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Platelet Transfusion Thresholds for Children Supported by Extracorporeal Membrane Oxygenation: The ECSTATIC Feasibility Clinical Trial

Marianne E Nellis, MD, MS¹, Bradley J Barney, PhD², Garrett Coles, MD³, Jill M Cholette, MD³, Tarif A Choudhury, MD⁴, Jamie Furlong-Dillard, DO⁵, Caroline Ozment, MD⁶, Jesse Bain, DO⁷, Robert A Niebler, MD⁸, Madhuradhar Chegondi, MD⁹, Aditya Badheka, MBBS, MS¹⁰, Ofer Schiller, MD, MBA¹¹, Eran Shostak, MD¹¹, Umesh Joashi, MB, BS¹, Matthew Paden, MD¹², Jessica S Alvey, MS¹³, Jennifer A Muszynski, MD, MPH¹⁴, Philip C Spinella, MD¹⁵, Marisa Tucci, MD¹⁶, Jacques Lacroix, MD¹⁶, Simon Stanworth, DPhil, MD¹⁷, Erika R O'Neil, MD¹⁸, Uri Pollak, MD¹⁹, Timothy Bahr, MD, MS²⁰, S Ram Kumar, MD, PhD²¹, Oliver Karam, MD, PhD²² on behalf of BloodNet and PediECMO, subgroups of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)

¹Department of Pediatrics, Weill Cornell Medicine, NY, NY, USA

²Department of Pediatrics, University of Utah, Salt Lake City, UT, USA

³Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Rochester Golisano Children's Hospital, Rochester, NY, USA

⁴Divisions of Pediatric Critical Care Medicine and Pediatric Cardiology, Morgan Stanley Children's Hospital at Columbia University School of School of Medicine, NY, NY, USA

⁵Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Louisville Norton Children's Hospital, Louisville, KY, USA

⁶Pediatric Critical Care Medicine, Duke University, Durham, NC, USA

⁷Division of Critical Care Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA

⁸Division of Critical Care, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA

⁹Pediatric Critical Care Medicine, University of Illinois College of Medicine and Children's Hospital of Illinois at OSF HealthCare, Peoria, IL, USA

¹⁰Division of Critical Care, Stead Family Department of Pediatrics, University of Iowa, Iowa City, IA USA

¹¹Pediatric Cardiac Intensive Care Unit, Schneider Children's Medical Center, Petach-Tikva and Tel-Aviv university Faculty of medicine and health sciences, Tel-Aviv, Israel

¹²Children's Healthcare of Atlanta – Emory, Atlanta, GA

Address Correspondence To: Marianne Nellis, MD, MS, Division of Pediatric Critical Care Medicine, New York Presbyterian Hospital – Weill Cornell Medical Center, 525 E 68th Street, Box 318, New York, NY 10065, man9026@med.cornell.edu.

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- ¹³Utah Data Coordinating Center, University of Utah, Salt Lake City, UT, USA
- ¹⁴Division of Critical Care Medicine, Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH, USA
- ¹⁵Trauma and Transfusion Medicine Research Center, Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA
- ¹⁶Pediatric Critical Care Medicine Service, Department of Pediatrics, Sainte-Justine Hospital, Université de Montreal, Montreal, Canada
- ¹⁷John Radcliffe Hospital, Oxford, UK
- ¹⁸United States Air Force, Department of Pediatrics, Brooke Army Medical Center, San Antonio, Texas, USA, and Uniformed Services University of Health Sciences, Bethesda, Maryland, USA
- ¹⁹Section of Pediatric Critical Care, Hadassah University Medical Center and Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
- ²⁰Division of Neonatology, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA
- ²¹Division of Pediatric Cardiothoracic Surgery, Children's Nebraska and University of Nebraska Medical Center, Omaha, NE, USA
- ²²Pediatric Critical Care Medicine, Department of Pediatrics, Yale, CT, USA

Abstract

Objectives: To evaluate the feasibility of randomizing children on extracorporeal membrane oxygenation (ECMO) to one of two prophylactic platelet transfusion thresholds.

Design: Randomized controlled trial

Setting: Ten ECMO centers (9 in United States, 1 in Israel)

Patients: Critically ill children (0 to <18 years), supported on ECMO, with no or minimal bleeding within 24 hours of cannulation.

Interventions: Children were randomized to a higher platelet threshold (transfused when platelet count $<90 \times 10^9/L$) or a lower platelet threshold (transfused when platelet count $<50 \times 10^9/L$). Primary feasibility outcome was pre-transfusion platelet count to test for a difference between strategies. Primary safety outcome was progression to severe bleeding, severe clotting, and/or all-cause mortality.

Measurements and Main Results: Of 159 patients screened for eligibility, 77% (123/159) met eligibility criteria. Sixty-five percent (80/123) of caregivers were approached for consent. Consent was obtained in 63% (50/80). Enrolled children had a median age of 0.2 years (IQR 0.0; 1.7) and 88% (44/50) were supported by veno-arterial (V-A) ECMO. The model-adjusted mean difference in pre-transfusion platelet count between the groups was $32 \times 10^9/L$ (p-value <0.001). Compliance with assigned transfusion threshold was 99.2%. Eleven (22%) children experienced the primary safety outcome. Progression to severe bleeding occurred in 14% (7/50) of patients, while progression to severe clotting was observed in 4% (2/50).

