Study Title: Optimal resuscitation in pediatric trauma—an EAST multicenter study

PI/senior researcher: Richard Falcone Jr. MD, MPH

Co-primary investigator: Stephanie Polites MD, MPH; Juan Gurria MD

My multicenter study proposal is Prospective

Outline burden of problem

Resuscitation of adult trauma patients in hemorrhagic shock includes minimizing crystalloid and early transfusion of blood products in balanced ratios based on prospective observational and interventional studies (1); however, the ideal resuscitation practices for children presenting in shock after injury concerning for hemorrhage are unknown. The 10th version of ATLS will continue to recommend pediatric trauma patients receive up to three 20 cc/kg crystalloid boluses, with consideration for blood products after the second bolus however recognizes a movement towards limiting crystalloid and damage control resuscitation in children following the first bolus (2). Adult trauma patients are recommended to receive one fluid bolus, with consideration for immediate transfusion if displaying signs of hemorrhage. While children who receive massive transfusion defined as greater than 40 cc/kg of blood transfusion have mortality in excess of 10%, retrospective evaluation of pediatric trauma patients has shown mixed results with respect to the optimal crystalloid volume and ratio of products (3).

Acker et al. found that high volume crystalloid resuscitation was not associated with increased risk of complications such as ARDS but was associated with greater duration of hospital stay and need for mechanical ventilation (4). Similarly, Department of Defense (DOD) data demonstrated greater ICU duration, ventilator duration, and length of stay in children who received >40 cc/kg of blood if they had received high volume crystalloid (5). In the same study, children who were transfused in balanced ratios of products had increased mortality. Retrospective data to be presented at the 2018 EAST Annual Assembly demonstrates that the chances of needing a transfusion are similar regardless of if two or more fluid boluses are given, suggesting that response to crystalloid plateaus with the second bolus.

In summary, existing retrospective data has not facilitated consensus on the optimal timing and composition of resuscitation in hemorrhaging pediatric trauma patients and there continues to be variability in practice. Additionally, existing retrospective and prospective studies on pediatric resuscitation are centered on a volume-based definition of massive transfusion or activation of a massive transfusion protocol (5, 6). Patients who would have benefited from early transfusion or massive transfusion but received a crystalloid-heavy resuscitation may be missed if they do not meet inclusion criteria of a massive transfusion activation or minimum volume of transfused products. The study proposed here aims to capture pediatric trauma patients presenting in shock at an earlier stage and focus on the initial administration of crystalloid—specifically the optimal volume and timing of transition to blood products.

Specific Aims

Primary Aim

To determine the impact on primary outcomes of crystalloid administration volume and timing prior to blood products in children presenting in shock following trauma,
hypothesizing that decreased use of crystalloid prior to transfusion is associated with improved outcomes.

Secondary Aims

To determine patient factors that predict need for early transfusion of blood productions in pediatric trauma patients presenting in shock.

To relate primary outcomes to ratio of blood products in pediatric trauma patients in shock who are transfused.

To define variability in pediatric trauma fluid and blood resuscitation practices between centers.

Experimental Design/Methods

This is a prospective, observational study. The PI has experience leading a multicenter prospective trauma study to completion and publication and currently participates in several prospective observational studies related to pediatric trauma (7).

Inclusion criteria

Age <18 years

Elevated age adjusted shock index (SIPA) (8)

Shock index = heart rate/systolic blood pressure on arrival

Ages ≤6 years elevated SIPA >1.2

Ages 7-12 elevated SIPA >1.0

Ages ≥13 elevated SIPA >0.9

Trauma team activation

Transported directly from scene

Exclusion criteria

>20% BSA burn

Burn/inhalation only injury

Asphyxiation injury

Non-EMS transport (personal vehicle, police)

Therapeutic interventions

Prospective observational study only. Patients will be managed according to surgeon’s discretion.

Outcomes Measures
**Primary Outcome**

Mortality, return to normal shock index

**Secondary Outcomes**

Total blood products in 24 hours
Total blood products during admission
ICU length of stay
Ventilator days
In-hospital complications (ARF, ALI/ARDS, CAUTI, HAP, BSI, Sepsis, DVT/PE)
Total length of stay

