes of limb/digit ischemia (one within 24 hours, two episodes beyond 48 hours of ACA initiation), one of gastrointestinal bleeding (pre-initiation of ACA), and one of mediastinal hematoma (within 24 hours of ACA initiation). Overall, 25.8% of patients survived to hospital discharge, which is similar to the overall survival for the postcardiotomy cardiac ECMO cohort during that period.

## DISCUSSION

The main objective of this study was to examine the use of  $\epsilon$ -ACA in pediatric cardiac patients on ECMO and its effects on bleeding, interventions, and coagulation parameters. This study demonstrates that ACA was used in 46% of cardiac ECMO patients and that there was a 26% decrease in bleeding amount in the first 24 hours after ACA administration, and a 65% decrease in bleeding amount in the following 24 hours. Similarly, RBC transfusions decreased by 19% and 65% in the first and second 24 hours following ACA administration, respectively. These represent a statistically significant reduction in bleeding amount and RBC transfusions after administration of ACA.

The evidence to support the use of ACA and other antifibrinolytics is well established in cardiac surgery with multiple well-conducted studies (4,5,9). There is paucity of such data in the more complex environment of pediatric cardiac ECMO. In 1993, Wilson et al. (7) reported their institutional experience of using ACA in patients at high risk for ECMO bleeding and compared them with historical controls. They reported a statistically significant reduction in the overall bleeding as well as blood transfusion needs

with the use of ACA. In their study, the use of ACA was preemptive. Therefore, whereas the reduction in bleeding and transfusion needs are similar to our study, the use of ACA in our patients was initiated only in patients with bleeding. This allowed for us to assess the effect of ACA with patients themselves serving as the control.

Downard et al. (8) compared patients at their center supported with ECMO who received ACA with overall ELSO registry patients. They found that the use of ACA was associated with significant reduction in surgical site bleeding, especially cardiac subgroup. They report the occurrence of surgical site bleeding in 10% of their patients treated with ACA compared with 30% in the ELSO registry ( $p = .001$ ). However, when they compared their own patients who received ACA with those who did not receive ACA, they did not find any significant difference in chest tube bleeding or blood transfusion needs. The primary analysis of study was performed using surgical bleeding as a categorical variable with binary response. Categorization of bleeding as binary variable limits the analysis as well as validity of the study, especially when one is trying to ascertain the impact of an intervention. The secondary analysis where patients receiving ACA were compared with those who did not receive ACA at their own institution is limited by the fact that these two patient groups may be inherently different because of their acknowledged institutional practice.

Previous studies have not evaluated the transfusion needs and use of non-pRBC blood products in detail. In our study, we assessed the use for FFP, platelets, cryoprecipitate, factor VII, and Cell Saver and found significant reduction in the need post-ACA initiation. These may be additional indicators of improvement in the hemostatic environment with administration of ACA. Of note, the decrease in Cell Saver is likely due to the fact that Cell Saver is administered for a limited time following surgery, and thus the decrease cannot be attributed to ACA.

As far as coagulation studies are concerned, PT, INR, and PTT all showed a statistically significant decrease with respect to ACA administration. This indicates that ACA may be effective in shifting both the extrinsic and intrinsic pathways of the coagulation cascade toward a more coagulative state (4). Buckley et al. (10) showed a significant reduction in elevated D-dimer levels and increase in a low starting fibrinogen level with initiation of ACA. In our study, there was no significant difference in TEG Ly30, TEG R heparinase, TEG MA heparinase, D-dimer, fibrinogen, and ACT relative to the timing of ACA administration. A potential explanation for the same is that our ECMO protocols dictate normalization of fibrinogen levels and maintenance of coagulation parameters with corrective measures continuously. Therefore, the reduction in need for products needed to maintain fibrinogen levels within range is an important finding.

Last, complications in these high-risk patients are common. Various pediatric ECMO studies report neurologic complications in ~20% of patients (1,2,11–13). We saw at least some form of neurologic injury in 32% of the patients when we included minor bleeds and radiologic findings. Prior studies related to ACA have focused only on intracranial hemorrhage which occurred between 0 and 23% (6,7). In our cohort, the overall incidence of ICH was 9.7% with occurrence distributed pre-, during, and post-ACA administration. The relationship of occurrence of ICH in relation to ACA or any other interventions cannot be surmised.

### Limitations

It is important to note that 39 of 62 patients received surgical intervention to address excessive bleeding which is dictated by clinical practice and need. In clinical practice, the patient demonstrating significant surgical bleeding is likely to get multiple interventions at the same time, and therefore, impact of individual interventions cannot be pored out. A randomized placebo-controlled trial looking at the impact of an antifibrinolytic in ECMO patients may be difficult to justify, given the existing data in other clinical scenarios such as cardiac surgery. The current study suggests that a multi-prong approach that includes ACA can effectively decrease bleeding and need for transfusion of blood products. In addition, the additive benefit of ACA beyond routine product replacements and surgical control cannot be ascertained. There is no control group for us to appropriately compare with, and the indication for use of ACA was not predefined. Reduction in bleeding can be attributed to multiple factors including time for clot formation and stabilization.

Another potential limitation of the study is that the side effects of ACA could not be evaluated well. Most common side effects are hypotension, cardiac arrhythmias, rhabdomyolysis, and renal dysfunction (4). However, these could not be discerned, given the patient population on ECMO where assessment most of these is difficult. Rhabdomyolysis was not tested for.

No arrhythmias were noted during the administration of ACA.

### CONCLUSION

In pediatric and neonatal cardiac patients supported on ECMO, bleeding complications are common and lead to

significant morbidity and mortality. The addition of  $\epsilon$ -ACA to the therapy in patients with bleeding is associated with the decrease in bleeding, decreased need for transfusion of blood products, and improvement in coagulation parameters. The study provides data to support consideration of routine use  $\epsilon$ -ACA, especially in this group of patients. Further studies could aim at patient selection and duration of therapy in these patients.

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