Conclusions: Non-bleeding children on ECMO can be screened, enrolled and randomized to different platelet transfusion strategies within 24 hours of cannulation. Compliance with the protocol was excellent with significant separation in pre-transfusion platelet counts between the arms. Severe bleeding and severe clotting occurred at similar rates in both thresholds. A larger, definitive trial is feasible and needed.

MESH Terms:

children; critical illness; platelet transfusion; ECMO; hemorrhage; thrombosis

Introduction

Due to thrombocytopenia, circuit-induced platelet dysfunction, and need for anticoagulation, children supported by extracorporeal membrane oxygenation (ECMO) are at high risk of bleeding.(1, 2) Up to 70% of children will have at least one episode of clinically relevant bleeding during their ECMO course.(3) Due to this risk of bleeding, platelet transfusions are given. Based on data from two large cohorts, children on ECMO receive platelet transfusions on two-thirds of ECMO days.(4, 5) Paradoxically, these transfusions have been independently associated with increased bleeding the following day and with higher mortality—findings consistent with other platelet transfusion trials.(6)

Considering well-recognized risks of platelet transfusion including infection, acute lung injury, circulatory overload and immunomodulation, (7–11) it is essential to define appropriate thresholds below which platelet transfusions should be given. However, there is little evidence to direct this decision. Current guidance from the Extracorporeal Life Support Organization encourages prophylactic platelet transfusion when the platelet count drops below $50\text{--}100 \times 10^9/\text{L}$.(12) The Transfusion-Anemia eXpertise Initiative-Control/Avoidance of Bleeding and the Pediatric ECMO Anticoagulation Collaborative consensus groups concluded there is not enough evidence to recommend a platelet transfusion threshold for non-bleeding children on ECMO.(13, 14)

A first step to understand the appropriate minimum prophylactic platelet transfusion threshold is to demonstrate feasibility of enrolling and randomizing patients to two separate threshold strategies in a safe manner. We designed a multi-centered, randomized controlled trial (RCT) to test two prophylactic platelet transfusion thresholds for children on ECMO to demonstrate this feasibility.

Methods

Study Design

The ECMO Hemostatic Transfusions in Children (ECSTATIC) trial was a multicenter, randomized, open-label, RCT evaluating the feasibility of comparing two prophylactic platelet transfusion strategies in children on ECMO. Regulatory approval was given by the Biomedical Research Alliance of New York (BRANY), protocol #23-10-085, approval 02/20/2023. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of

1975. Informed consent was obtained from caregivers for all participants. The study was registered with clinicaltrials.gov (ID# [NCT05796557](https://clinicaltrials.gov/ct2/show/study/NCT05796557)).

We screened patients at ten pediatric, cardiac and neonatal intensive care units (ICUs) in two countries (Israel and United States). Children <18 years who were on ECMO and had no/minimal bleeding within 24 hours of cannulation were eligible. Bleeding was considered minimal per the Bleeding Assessment Scale in Critically Ill Children (BASIC) definition. (15) Exclusion criteria are listed in Figure 1. The study protocol is available in the Supplemental Digital Content (SDC).

Participants were randomized in a 1:1 ratio to either a low or high prophylactic platelet transfusion threshold strategy using an online system. In the higher platelet transfusion strategy group, the platelet count threshold for transfusion was $<90 \times 10^9/L$. In the lower platelet transfusion strategy group, the threshold was $<50 \times 10^9/L$. To ensure equipoise, these thresholds were chosen based on observational and survey data and approximate the 25th and 75th percentile of real-life transfusion thresholds (16, 17). Participants were stratified by age (≤ 28 vs > 28 days) because of safety concerns around lower transfusion strategies in neonates.

Platelet counts were to be monitored at least twice daily. Platelets were to be transfused within 12 hours of the threshold value being reached. The transfusion dose was 10–20 mL/kg. Platelet count was to be assessed 2–4 hours after the end of the platelet transfusion.

The protocol could be temporarily suspended for up to 24 hours at the discretion of the attending physician if the clinical situation warranted immediate transfusion for conditions including: 1) chest-tube insertion; 2) surgical intervention while on ECMO; 3) ECMO circuit change; or 4) in preparation for decannulation.

To ensure patients were managed identically in both arms, we required sites to adhere to the latest international guidelines regarding anticoagulation and other hemostatic interventions (14). Furthermore, sites were required to follow their local guidelines for plasma transfusions, anticoagulation, cryoprecipitate or fibrinogen concentrate administration, antithrombin administration, and ECMO circuit priming. Local guidelines could not be changed based on the arm to which the patient was assigned; compliance with these guidelines was tracked for each patient. The highest and lowest Anti-Xa and activated partial thromboplastin time (aPTT) were recorded daily to follow compliance with anticoagulation protocols.

