Use of Inhaled Tranexamic Acid (TXA) in Pulmonary Hemorrhage for Pediatric Patients on Extracorporeal Membrane Oxygenation Support (ECMO)

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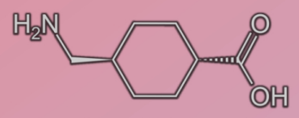
Background:

- Extracorporeal membrane oxygenation (ECMO) is a form of mechanical support used when patients have been refractory to intensive medical therapies.
- While on ECMO, patients are highly anticoagulated and prone to bleeding.
- Tranexamic acid (TXA) is a lysine analog that competitively inhibits plasminogen's activation to plasmin, minimizing fibrinolysis and increasing the chance for hemostasis.



- Inhaled tranexamic acid has been used with good success in multiple populations to treat pulmonary hemorrhage but has only recently been used in ECMO patients.

Objectives:

- This study will evaluate the use of inhaled TXA for patients currently on ECMO that are experiencing pulmonary hemorrhage.
- **Hypothesis**: The use of inhaled TXA in patients on ECMO with pulmonary hemorrhage causes cessation of pulmonary hemorrhage and decreases the need for transfusion of blood products.

Methods:

- Single-center retrospective observational study that included pediatric patients <18 years of age who underwent ECMO, experienced pulmonary hemorrhage, and received inhaled tranexamic acid between January 2018 and August 2022
- 359 runs of ECMO were completed on 327 unique patients during the study period; 60 patients received inhaled TXA and of these, 7 patients were excluded according to the following exclusion criteria:
  - Patients treated with inhaled TXA 72 hours prior to ECMO initiation
  - Patients placed on ECMO primarily for treatment of pulmonary hemorrhage
  - For patients with multiple ECMO runs within the study period, only the index run of ECMO that was associated with new pulmonary hemorrhage was included
- Patient data was collected from the electronic medical record (EMR) and included age, sex, race, height, weight, primary diagnosis, comorbidities, and details of ECMO cannulation and TXA administration, etc.
- TCH ECMO Bleeding Scale used to measure hemorrhage (decrease from 2 to 0-1)
- Primary outcomes:
  - Cessation of pulmonary hemorrhage after inhaled TXA use
  - Decrease in blood product transfusion requirements 48 hours after initiation of inhaled TXA
- Secondary outcomes:
  - Changes in systemic anticoagulation dosage 48 hrs after use of inhaled TXA
  - ICU length of stay
  - Hospital length of stay
  - Mortality

*Values are presented as median (IQR 25th-75th percentile) or count (percentage). BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; TXA, tranexamic acid; VA-VV, venoarterial ECMO transitioning to venovenous ECMO; ECPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; LOS, length of stay.

Table 1 - Demographics

Variable	Patients (n=53)
Sex	
Male, n (%)	36 (67.92)
Female, n (%)	17 (32.07)
Age (months), median (IQR)	**11 (1.12-156)**
Neonates (<30 days), n (%)	12 (22.64)
Infants (≥30 days to <1 year), n (%)	15 (28.30)
Children (≥1 years to <5 years), n (%)	6 (11.32)
Older children (≥5 years to ≤18 years), n (%)	20 (37.74)
Weight (kg), median (IQR)	9.46 (5.40-41.20)
Height (cm), median (IQR)	74.60 (57.68-150.15)
BMI (kg/m²), median (IQR)	17.30 (14.29-19.46)
Race	
Hispanic or Latino, n (%)	19 (35.85)
Not Hispanic or Latino, n (%)	31 (58.49)
Asian, n (%)	4 (7.55)
Black or African American, n (%)	17 (32.07)
White, n (%)	30 (56.60)
Unable to obtain, n (%)	5 (9.43)
Diagnosis	
Respiratory, n (%)	18 (33.96)
Cardiac, n (%)	10 (18.87)
Structural abnormality (congenital heart disease, congenital diaphragmatic hernia, tracheal stenosis), n (%)	18 (33.96)
Multisystem (sepsis, autoimmune), n (%)	7 (13.21)
ECMO	
Indications for ECMO	
Respiratory failure, n (%)	25 (47.17)
Cardiogenic shock, n (%)	19 (35.85)
Post-operative cardiogenic shock, n (%)	7 (13.21)
Bridge to transplant, n (%)	2 (3.77)
Duration of ECMO support (days), median (IQR)	13.83 (8.62-24.87)
ECMO Type	
Venovenous ECMO, n (%)	17 (32.07)
Venoarterial ECMO, n (%)	31 (58.49)
VA-VV, n (%)	5 (9.43)
ECPR (yes/no), n (%)	10/43 (18.87/81.13)

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Texas Children's Hospital ECMO Clinical Bleeding Scale

