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Early coagulopathy and metabolic acidosis predict transfusion of packed red blood cells in pediatric trauma patients

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ABSTRACT

Background: Severely injured pediatric trauma patients often present to hospital with early coagulopathy and metabolic acidosis. These derangements are associated with poor outcomes, but it is unclear to what degree they predict transfusion of packed red blood cells (pRBC).

Methods: We retrospectively identified pediatric trauma patients from a level 1 trauma center from 2006 to 2013. Inclusion criteria were age less than 18 years, Injury Severity Score greater than 12, and pRBC transfusion within 24 h of admission.

Results: We identified 96 pediatric trauma patients who underwent pRBC transfusion within 24 h of presentation to hospital. On admission, 43% of these patients had one or more signs of coagulopathy, and 81% had metabolic acidosis. Size of pRBC transfusion in the first 24 h ranged from 3 to 177 mL/kg (mean 29 mL/kg), and nineteen patients (20%) underwent massive transfusion (>40 ml/kg in 24 h). Univariate analysis indicated that size of pRBC transfusion was associated with initial base excess ($r = 0.46$), international normalized ratio ($r = 0.35$), partial thromboplastin time ($r = 0.41$), fibrinogen ($r = 0.46$), and BIG score (Base deficit, INR, Glasgow Coma Scale (GCS), $r = 0.36$). Platelet count, age, GCS, and direct versus referred presentation were not predictive. Multivariable linear regression confirmed that coagulopathy and metabolic acidosis remained predictive after adjusting for direct versus referred presentation ($R^2 = 0.30$).

Conclusions: Early coagulopathy and metabolic acidosis predict size of pRBC transfusion among pediatric trauma patients. Further research is needed to develop massive transfusion protocols and guidelines for activation.

Injury is the leading cause of death among children in developed countries [1,2]. While children are classically thought to have more physiologic reserve than adults, many severely injured pediatric trauma patients require transfusion of packed red blood cells (pRBC) and other blood products within 24 h of admission [3]. During the course of resuscitation, some patients may reach the threshold of massive transfusion. In adults, this is defined as 10 units of pRBC (i.e., one blood volume) in a 24-h period [4–6]. In children, *massive transfusion* is defined as greater than 40 mL/kg of pRBC or 70 mL/kg of total blood products [3,7,8]. In both the adult and pediatric trauma populations, the incidence of massive transfusion in non-war settings ranges from 3 to 8% [9–12]. These patients have severe injuries and worse outcomes compared to those who do not require massive transfusion [13].

The fact that trauma and tissue damage can induce coagulopathy was first observed in the head-injured population [14,15]. Emerging evidence suggests that even patients with head-sparing injuries have tissue destruction that may lead to the release of factors that generate a clinically significant coagulopathy. When present, this phenomenon is a marker of injury severity and is associated with increased mortality [16]. Early coagulopathy can be worsened with overly aggressive crystalloid resuscitation, leading to dilution of clotting factors [17]. Recognition of these findings, and the resuscitative success of using whole blood in war zone trauma [18], have led to the concept of balanced resuscitation. With this strategy, plasma, platelets and cryoprecipitate are used early on and in parallel with pRBC transfusion [19–21].

Recognition of the coagulopathy of trauma, the risks of overly aggressive crystalloid resuscitation, and the concept of massive transfusion have lead to the development of massive transfusion protocols in adults [22,23]. These protocols facilitate early transfusion of blood products in a balanced manner to replenish red blood cell loss, correct early coagulopathy, and prevent further dilution of clotting factors. The implementation of these protocols in the adult population has been shown to decrease mortality [24,25]. This has generated significant interest among pediatric clinicians and researchers to develop protocols appropriate for children [7,26,27].

While rapid transfusion can be life-saving, large volume transfusion is not without risk. A dose-dependent relationship between the amount of

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product transfused and infection and mortality has been demonstrated [3,28–30]. Hypothermia, acidosis, electrolyte abnormalities, citrate toxicity, and transfusion-associated lung injury have all been described secondary to massive transfusion [31]. As a result, clinicians need to carefully select pediatric trauma patients in need of aggressive transfusion. This challenge is exacerbated by the fact that the concept of massive transfusion is often applied retrospectively, after a certain volume of blood products has been administered. This does not help clinicians prospectively identify which patients would benefit from an aggressive, balanced transfusion strategy, or determine when to activate of massive transfusion protocols.

The "BIG Score" has been shown to predict poor clinical outcomes in pediatric trauma patients. This scoring system is based on observation from military databases that initial base excess, International Normalized Ratio (INR), and Glasgow Coma Scale (GCS) are independent predictors of mortality among pediatric trauma patients [32]. In civilian settings, early coagulopathy has also been shown to be an independent predictor of mortality [33,34]. Thus, while the association between early coagulopathy and mortality is well-recognized, it is unclear to what degree these physiologic derangements predict size of pRBC transfusion.

The purpose of this study was to determine to what degree early coagulopathy, metabolic acidosis, and GCS predict the amount of pRBC used in severely injured pediatric trauma patients. Our center is a level 1 pediatric and adult trauma center that treats approximately 80 severely-injured pediatric trauma patients per year, but does not have a massive transfusion protocol in place for children. In the current study, we focused specifically on patients who received pRBC in the first 24 h after admission and attempted to predict which patients went on to receive large-volume transfusions.

1. Patients and methods

1.1. Study design

This study received approval from the Research Ethics Board at Western University. All pediatric trauma patients were identified through the trauma database at Children's Hospital, London Health Sciences Centre. Inclusion criteria were age less than 18 years, Injury Severity Score (ISS) greater than 12, and pRBC transfusion within 24 h of admission.

1.2. Data collection

Data retrieved from the trauma database included age, gender, weight, presentation, mechanism of injury, mortality, and GCS. Data on use of pRBC, fresh frozen plasma (FFP), platelets, cryoprecipitate, and recombinant Factor VIIa was obtained from the blood bank at our center. We used this information to calculate the amount of pRBC transfused in the first 24 h post-admission (reported in ml/kg).

Each participant's electronic medical record was reviewed to determine initial INR, partial thromboplastin time (PTT), platelet count, fibrinogen, and base excess. In all cases, we used the first available value after presentation to our center. In cases where certain bloodwork could not be obtained immediately, particularly in younger children with poor venous access, we used the first available value up until 4 h after initial presentation. Missing data were not imputed.

1.3. Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) Version 20. Descriptive statistics included mean, standard deviation (SD), median, range, and frequency. Differences between groups was analyzed with one-way analysis of variance (ANOVA) for continuous data and the chi-squared test for dichotomous values.

Univariate analyses for predictors of size of pRBC transfusion were explored using Pearson's correlation coefficients. Following this, we developed a multivariable linear regression model using size of pRBC transfusion (in ml/kg) as the dependent variable. We reported standardized beta coefficients for each independent variable (i.e., baseline predictor), as well as the overall R^2 value for the multivariable model. Testing of the multivariable regression model included graphing residuals to assess for normality, and assessing the variance inflation factor and tolerance for each covariate to rule out collinearity.

2. Results

2.1. Patient characteristics

We identified 96 severely injured pediatric trauma patients who received a transfusion of pRBC within 24 h of presentation to our center (Table 1). These patients were captured more than an eight-year period, between January 1, 2006 and December 31, 2013. Mean age was 9.5 years (standard deviation 7.0 years) and 64% were male.

Patterns of injury were predominantly blunt (96%) with few cases of penetrating injuries (4%). Mechanisms of injury included motor vehicle collisions involving passengers or pedestrians (41%); non-accidental trauma to infants (15%); all-terrain vehicle (ATV), dirt bike, and snowmobiling injuries (11%); farming injuries (8%); assault (6%); biking (6%); falls (6%); sports injuries (5%); and lawnmower injuries (2%).

Forty-eight percent of patients were intubated on arrival. Initial GCS at our center was 3–8 for 56% of patients, 9–12 for 6%, and 13–15 for 38%. ISS ranged from 13 to 75 with a mean of 29.1 (SD = 11.6).

Table 1
Baseline characteristics of severely injured pediatric trauma patients who required a transfusion of packed red blood cells within 24 h of admission.

Characteristic	*Direct presentation*	*Transferred from another hospital*	*p*	*All patients*
n (%)	34 (35%)	62 (65%)	–	96 (100%)
Age, mean (SD)	11.0 (6.9) yrs	8.6 (6.9) yrs	0.11	9.5 (7.0) yrs
Median	13.4 yrs	6.8 yrs		11.2 yrs
Range	1 mo–17.9 yrs	1 mo–17.9 yrs		1 mo–17.9 yrs
Male	16 (47%)	45 (73%)	0.01	61 (64%)
Female	18 (53%)	17 (27%)		35 (36%)
Blunt	30 (88%)	62 (100%)	0.03	92 (96%)
Penetrating	4 (12%)	0 (0%)		4 (4%)
Known time of injury, n (%)	23/34 (68%)	46/62 (74%)		69/96 (72%)
Time to trauma center, mean (SD)	1:10 (1:09)	3:42 (1:41)	<0.001	2:51 (1:56)
Initial Glasgow Coma Scale				
3–8	12 (35%)	41 (66%)	0.02	56 (55%)
9–12	3 (9%)	3 (5%)		3 (6%)
13–15	19 (56%)	18 (29%)		37 (39%)
Injury Severity Score, mean (SD)	29.4 (13.1)	29.0 (10.8)	0.90	29.1 (11.6)
Range	16–75	13–50		13–75

SD = standard deviation.