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Elevated international normalized ratio is correlated with large volume transfusion in pediatric trauma patients

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ABSTRACT

Background: Pediatric trauma patients may benefit from a balanced transfusion strategy, however, determining when to activate massive transfusion protocols remains uncertain. The purpose of this study was to explore whether certain scoring systems can predict the need for large volume transfusion.

Methods: We conducted a retrospective review of pediatric trauma patients who presented to our center and required a transfusion of packed red blood cells. Baseline laboratory and clinical data were used to calculate Trauma Associated Severe Hemorrhage (TASH) score and a previously reported composite of acidosis and coagulopathy.

Results: We identified 518 pediatric trauma patients who presented to our center between January 1, 2013 and December 31, 2018. These patients were less than 18 years of age (mean 9.6 years) and had an injury severity score ranging from 1 to 50 (mean 11.3). Forty-three patients (8.3%) received a transfusion within 24 hours of presentation, ranging from 4 to 139 mL/kg of packed red blood cells (mean 23.1 mL/kg). Transfusion volume was associated with acidosis and coagulopathy scores ($r = 0.37$, $p = 0.033$) and international normalized ratio (INR) ($r = 0.34$, $p = 0.03$) but not TASH ($p = 0.72$). Patients with INR$\geq$1.3 received a higher mean volume of packed red cells compared to those with normal values (34 versus 18 mL/kg, $p = 0.046$).

Conclusion: Pediatric trauma patients who undergo transfusion of packed red blood cells are likely to require large volume transfusion if their baseline INR is $\geq$1.3. These patients may benefit from a balanced transfusion strategy, such as utilization of massive transfusion protocols or whole blood.

1. Introduction

Trauma is the leading cause of death in children, with most fatalities caused by brain injury or hemorrhage [1,2]. The presence of ongoing bleeding can lead to metabolic acidosis and coagulopathy, which is associated with increased morbidity and mortality [2–6]. Children who require a transfusion within the first 24 hours of presentation to the emergency department are more likely to have coagulopathy and abnormal serum lactate [7]. Similarly, abnormal base deficit is an independent predictor of transfusion requirements and mortality among pediatric trauma patients [8].

Coagulopathy may develop early in pediatric trauma patients, possibly due to the degree of tissue injury, shock, hypothermia, acidosis, platelet dysfunction, and excess fibrinolysis [4,9]. The iatrogenic worsening of coagulopathy (due to excessive crystalloid use and/or development of hypothermia) has led to changes in patient management [4,10]. In an effort to improve patient outcomes, there have been multiple studies exploring the optimal use of blood products and the development of transfusion strategies [6,10,11,12]. These include the use of massive transfusion protocols, which incorporate the use of packed red blood cells (pRBC), platelets, and fresh frozen plasma, rather than pRBC alone [13,14,15]. These protocols must be used judiciously, however, given the morbidity associated with the use of any blood products, including volume overload, lung injury, and infection [16,17].

One of the challenges of implementing a massive transfusion protocol for pediatric trauma patients is determining when it should be activated. Simply put, when should clinicians shift from using pRBC alone to a balanced strategy, which incorporates the administration of pRBC, platelets, and plasma? Scoring systems, such as the Trauma-Associated Severe Hemorrhage (TASH) score,

Abbreviations: PACS, Pediatric Acidosis and Coagulopathy Score; pRBC, Packed Red Blood Cells; TASH, Trauma Associated Hemorrhage Score.

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may assist with decision-making. This measure was developed using retrospective data from an adult trauma database, but has also been applied to pediatric trauma patients [18,19]. Unfortunately, the TASH score relies on clinical variables that may not be easily obtained on initial presentation, such as the presence of intra-abdominal fluid and complex long bone or pelvic fractures.

An alternative scoring system was reported by Smith et al. in 2016 [20]. In this retrospective study, the authors conducted an analysis of 96 pediatric trauma patients who received a transfusion of pRBC within 24 hours of presentation to hospital. They found that baseline laboratory markers of metabolic acidosis and coagulopathy were predictive of the volume of pRBC transfusion (in mL/kg). The results were used to create a simple scoring system based on five laboratory values: base excess (0-2 points); platelet count (0-1 points); international normalized ratio (INR) (0-1 points); partial thromboplastin time (PTT) (0-1 points); and fibrinogen (0-1 points) [20]. The values are added, resulting in a total score ranging from 0 to 6 points. Missing or unavailable data are coded 0 by default. In the retrospective analysis, the 6-point model had an R^2 value of 0.29 ($r = 0.54$) for predicting the volume of pRBC (in mL/kg). The authors concluded that this scoring system served as a "proof of concept" but required further validation before being used in a clinical setting.

The purpose of this study was to assess the predictive value of the TASH score and scoring system developed by Smith et al., which we will refer to as the Pediatric Acidosis and Coagulopathy Score (PACS). We used retrospective data to determine how well the TASH and PACS scores were able to predict the size of transfusion of pRBC (in mL/kg). Our hope was that this analysis will provide clinicians with additional guidance about when to transfuse pediatric trauma patients using a balanced strategy, such as a massive transfusion protocol. We hypothesized that pediatric trauma patients with higher TASH and PACS scores at baseline were more likely to receive large volume transfusion of pRBC.

2. Methods

2.1. Study design

This study was a retrospective review of pediatric trauma patients who received a transfusion of pRBC within 24 hours of presentation to our institution. Participants were identified from a pre-existing database of pediatric trauma patients who presented to either McMaster Children's Hospital (which is a Level 1 Pediatric Trauma Center) or Hamilton General Hospital (which is a Level 1 Adult Trauma Center) between January 1, 2013 and December 31, 2018. Patients from this database were included if they were less than 18 years old and presented to the emergency department following a traumatic injury. Outcomes included volume of pRBC transfusion and mortality. This study was approved by the Hamilton Integrated Research Ethics Board.

2.2. Data Collection

Electronic medical records were reviewed to obtain demographic and clinical data, including age, gender, weight, time of injury, mechanism of injury, injury severity score, and regional abbreviated injury scores. Data to calculate the TASH and PACS scores were also abstracted. These variables included initial heart rate, systolic blood pressure, base excess, hemoglobin, platelet count, PTT, INR, fibrinogen. Finally, we collected the volume of all blood products administered within the first 24 hours of presentation.

Data were de-identified and stored in a secure, online database developed using Research Electronic Data Capture (REDCap) software [21,22].

2.3. Statistical analysis

Descriptive statistics were used to report the baseline characteristics of all participants. These included mean with standard deviation or median with interquartile range (IQR) for continuous data and counts with percentages for categorical variables. All transfused blood products were converted to volume per body weight (i.e., mL/kg). Baseline clinical and laboratory data were used to calculate the TASH and PACS scores. Associations between ordinal baseline variables (e.g., PACS score) and outcomes (e.g. transfusion volume of pRBC) were assessed using Spearman's rank correlation coefficient. A p-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Package Version 25.

3. Results

3.1. Participants

We identified 518 pediatric trauma patients who were treated at our institutions. The majority were male (328/518, 63%) with a mean age of 9.6 (SD=5.4) years. Median Injury Severity Score (ISS) was 10 (IQR 2-17) and the Trauma Team was activated for 420 (81%) participants. Median length of stay in hospital was 2 (IQR 1-6) days. Only two patients (aged 2 and 15 years) were initially treated at our adult trauma centre (Hamilton General Hospital) and eventually transferred to McMaster Children's Hospital for definitive management. Neither of these patients received a transfusion of PRBCs. Participant characteristics are shown in Table 1.

3.2. Transfusion data

Forty-three of 518 participants (8.3%) received a transfusion of pRBC within 24 hours of presenting to hospital. Absolute volume transfused ranged from 100 to 5000 mL. Weight-based volume of pRBC transfused ranged from 4 to 139 mL/kg with a mean of 23.1 (SD=22.6) mL/kg. Compared to participants who did not receive a transfusion of pRBC, transfused participants were more likely to be male (79.1% versus 61.9%, $p = 0.025$); have a higher mean ISS (21.8 versus 10.3, $p < 0.001$), and experience increased length of stay in hospital (22.9 versus 5.6 days, $p < 0.001$). There were no significant differences between groups in terms of mean age (8.7 versus 9.7 years, $p = 0.246$) and frequency of trauma team activation (90.1% versus 80.2%, $p = 0.093$).

Most patients received a transfusion in the operating room (51.2%), followed by the ward or intensive care unit (32.6%), and the emergency room (30.2%). Note that percentages do not add up to 100% since thirteen patients received PRBCs in multiple locations. Ten patients (23.3%) received a transfusion at a peripheral hospital emergency department with an average of 7 mL/kg (range 4-12.5 mL/kg).

Within our study population, fifteen patients received tranexamic acid (TXA), which is a common adjunct to transfusion of blood products. Eight received a bolus dose prior to arrival and seven were given a bolus at our centre. Two patients received TXA infusions in addition to the bolus dosing. Six of the patients who received TXA did not receive a transfusion.

3.3. Trauma-associated severe hemorrhage score

The mean TASH score for the entire cohort was 4.4 (SD=3.5). The mean score was higher among those who received a transfusion of pRBC compared to those who did not (9.8 versus 4.4, $p < 0.001$). Among participants who were transfused, however, there was no statistically significant association between the TASH score and the volume of pRBC transfusion ($p = 0.72$) (Fig. 1).

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Table 1
Characteristics of pediatric trauma patients.

Baseline characteristic	*Total (n = 518)*	*No pRBC transfusion (n = 475)*	*pRBC transfusion (n = 43)*	*p-value*
Age, mean (SD)	9.6 (5.4) years	9.7 (5.5) years	8.7 (5.0) years	0.246[1]
Gender, n (%)				
Male	328 (63.3%)	294 (61.9%)	34 (79.1%)	0.025[2]
Female	190 (36.7%)	181 (38.1%)	9 (20.9%)	
Weight, mean (SD)	40.4 (24.0) kg	40.7 (24.2) kg	36.5 (22.4) kg	0.244[1]
Injury Severity Score, mean (SD)	11.3 (9.2)	10.3 (8.5)	21.8 (10.4)	<0.001[1]
Trauma team activation, n (%)	420 (81.0%)	381 (80.2%)	39 (90.1%)	0.093[2]
Length of stay, mean (SD)	7.3 (15.5) days	5.6 (13.2) days	22.9 (24.8) days	<0.001[1]

SD = standard deviation.
[1] independent samples t-test.
[2] chi-squared test.

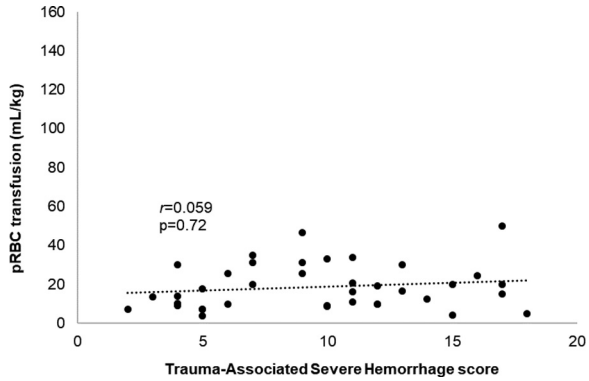

Fig. 1. Scatterplot of packed red blood cell (pRBC) transfusion volume and Trauma-Associated Severe Trauma (TASH) score.

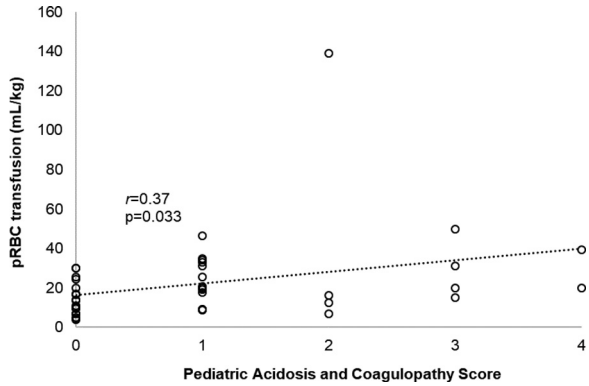

Fig. 2. Scatterplot of packed red blood cell (pRBC) transfusion volume and Pediatric Acidosis and Coagulopathy Score (PACS).

3.4. Pediatrics acidosis and coagulopathy score

The mean PACS for the entire cohort was 0.22 (SD=0.70). Like the TASH score, mean PACS was higher among those who received a transfusion compared to those who did not (0.98 versus 0.27, $p = 0.004$). Unlike the TASH score, however, PACS was positively associated with total transfusion volume among participants who were transfused pRBC within the first 24 hours of presentation to hospital, as seen in Fig. 2 ($r = 0.37$, $p = 0.033$).

3.5. International normalized ratio

Secondary analysis of the components of the TASH and PACS scoring systems identified a positive linear correlation between INR and transfusion volumes ($r = 0.34$, $p = 0.03$). Further analysis showed that participants with INR greater than or equal to 1.3 received a larger pRBC transfusion (mean 34 versus 18 mL/kg, $p = 0.046$) (Fig. 3).

4. Discussion

This study explored the predictive value of the TASH and PACS scoring systems among pediatric trauma patients. Interestingly, baseline TASH score predicted the need for any transfusion of pRBC but was not associated with total transfusion volume. Thus, in theory, a high TASH score might suggest the need for a transfusion but may not predict which pediatric trauma patients need a large volume transfusion and are more likely to benefit from a balanced transfusion strategy, such as a massive transfusion protocol.

The PACS scoring system, however, was moderately associated with total transfusion volume among patients who received any transfusion of pRBC within 24 hours of presentation to hospital. Unlike the TASH score, a high baseline PACS would suggest the need to shift from transfusing pRBC alone to a more balanced strategy. Further analysis indicated that baseline INR alone is almost as predictive as PACS. Indeed, participants with a baseline INR≥1.3 had a mean pRBC transfusion volume (in mL/kg) that was almost twice as high compared to those with values in the normal range (34 versus 18 mL/kg).

The findings from the current study are similar to those reported by Smith et al. [20]. The predictive value of INR alone was almost identical in both studies ($r = 0.34$ versus 0.35). The predictive value of the PACS scoring system was higher in the study by Smith et al. ($r = 0.54$ versus $r = 0.37$). This may have been due to the lower statistical power in the current study with a sample of only 43 participants who were transfused pRBC compared to 96 in Smith et al. The other possibility is that the PACS scoring system was more predictive in the “development cohort” (by Smith et al.) compared to this “validation cohort” (i.e., data from the current study). Whatever the case, these two studies suggest that baseline metabolic acidosis and coagulopathy predict the need for large volume transfusion in pediatric trauma patients.

The use of INR as a transfusion trigger has also been reported in adult trauma patient populations. A study by Callcut et al. using data from the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study showed that an INR>1.5 resulted in the greatest volume of pRBC transfusion and had the highest likelihood of requiring a massive transfusion [23]. A cut-off of INR≥1.3 was associated with a higher incidence of massive transfusion in a study of adolescent and adult trauma patients greater than 12 years old [24].

The use of blood products, especially as prescribed by a massive transfusion protocol, is resource intensive and associated with a variety of possible complications. In the trauma bay, clinicians can find themselves torn between the need to not overuse blood products and not delaying the initiation of a balanced transfusion strategy. Furthermore, these decisions must be made in a chaotic

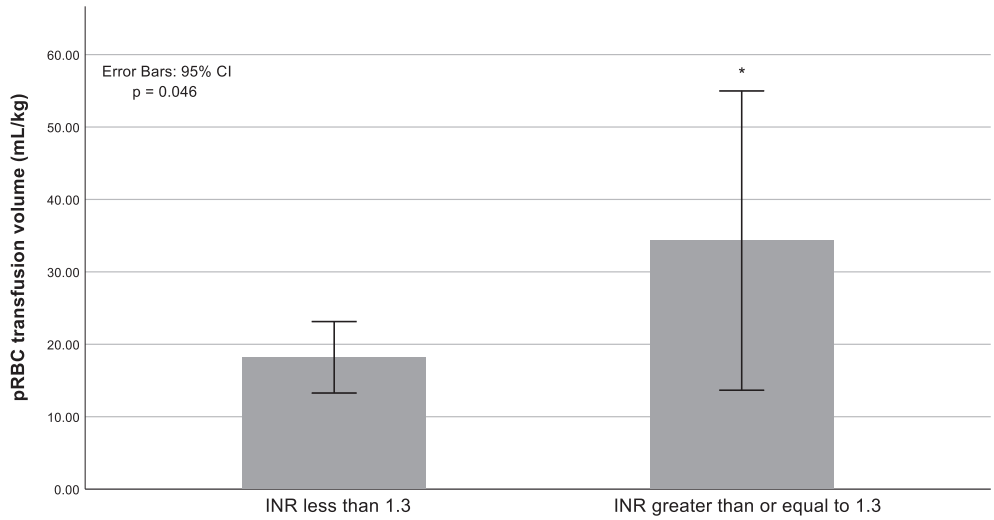

Fig. 3. Bar graph of average packed red blood cell (pRBC) transfusion by INR group.

and fast-paced environment. To deal with this issue, some centers have implemented massive transfusion protocols. These clinical pathways must be based on sound evidence and be feasible to implement in real-time. Scoring systems that have complex formulas or involve data that are not immediately available cannot be easily used in the pediatric trauma bay. The current study affirms that baseline acidosis and coagulopathy, and even simply an INR$\geq$1.3, should suggest to the pediatric trauma team leader to consider activating a massive transfusion protocol and/or using a balanced transfusion strategy.

The obvious drawback of the basing of decisions about transfusion strategy on laboratory values is that the necessary bloodwork cannot always be easily obtained. This is particularly important in younger pediatric trauma patients, in whom obtaining bloodwork and even intravenous access can be a significant challenge. When bloodwork is obtained, the results may not be available in a timely fashion. Thus, guidelines around the activation of massive transfusion protocol need to be specific to the resources of individual centers.

Some institutions have taken a different approach to the transfusion of pediatric trauma patients through the use of the thromboelastography (TEG). These devices create a coagulopathy profile and facilitate a "goal-directed" approach to decisions around the use of blood products [25,26]. A massive transfusion protocol, however, often involves an "empiric" strategy that does not necessarily incorporate results from TEG. Further research is needed to determine which strategy is superior in pediatric trauma patients. For centers that do not have access to TEG, using a balanced transfusion strategy remains a reasonable option.

TXA is one of the adjuncts that has been studied alongside balanced transfusion strategies and MTPs. It was shown to be effective in reducing all-cause mortality and death from hemorrhage in adult trauma patients [27]. For pediatric patients, most research on the use of TXA has centred on elective surgeries that historically resulted in significant blood loss (e.g. cardiac, craniofacial, and spinal procedures) [28, 29] and combat trauma patients [30]. Despite its proven benefits in reducing mortality, particularly from hemorrhage, TXA was not used frequently or consistently in our study population. The previously studied benefits of TXA indicate that further research should examine its role in pediatric MTPs.

This study has several limitations. First, this was retrospective chart review and data collection was limited to what was documented in each patient's electronic medical records. Due to the variation in patient work-up and management, some markers of metabolic acidosis and coagulopathy were not consistently obtained. Second, the relatively small sample size of pediatric trauma patients who received a transfusion of pRBC threaten the validity and generalizability of our findings. For example, a larger sample size may reveal that the PACS score predicts both the need for transfusion (i.e., yes or no) and the eventual size of pRBC transfusion (i.e., in mL/kg). These limitations can be addressed in the future through robustly designed, multicenter studies.

In conclusion, pediatric trauma patients who receive blood products are more likely to require large volume transfusion if they have a high PACS score or INR$\geq$1.3. TASH score appears to differentiate patients who require any transfusion of pRBC compared to those who do not, but may not be predictive of the transfusion volume. Our findings also suggest that an elevated INR could be used as indication to activate a massive transfusion protocol in pediatric trauma patients. Future studies are needed to confirm these preliminary findings and determine whether clinicians should rely on a goal-directed strategy, such as the use of TEG, or an empiric approach, as prescribed by a massive transfusion protocol.

Previous communication

None.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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