**Variables to be collected and analyzed (see Data Collection Form for more details)**

Date and time of arrival
Demographics (age, sex, race)
Weight
Injury mechanism and type
Mode of transport
Time between injury and arrival
Field/transport vital signs
Pre-hospital fluids, blood products
  - Crystalloid
  - RBCs
  - Platelets
  - Plasma
  - Cryo
  - Other product (write in)
TxA (yes/no)
Arrival vital signs
Initial labs
  - Hemoglobin
  - Platelets
  - Creatinine
INR
TEG/ROTEM obtained (yes/no)
  If yes, results
ED infusions (type- crystalloid/blood products, amount in cc, start time)
ED vitals every 15 minutes (stop at 2 hours)
ED disposition (OR, ICU, floor) with time
Vitals and fluid totals on new unit/OR/IR arrival
OR/IR procedures with date and time
After ED disposition, vitals, labs, fluid totals at 1, 3, 6, 12, and 24 hours
  Specify time of return to normal SIPA and normal coagulation parameters if abnormal
Ventilator days, ICU days, length of stay
Complications and date of occurrence: acute renal failure (ARF), acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), catheter associated urinary tract infection (CAUTI), hospital acquired pneumonia (HAP), blood stream infection (BSI), sepsis, deep venous thrombosis (DVT)/pulmonary embolism (PE)
Alive vs deceased at discharge
GCS at discharge (if <15 initially)
Retrospective: ISS, AIS scores, comorbidities, diagnoses, procedures

Data Collection and Statistical Analysis

A data collection form will be started for each patient meeting inclusion criteria upon their arrival or within 24 hours. Data collection forms will be turned in to study coordinators/staff/participating physicians who will review the previous 24 hours’ patients and complete the data collection form up to the section requiring retrospective review following discharge. This information is expected to be present in patients’ medical records though participating institutions may choose to collect it real-time. This information will be abstracted from the trauma registry. All procedures are observational and involve recording of data, there is no intervention associated with this study. These data points will be used to achieve the aims and analysis plans below.

This will be a multicenter study with CCHMC as the coordinating center. Collaborating centers will be identified in the future and this protocol will be amended accordingly. All institutions will obtain their own IRB approval. A Redcap standardized data collection tool will be created for deposition of de-identified data on each patient. Each patient will receive a unique study number as will each participating institution. Data collections sheets can be submitted to the coordinating institution for data entry into Redcap or participating institutions may enter data directly into Redcap.
Aim 1: To determine the impact on primary outcomes of crystalloid administration volume and timing prior to blood products in children presenting in shock following trauma.

The primary outcomes of this study are mortality and return to normal age-adjusted shock index. Secondary outcomes are intensive care days, ventilator days, complications, total blood products, and hospital length of stay in days. Weight based volumes of crystalloid and blood products at various time points will be determined and associated with the aforementioned outcomes using univariate and multivariable analyses. Cox logistic regression analysis will be used to evaluate the relationship with time-dependent, categorical outcomes such as 24 hour, 7 day, and 30 day survival. Patients discharged prior to the mortality cut off will be right-censored as surviving. Adjusted survival curves will be generated to determine the impact of crystalloid volume on time to return of normal age adjusted shock index. Stratified analysis by age group may be performed. Since this is an observational study, adjustments will be made to account for clustering of patients at individual centers.

Aim 2: To determine patient factors that predict need for early transfusion of blood products in pediatric trauma patients presenting in shock.

Additional univariate and time-dependent multivariable analyses will be performed with blood transfusion as the outcome to identify factors independently associated with transfusion.

Aim 3: To relate primary outcomes to ratio of blood products in pediatric trauma patients in shock who are transfused.

Among the subset of patients who are transfused, multivariable logistic regression will be used to determine the impact of blood product ratio on primary outcomes described above. Time-dependent analysis will be performed for the outcome of mortality.

Aim 4: To define variability in pediatric trauma fluid and blood resuscitation practices between centers.

A unique center ID will be assigned to each participating center so that patients from a single center can be identified. Differences in baseline characteristics and injury severity by center will be determined as well as variability in crystalloid volume and time to transfusion among those patients who were transfused.

475 patients are needed to detect a decrease in mortality between the published approximately 15% for children who require transfusion and 7.5%. Based on adult studies, this is the short-term survival benefit associated with optimal resuscitation (1). This sample size is a conservative estimate and will also ensure power to detect a difference in intensive care length of stay and hospital length of stay.

Consent Procedures

This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers. Only authorized study personnel will have access to the secure Redcap database. Datasheets will be kept in a locked file cabinet that only authorized study personnel may access.

Risk/Benefit Analysis
Institutional Review Board approval will be obtained at all institutions and data use agreements will be obtained when required. This is a prospective observational study designed to record data on patients managed according to institutional patient management protocols. There is no intervention conducted in this trial therefore the greatest risk involved in participating is a breach of confidentiality. This risk will be minimized by de-identification of all patient information and storing all study data on a secure password protected server (Redcap) that is only accessible by authorized study personnel.

References