The platelet transfusion threshold was applied for up to 21 days, until progression to severe bleeding and/or severe clotting (outside of temporary suspensions), end of ECMO support (as defined by cessation of flow through the ECMO circuit), temporary suspension lasting more than 24 hours, or withdrawal from the study, whichever occurred first.

The primary endpoint was the separation in pre-transfusion platelet count between the two arms, excluding temporary suspensions. The protocol defined 10 feasibility criteria as secondary endpoints; at least five were required to declare the trial successful. Details of the feasibility criteria are provided in the SDC. Platelet transfusion compliance was

achieved when a platelet transfusion was appropriately administered within 12 hours after a below-threshold platelet count, or by not transfusing any platelets when there was no below-threshold platelet count (unless during a temporary suspension).

The primary safety outcome was progression to severe bleeding and/or severe clotting outside of a temporary suspension and/or all-cause mortality within 24 hours after the transfusion strategy ended. Severe bleeding was defined by the BASIC definition (15) with the addition of new intracranial hemorrhage. Severe clotting was defined by an NHLBI Consensus Conference.(18) The primary safety outcomes were adjudicated by two members of a three-member adjudication committee blinded to randomization. Adjudicators reported whether they agreed with the bedside determination of severe bleeding and/or severe clotting; in the event of conflicting responses, the third adjudicator reviewed the event.

Additional clinical outcomes included survival status on ECMO and at 28 and 90 days, blood product exposure, duration of ECMO (defined as 90-day ECMO-free days), 90-day ICU-free days, and functional outcomes.

Statistical Analysis

We estimated a sample size of 50 patients to detect a difference in pre-transfusion platelet counts between the two arms. The Statistical Analysis Plan (SAP) in the SDC provides the detailed sample size justification. The SDC also contains an addendum noting key differences between the SAP and the analysis presented in this manuscript for six areas: (1) handling of temporary suspensions; (2) definition of transfusion protocol compliance; (3) application of interim primary safety outcome testing at different timepoints; (4) changes in testing for additional analyses (that should be considered as exploratory); (5) subgroup analyses for subgroups specified in the SAP not conducted; and (6) clarification in the interpretation of compliance with non-study protocols. Planned interim safety analyses consisted of meetings of an independent data safety monitoring board (after approximately 10, 25, and 40 enrollments) to review study data, and statistical testing after every 5 participants who had site-reported primary safety outcomes.

Continuous data were summarized using medians and interquartile ranges and categorical data were summarized with counts and percentages. The primary study hypothesis was tested using a one-sided test at $\alpha=0.025$ of the linear regression coefficient that compares the between-arms difference in mean pre-transfusion platelet count; the regression model accounted for repeated measures (see SAP and Addendum in SDC). No p-value adjustments were made for multiple comparisons. Data were analyzed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

From November 2023 to December 2024, 159 patients were screened for eligibility and 77% (123/159) met eligibility criteria. Sixty-five percent (80/123) of caregivers were approached for consent. Consent was obtained in 63% (50/80). We enrolled 50 participants. Screening and enrollment data are provided in Figure 1.

Ninety-four percent (47/50) of participants were enrolled in the US and 6% (3/50) in Israel. Median age of participants was 0.2 years (IQR 0.0; 1.7). Forty-four percent (22/50) were male sex. Fifty-four percent (27/50) were white, 22% (11/50) black, and 22% (11/50) had unknown race.

The most common primary diagnoses were acute respiratory failure 52% (26/50) and acute cardiac failure 18% (9/50). Twelve percent (6/50) received veno-venous (V-V) ECMO, and 88% (44/50) received V-A ECMO. Median time between cannulation and randomization was 18.1 hours (IQR 10.9;22.8). Prior to randomization, 30% (15/50) of participants received at least one platelet transfusion. Details by group are provided in Table 1. Details on priming of the circuit and central cannulations are in SDC eTable 1.

The median pre-transfusion platelet count in the higher threshold group was $79 \times 10^9/L$ (IQR 70; 86) compared to $43 \times 10^9/L$ (IQR 39; 47) in the lower threshold group. To account for repeated measures, the model-adjusted mean difference in pre-transfusion platelet count between the two groups was $32 \times 10^9/L$ ($p < 0.001$). Platelet counts between the two groups are illustrated in Figure 2 (by day) and SDC eFigure 1 (overall).

Overall, 56% (28/50) of participants received at least one platelet transfusion during the intervention period (outside of temporary suspensions). At the participant level, median rate of platelet transfusions per intervention day was 0.3 transfusions/day (IQR 0.0;1.2) and median transfusion dose rate (total dose/kg/intervention days) was 2.4 mL/kg/day (IQR 0.0;16.6). The time to first platelet transfusion after randomization is shown in SDC eFigure 2.

Outside of temporary suspensions, 22% (11/50) of participants received plasma transfusions, and 16% (8/50) received cryoprecipitate concentrate transfusions. Details by group are provided in Table 2.

Anticoagulation strategies varied across participants, with 94% (47/50) receiving heparin as the initial agent. The median initial heparin bolus dose was 100 IU/kg (IQR 50;100) and median initial infusion rate of heparin was 20 IU/kg/hr (IQR 10;22). Among those with bivalirudin as the initial agent (4%, 2/50), the median initial bivalirudin bolus dose was 0.1 mg/kg (IQR 0.0;0.1) and median initial bivalirudin infusion rate was 0.2 mg/kg/hr (IQR 0.2;0.3). In participants receiving heparin, the median of each patient's average of daily peak anti-Xa levels was 0.5 IU/mL (IQR 0.4;0.6). Details by group are provided in Table 2.

Progression to severe bleeding (excluding temporary suspensions) occurred in 14% (7/50) of participants, while progression to severe clotting (excluding temporary suspensions) was observed in 4% (2/50). Details by group are provided in Table 3, SDC eTable 1, and SDC eFigure 3. Of nine site-reported progressions to severe bleeding or severe clotting, adjudicators gave a final determination that progression to severe bleeding or severe clotting occurred in 100% (9/9) of cases.

The median duration of ECMO support was 5.8 days (IQR 3.8;9.9), with median of 83 ECMO-free days within 90 days (IQR 75;86). Median ICU length of stay was 33 days (IQR 22;62), and median ICU-free days was 48 (IQR 0;69). Mortality during ECMO or within 24

hours of decannulation was 6% (3/50), with 28-day and 90-day mortality rates of 14% (7/50) and 25% (12/48), respectively. Time to progression to severe bleeding and/or severe clotting and/or death during intervention or within 24 hours of end of intervention is shown in SDC eFigure 4. Functional outcomes showed a median POPC (Pediatric Overall Performance Category) score of 2 (IQR 1;6) and a median PCPC (Pediatric Cerebral Performance Category) score of 1 (IQR 1;6).

Compliance with platelet transfusion strategy was 99.2% (702/708) overall, with 99.2% (386/389) in the lower threshold arm and 99.1% (316/319) in the higher threshold arm. Compliance with non-platelet transfusion management protocols was 100%.

Temporary protocol suspensions occurred in 28% (14/50) of participants. Surgical procedures included repair of congenital diaphragmatic hernia, cardiac repair, and chest tube insertion, as summarized in SDC eTable 2.

Non-serious adverse events occurred in 20% (10/50) of participants, while serious adverse events were reported in 20% (10/50). No study-related adverse events were reported outside of bleeding and clotting events. Detailed descriptions are provided in SDC eTable 3.

Withdrawals from the study occurred in 8% (4/50) of participants. Physician discretion accounted for all withdrawals. Median time to withdrawal after randomization was 4.6 days (IQR 1.9; 6.2). Details by group are provided in SDC eTable 4.

Overall, we achieved seven of ten specified feasibility criteria (Table 4).

Discussion

In this feasibility RCT of 50 non-bleeding children on ECMO, we have demonstrated that children can be enrolled, randomized and transfused in two separate platelet transfusion threshold strategies in a safe manner. The children enrolled are representative of the general pediatric ECMO population. Definitions used to describe severe bleeding and severe clotting were adjudicated successfully. We have demonstrated feasibility to move forward to a larger, definitive trial.

The primary outcome was to investigate the ability to separate pre-transfusion platelet counts based on two transfusion thresholds arms. It was important to prove that even with a substantial drop in platelet count with cannulation that may persist, the pre-transfusion platelet count in the two arms was statistically different. We demonstrated that the two arms were separated by an estimated $32 \times 10^9/L$, representing a clinically meaningful difference.

Families of children admitted to the ICU have appropriately high levels of acute anxiety as well as post-traumatic stress disorder.(19, 20) Likewise, a recent meta-analysis showed that nearly one-third of parents of children on ECMO had at least one trauma-related psychopathology.(21) Approaching these families for consent into a clinical trial within 24 hours of cannulation may be extremely challenging. Despite these challenges, we were able to approach 65% of eligible subjects within 24 hours of cannulation and 63% of families who were approached consented to the study.

Though they may appear young with a predominance of V-A ECMO, the enrolled patients are representative of the overall pediatric ECMO population. For example, in a prospective cohort of 514 children on ECMO from 2012–2014, the median age was 0.23 years and only 15% were supported by V-V ECMO. The predominance of V-A ECMO is likely secondary to the frequent use of carotid artery cannulation for neonatal respiratory failure.(22) These findings support the generalizability of the results of the future definitive trial.

Bleeding and clotting as study outcomes have the potential to be problematic given the variety of definitions applied to each.(23) Significant time was invested in developing the BASIC definition for bleeding and validating it in critically ill children.(15, 24) Likewise, experts were convened by the NHLBI and Department of Defense to develop the definition of severe clotting for extracorporeal circuits.(25) It was important to demonstrate that the definitions could be applied to children on ECMO. All progression to severe bleeding and/or clotting events that occurred outside of temporary suspensions were confirmed by an adjudication committee demonstrating applicability of the definitions.

The study is not without limitations. Varying sizes of ECMO programs were included, but sites only represented two countries and therefore may not be feasible in all settings. Consent forms were only available in English and Spanish in the US and therefore our results may not represent consent rates of all non-English speaking populations. While the BASIC definition has been validated in critically ill children, there are other definitions of bleeding that were not used and information regarding bleeding prevalence using these cannot be reported. We only collected information on pre-transfusion platelet counts and not baseline platelet counts. Platelet counts may have varied based on the patient's underlying pathology, mode of ECMO, priming of the circuit and/or age. Whereas the ECMO circuitry may affect platelet function more than platelet count, because there are no validated tests of platelet function in children that are routinely conducted in ECMO centers, we did not base transfusion thresholds on measures of platelet function. We did not collect information about indications for procedures necessitating temporary suspensions. Favoring a pragmatic design to improve generalizability, we did not control other clinical factors that may affect bleeding and/or clotting such as priming of the circuit, transfusion of other blood components or anticoagulation. However, we required that each site had a protocol in place for these interventions and did not vary in their practice between the two arms. While we tracked compliance with non-study protocol of hemostatic agents to confirm no variation between arms, unmeasured factors may have influenced bleeding and clotting outcomes as the clinical team was not blinded to the intervention. We were only powered to detect a difference in the pre-transfusion platelet counts and all other p-values listed should generally be considered exploratory.

The next stage will be to conduct a definitive trial using a similar study design. Clinical equipoise will be surveyed again prior to the start of the study. Prevalence of measured outcomes can be used to determine the proper sample size. To improve the number of families approached, consent forms will be available in multiple languages and where permitted, online consent will be obtained. Patients will again be stratified by age, but also by V-A versus V-V ECMO. Functional outcomes will include a six-month follow-up at

which time the Pediatric Quality of Life Inventory will be assessed.(26) In addition, bedside tests that relate to platelet function will be explored.

Conclusions

Non-bleeding children on ECMO can be successfully screened, enrolled and treated according to two different platelet transfusion thresholds. Severe bleeding and clotting outcomes can be adjudicated. Successful completion of a definitive trial will provide necessary evidence for recommendations regarding prophylactic platelet transfusion strategies for pediatric ECMO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS:

Question:

Children on ECMO are at high risk of bleeding. Despite frequent use, there is limited evidence to guide safe and effective platelet transfusion thresholds. Is it feasible to enroll children in a trial testing two platelet transfusion thresholds?

Findings:

The ECSTATIC feasibility study was a multicenter RCT testing two prophylactic platelet transfusion thresholds ($<90 \times 10^9/L$ vs. $<50 \times 10^9/L$) in pediatric ECMO patients. The study enrolled 50 patients, demonstrated high protocol adherence and successful differentiation in platelet counts between the two arms.

Meaning:

The trial met 7 of 10 feasibility criteria indicating that a larger, definitive trial is feasible.

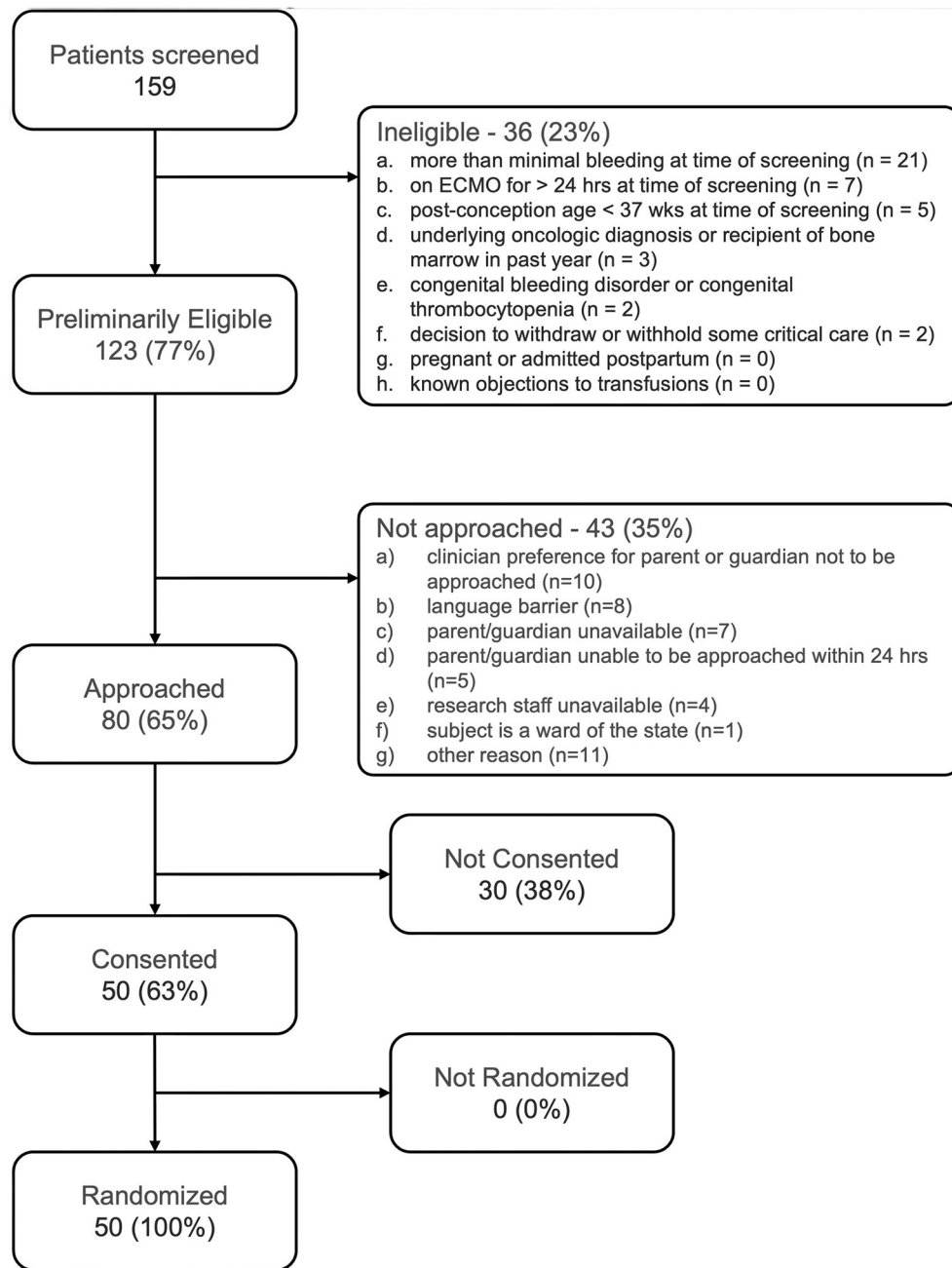


Figure 1:
CONSORT diagram. Note that more than one reason can be indicated for not approached.

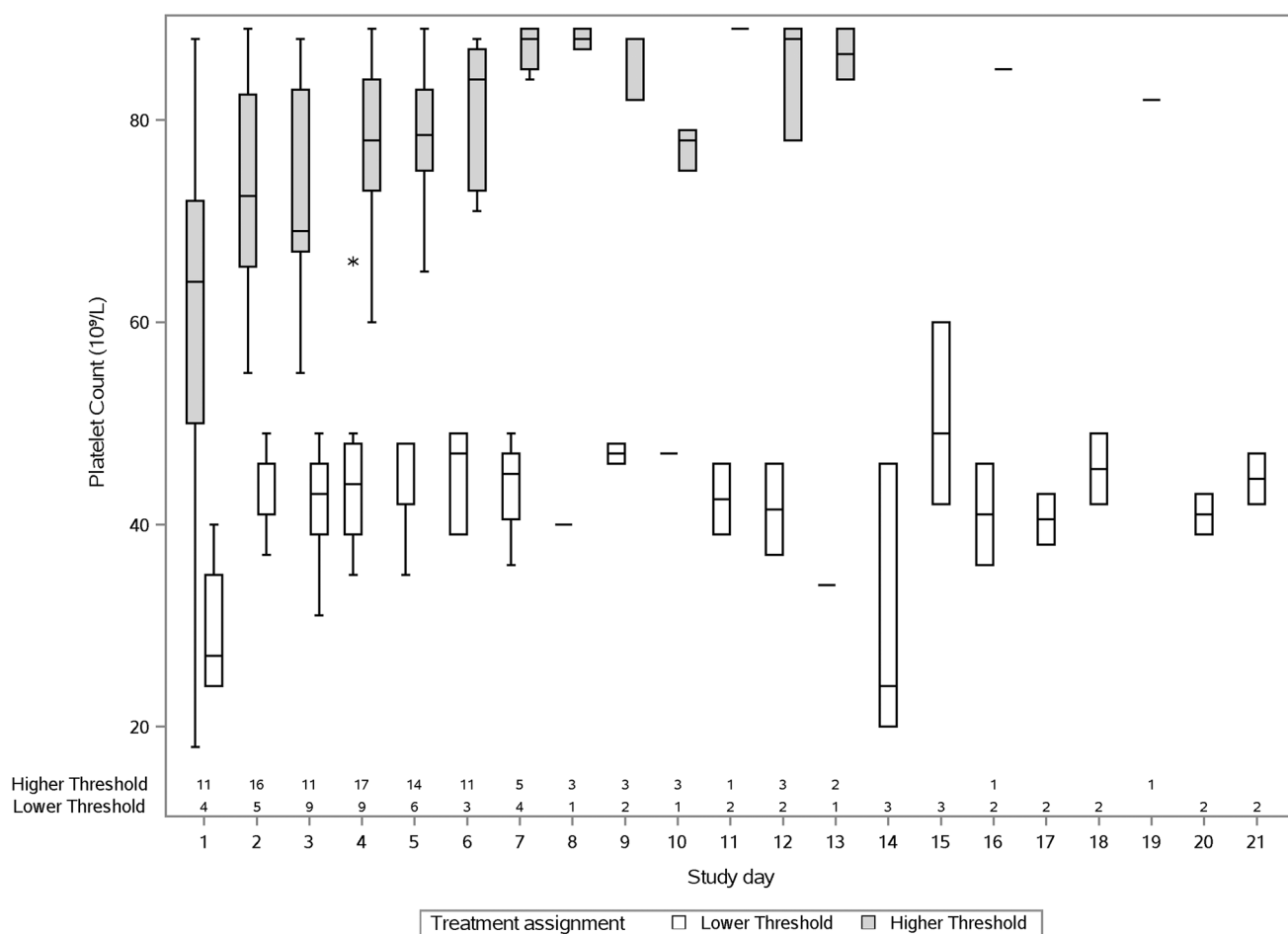


Figure 2:
 Boxplot of pre-transfusion platelet count per study day and per arm ($p < 0.001$).
 Summarizes the most recent platelet count immediately prior to each transfusion that occurred outside of temporary suspension periods. Note that one transfusion did not have an eligible pre-transfusion platelet count recorded.

Table 1:

Demographics

Variable	Lower Platelet Transfusion Strategy n=25	Higher Platelet Transfusion Strategy n=25
Age (years)	0.2 (0.0;3.2)	0.1 (0.0;0.8)
Age ≤ 28 days	11/25 (44%)	12/25 (48%)
Sex (male)	10/25 (40%)	12/25 (48%)
Race		
Black or African American	4/22 (18%)	7/17 (41%)
White	18/22 (82%)	9/17 (53%)
Multiracial	0/22 (0%)	1/17 (6%)
Ethnicity		
Hispanic or Latino	3/23 (13%)	8/23 (35%)
Not Hispanic or Latino	20/23 (87%)	15/23 (65%)
Country		
United States of America	24/25 (96%)	23/25 (92%)
Israel	1/25 (4%)	2/25 (8%)
Primary reason for ICU admission		
Acute respiratory failure	13/25 (52%)	13/25 (52%)
Acute cardiac failure	6/25 (24%)	8/25 (32%)
Following cardiopulmonary bypass	4/25 (16%)	2/25 (8%)
Altered mental status	0/25 (0%)	1/25 (4%)
Sepsis/septic shock	1/25 (4%)	0/25 (0%)
Other surgery	1/25 (4%)	1/25 (4%)
PELOD-2 score on day 1	10 (7;13)	7.0 (6;9)
ECPR	1/25 (4%)	2/25 (8%)
ECMO Cannulation; veno-arterial	24/25 (96%)	20/25 (80%)
Time between cannulation and randomization (hours)	17.7 (11.5;22.4)	18.7 (10.9;22.9)
Platelet transfusions before randomization (number of patients)	7/25 (28%)	8/25 (32%)
Number of platelet transfusions before randomization	1.0 (1.0;1.0)	1.0 (1.0;2.0)

Results are presented as median and interquartile range, or number and percentage, as appropriate. ECMO, extracorporeal membrane oxygenation; PELOD-2, Pediatric Logistic Organ Dysfunction 2; ECPR, extracorporeal membrane oxygen cardiopulmonary resuscitation

Table 2:
Treatment characteristics (during intervention period outside of temporary suspensions)

Variable	Lower Platelet Transfusion Strategy n=25	Higher Platelet Transfusion Strategy n=25	p-value
Anticoagulation Strategies			
Initial agent			0.49 ¹
Heparin	24/25 (96%)	23/25 (92%)	
Bivalirudin	0/25 (0%)	2/25 (8%)	
None	1/25 (4%)	0/25 (0%)	
Heparin as initial agent			
Initial bolus dose (IU/kg)	100 (54;100)	100 (50;100)	0.40 ²
Initial infusion rate (IU/kg/hr)	20 (10;20)	20 (15;22)	0.48 ²
Average highest anti-Xa level (units/mL)	0.4 (0.3;0.6)	0.5 (0.4;0.7)	0.17 ²
Average lowest anti-Xa level (units/mL)	0.3 (0.2;0.4)	0.4 (0.3;0.5)	0.09 ²
Bivalirudin as initial agent			
Initial bolus dose (IU/kg)	none	0.1 (0.0;0.1)	
Initial infusion rate (IU/kg/hr)	none	0.2 (0.2;0.3)	
Platelets			
Received ≥ 1 platelet transfusion	11/25 (44%)	17/25 (68%)	0.15 ¹
Time from randomization to first plt tx (hrs)	45.2 (8.6;84.0)	5.7 (2.8;22.3)	0.06 ²
Transfusions per intervention day	0.0 (0.0;0.5)	0.7 (0.0;1.2)	0.11 ²
Transfusion dose (mL/kg/day)	0.0 (0.0;8.4)	7.4 (0.0;16.6)	0.11 ²
Received at least 1 whole blood derived plt tx	1/11 (9%)	1/17 (6%)	1.00 ¹
Cryoprecipitate			
Received ≥ 1 cryoprecipitate transfusion	2/25 (8%)	6/25 (24%)	0.25 ¹
Transfusions per intervention day	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.13 ²
Transfusion dose (mL/kg/day)	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.15 ²
Prothrombin complex concentrate			
Received ≥ 1 PCC transfusion	0/25 (0%)	0/25 (0%)	1.00 ¹
Red blood cells			
Received ≥ 1 red blood cell transfusion	19/25 (76%)	19/25 (76%)	1.00 ¹
Transfusions per intervention day	0.4 (0.1;0.6)	0.3 (0.1;0.7)	0.80 ²
Transfusion dose (mL/kg/day)	4.7 (0.5;9.1)	4.5 (0.5;10.0)	0.83 ²
Plasma			
Received ≥ 1 plasma transfusion	6/25 (24%)	5/25 (20%)	1.00 ¹
Transfusions per intervention day	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.59 ²
Transfusion dose (mL/kg/day)	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.57 ²

Results are presented as median and interquartile range, or number and percentage, as appropriate. PCC, prothrombin complex concentrate.

¹Fisher's exact test and

²Wilcoxon rank-sum test.

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Table 3:
Outcomes

Variable	Lower Platelet Transfusion Strategy n=25	Higher Platelet Transfusion Strategy n=25	p-value
Pre-transfusion platelet count (10^9 cell/L)	43 (39;47)	79 (70;86)	<0.001 ¹
Progression to severe bleeding, progression to severe clotting, or death within 24 hours of end of intervention (primary safety outcome)	6/25 (24%)	5/25 (20%)	1.00 ⁵
Progression to severe bleeding	4/25 (16%)	3/25 (12%)	1.00 ⁵
Progression to severe clotting	1/25 (4%)	1/25 (4%)	1.00 ⁵
Experienced at least one non-serious AE	5/25 (20%)	5/25 (20%)	1.00 ⁵
Experienced at least one SAE	6/25 (24%)	4/25 (16%)	0.73 ⁵
Duration of ECMO (days) ²	6.5 (4.5;8.1)	5.8 (3.8;12.7)	0.83 ⁴
ECMO-free days within 90 days ³	83 (75;85)	84 (47;86)	0.49 ⁴
Length of stay (days) ²	30 (19;47)	39 (23;82)	0.24 ⁴
ICU-free days within 90 days ³	59 (12;72)	29 (0;68)	0.22 ⁴
Death during intervention or within 24 hours of end of intervention	2/25 (8%)	1/25 (4%)	1.00 ⁵
Death at 28 days	3/25 (12%)	4/25 (16%)	1.00 ⁵
Death at 90 days	5/24 (21%)	7/24 (29%)	0.74 ⁵
Pediatric Overall Performance Category at discharge			
Not yet discharged	0/25 (0%)	2/25 (8%)	0.81 ⁴
1: Good overall performance	10/25 (40%)	13/25 (52%)	
2: Mild overall disability	7/25 (28%)	1/25 (4%)	
3: Moderate overall disability	1/25 (4%)	1/25 (4%)	
4: Severe overall disability	2/25 (8%)	0/25 (0%)	
5: Coma or vegetative state	0/25 (0%)	0/25 (0%)	
6: Brain death	5/25 (20%)	8/25 (32%)	
Pediatric Cerebral Performance Category at discharge			0.92 ⁴
Not yet discharged	0/25 (0%)	2/25 (8%)	
1: Normal	12/25 (48%)	13/25 (52%)	
2: Mild disability	7/25 (28%)	1/25 (4%)	
3: Moderate disability	0/25 (0%)	1/25 (4%)	
4: Severe disability	1/25 (4%)	0/25 (0%)	
5: Coma or vegetative state	0/25 (0%)	0/25 (0%)	
6: Brain death	5/25 (20%)	8/25 (32%)	

AE, adverse event; SAE, serious adverse event; ECMO: Extracorporeal Membrane Oxygenation; ICU, intensive care unit.

¹Based on model-adjusted means, rather than a test of the medians;

²Truncated at 90 days, if applicable;

³Regarded as 0 days if participant died on or before day 90;

⁴Wilcoxon rank-sum test; and

⁵Fisher's exact test.

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Table 4:

Feasibility criteria

Criteria	A priori goal	Results from the pilot trial	Achieved or failed
Separation between the higher and lower platelet threshold arms	> 30×10 ⁹	32×10 ⁹	✓
Eligibility rate (patients per site per year)	> 7.9	13.94	✓
Proportion of patients whose parents were approached for consent within 24 hours of cannulation	> 90%	65%	✗
Proportion of approached patients for whom informed consent was obtained	> 50%	63%	✓
Randomization of consented patients	> 66%	100%	✓
Proportion of compliant platelet transfusion actions	> 90%	99%	✓
Proportion of patients with one or more temporary suspensions not due to preparation for decannulation	< 10%	22%	✗
Proportion of patients who withdrew from the study and/or were lost to follow-up	< 6%	12%	✗
Proportion of patients with non-platelet transfusion protocol violations	< 5%	0%	✓
Ability to adjudicate progression to severe bleeding and/or severe clotting (excluding temporary suspensions) based on site-provided data	> 90%	100%	✓