0	**No or Minimal Bleeding**	- Oozing from catheter site or mucosa that requires no intervention
1	**Mild Bleeding**	- Oozing from catheter site or mucosa that requires minor intervention or surgical consult
2	**Moderate Bleeding**	- Peritoneal bleed, hemothorax, pulmonary bleed, hematuria that does not require surgical intervention - Documented blood loss >1 mL/kg/hr (averaged over 4 hours) but less than 4 mL/kg/hr - Clinical bleeding requiring a decrease in anti-Xa/ACT goal, increase in platelet transfusion threshold, or immediate transfusion of platelet, FFP, or PRBCs - Use of IV antifibrinolytics (Aminocaproic acid or tranexamic acid)
3	**Severe Bleeding**	- Peritoneal bleed, hemothorax, pulmonary bleed, and/or hematuria that requires surgical intervention - Documented blood loss >4 mL/kg/hr (avg over 4 hours) - Heparin drip held (unless in preparation for planned surgical procedure or excessive heparin level/ACT) - Bleeding leading to hemodynamic changes that requires blood transfusion - New CNS bleed not requiring discontinuation of ECMO
4	**Catastrophic Bleeding**	- Bleed resulting in death or requiring discontinuation of ECMO

Table 2 - Lab Values

Variable	48 hours before TXA, median (IQR)	24 hours before TXA, median (IQR)	24 hours after TXA, median (IQR)	48 hours after TXA, median (IQR)
Fibrinogen (mg/dL)	338.5 (267.5-439)	291 (231.5-414)	285 (232-417)	319 (235-432.25)
Hematocrit (%)	32.8 (29.45-37)	31.9 (28.6-35.75)	31.55 (28.02-35.35)	30.3 (27.4-35.45)
Hemoglobin (g/dL)	11.2 (10.3-13.2)	10.9 (9.85-12.3)	10.5 (9.8-11.3)	10.2 (9.6-11.7)
International normalized ratio	1.6 (1.2-1.8)	1.6 (1.2-1.9)	1.5 (1.3-1.9)	1.5 (1.3-1.8)
Platelet count ($10^3/\mu L$)	116 (94-148)	109 (88-136)	111 (94-139.25)	107 (91.25-129.25)
Prothrombin time (s)	19 (15.37-21.35)	19.2 (15.7-21.55)	18.6 (15.9-22.3)	18.2 (15.9-21.1)
Partial thromboplastin time (s)	71.1 (53.97-82.7)	66.5 (50.8-77.4)	67.2 (51.6-79.52)	66.7 (54.37-77.52)
Partial thromboplastin time, Hepzymed (s)	39.7 (30.3-66.25)	40.8 (31.05-60)	40.7 (32.9-62.15)	47.6 (32.75-62.3)

Table 3 - Blood Products

Variable	48 hours before TXA, median (IQR)	24 hours before TXA, median (IQR)	24 hours after TXA, median (IQR)	48 hours after TXA, median (IQR)
Cryoprecipitate	15 (15-23)	15 (15-22.25)	25.5 (21.5-75)	8.37 (7.19-22)
Fresh frozen plasma	167.83 (60-218)	45 (9-125)	35 (24-80)	34.5 (18-60)
Platelets	47 (28-90)	40 (18.21-70)	40 (25-109.75)	41 (30-105)
Red blood cells	55.5 (35-128.75)	40.41 (19.5-137)	35 (20.12-148)	40 (15-120)

Results:

- The cohort consisted of 53 patients with a median age of 11 months (Table 1). The majority of the patients were male (68%), white (57%), with a primary diagnosis of either respiratory etiology (34%) or structural abnormality (congenital heart disease, congenital diaphragmatic hernia, or tracheal stenosis) [34%].
- Primary indication for initiation of ECMO was respiratory failure (47%), most often from pneumonia of viral etiology. The most common comorbidities among the cohort were congenital heart disease, genetic disorders, and pulmonary hypertension.
- 89% of patients had cessation of pulmonary hemorrhage after inhaled TXA use, with 19% of patients experiencing rebleeding within 96 hours of the initial TXA dose. 11% of patients did not respond to inhaled TXA with cessation of hemorrhage.
- Blood product requirements globally decreased by the following percentages: 44% - cryoprecipitate, 79% - fresh frozen plasma, 13% - platelets, and 28% - RBCs.
- Hospital mortality and discharge to home were evenly split at 49% each, with one patient discharged to another facility.

Table 4 - Outcomes

ICU LOS (days), median (IQR)	45.12 (26.00-70.95)
Hospital LOS (days), median (IQR)	59.19 (37.75-98.25)
Weaned off ECMO, n (%)	36 (67.92)
Death on ECMO, n (%)	16 (30.19)
Bridge to other assistance, n (%)	1 (1.89)
Hospital mortality, n (%)	26 (49.06)
Discharge to other facility, n (%)	1 (1.89)
Discharge home, n (%)	26 (49.06)

Discussion:

- Patients who are supported with extracorporeal membrane oxygenation often experience bleeding and hemorrhage as a complication; pulmonary hemorrhage is associated with higher mortality.
- Inhaled tranexamic acid has been shown to be 95% effective in treating pulmonary hemorrhage in critically ill children.
- Nebulized tranexamic acid has been studied in ECMO patients in a case study of three patients that showed that inhaled tranexamic acid can be a useful intervention in this fragile population.

Conclusions:

- Our study is the largest population that has been studied thus far and shows that inhaled TXA is an effective option for pediatric patients on extracorporeal membrane oxygenation.
- Inhaled tranexamic acid is a viable option for patients maintained on extracorporeal membrane oxygenation to treat pulmonary hemorrhage. Additional study, specifically a randomized controlled trial, should be done to further clarify the efficacy of this intervention.

References: