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Hypofibrinogenemia following injury in 186 children and adolescents: identification of the phenotype, current outcomes, and potential for intervention

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ABSTRACT

Objectives Recent studies evaluating fibrinogen replacement in trauma, along with newly available fibrinogen-based products, has led to an increase in debate on where products such as cryoprecipitate belong in our resuscitation strategies. We set out to define the phenotype and outcomes of those with hypofibrinogenemia and evaluate whether fibrinogen replacement should have a role in the initial administration of massive transfusion.

Methods All patients <18 years of age presenting to our trauma center 11/17–4/21 were reviewed. We then evaluated all patients who received emergency-release and massive transfusion protocol (MTP) products. Patients were defined as hypofibrinogenemic (HYPOFIB) if admission fibrinogen <150 or rapid thrombelastography (r-TEG) angle <60 degrees. Our analysis sought to define risk factors for presenting with HYPOFIB, the impact on outcomes, and whether early replacement improved mortality.

Results 4169 patients were entered into the trauma registry, with 926 level 1 trauma activations, of which 186 patients received emergency-release blood products during this time; 1%, 3%, and 10% were HYPOFIB, respectively. Of the 186 patients of interest, 18 were HYPOFIB and 168 were non-HYPOFIB. The HYPOFIB patients were significantly younger, had lower field and arrival Glasgow Coma Scale, had higher head Abbreviated Injury Scale, arrived with worse global coagulopathy, and died from brain injury. Non-HYPOFIB patients were more likely to have (+)focused assessment for the sonography of trauma on arrival, sustained severe abdominal injuries, and die from hemorrhage. 12% of patients who received early cryoprecipitate (0–2 hours) had higher mortality by univariate analysis (55% vs 31%, p=0.045), but no difference on multivariate analysis (OR 0.36, 95% CI 0.07 to 1.81, p=0.221). Those receiving early cryoprecipitate who survived after pediatric intensive care unit (PICU) admission had lower PICU fibrinogen and r-TEG alpha-angle values.

Conclusion In pediatric trauma, patients with hypofibrinogenemia on admission are most likely younger and to have sustained severe brain injury, with an associated mortality of over 80%. Given the absence of bleeding-related deaths in HYPOFIB patients, this study does not provide evidence for the empiric use of cryoprecipitate in the initial administration of a massive transfusion protocol.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hypofibrinogenemia has been associated with increased mortality in the acutely injured adult patient, although data are limited in the pediatric patient population.
⇒ Our goal was to determine the phenotype and outcomes of the acutely injured pediatric patient with hypofibrinogenemia and whether empiric attempts at correcting this pathology has a potential role in improving outcomes.

WHAT THIS STUDY ADDS

⇒ Pediatric patients with hypofibrinogenemia had increased mortality and were far more likely to die of traumatic brain injury than their counterparts with normal fibrinogen.
⇒ In fact, no patients with hypofibrinogenemia died of hemorrhage in our study, which indicates empiric administration of fibrin-rich products would be unlikely to improve their outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study indicates that patients with hypofibrinogenemia related to trauma do not die of hemorrhage and likely would not benefit from empiric treatment with fibrin-rich products administered with other massive transfusion products.
⇒ This supports keeping with current practice and administering cryoprecipitate as a product that is administered on demand.

Level of Evidence Level III - Therapeutic/Care Management.

BACKGROUND

Although global pediatric mortality rates related to trauma have improved over the past 30 years, hemorrhage remains a leading cause of potentially preventable death in this population.[1–3] Traumatic brain injury is the leading cause of death overall in pediatric trauma patients and progression of traumatic head bleeds can contribute significantly to long-term disability.[1 3 4] Identifying and treating trauma-induced coagulopathy in this population will be paramount as we strive to continue improving trauma outcomes in these patients.

While many factors contribute to trauma-induced coagulopathy, hypofibrinogenemia has been identified as predictor of poor outcomes in adult trauma patients.[5–7] Fibrinogen plays a key role in the coagulation cascade as its activated substrate fibrin is used in combination with platelets to form the final product of hemostasis, clot.[8] The source of hypofibrinogenemia in the trauma patient is likely multifactorial. Increased consumption in the setting of hemorrhage and clot formation likely plays a role. Other factors that likely contribute to hypofibrinogenemia include dilution secondary to fluid administration, decreased synthesis in the setting of hypothermia, and decreased utilization secondary to increased levels of protein C and thrombomodulin often found in trauma coagulopathy.[6 9–13]

Fibrinogen levels can be calculated using several different methods including: the Clauss fibrinogen assay, levels derived from a prothrombin time standard curve, and viscoelastic studies.[14] Traditional measurements may take up to 80 min to provide results, while viscoelastic tests such as thrombelastography (TEG) can provide results in <15 min. Several studies have demonstrated that K-time, α-angle, and maximum amplitude (MA) are reliable in diagnosing hypofibrinogenemia.[15 16] An α-angle <60 has been previously demonstrated to correlate strongly to traditional Clauss fibrinogen assay.[16] These modalities offer an opportunity to rapidly identify and intervene on hypofibrinogenemia in the trauma patient.

To date, the role that hypofibrinogenemia plays in the pediatric patient population has not been a source of significant investigation. Leeper *et al* identified abnormalities in fibrinolysis to be an independent risk factor for mortality in pediatric trauma patients, with fibrinolysis shutdown being a particularly poor indicator.[17] Given the prevalence of hypofibrinogenemia in trauma patients and its association with mortality, the role of fibrinogen replacement has been a topic of increased attention. It has been suggested that early correction of hypofibrinogenemia may lead to improved outcomes and the early administration of fresh frozen plasma or fibrinogen in patients with hypofibrinogenemia is recommended by the Task Force for Advanced Bleeding Care in Trauma.[18–20] Whether this applies to the pediatric population is unknown. If pediatric patients with hypofibrinogenemia are predominantly dying because of hemorrhage, rapid correction of coagulopathy would be of the utmost importance. To better answer this question, a full understanding of the prevalence and outcomes of pediatric patients with hypofibrinogenemia is needed. The aim of this study was to evaluate the role that fibrinogen plays in the pediatric trauma patient receiving massive transfusion. It is hoped that a better understanding of this aspect of trauma coagulopathy will help inform what role cryoprecipitate and other concentrated fibrinogen products play in the initial resuscitation of traumatically injured pediatric patients.

METHODS

Study setting and population

Following institutional review board approval, we evaluated all patients under the age of 18 years who were transported to our level 1 adult and pediatric trauma center between November 2017 and April 2021. The Strengthening the Reporting of Observational Studies in Epidemiology guideline was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content (SDC) 1). Only those patients who received emergency-release blood products in the prehospital and/or emergency department (ED) settings were included in our final analysis. Patients who were dead on arrival or were pronounced dead immediately on arrival to the trauma bay were not included in our analysis. A TEG was obtained immediately after arrival to the trauma bay. Patients were then defined as hypofibrinogenemic (HYPOFIB) if either admission fibrinogen <150 or rapid TEG (r-TEG) angle <60 degrees. Those with admission values greater than these cut-points were defined as NORMAL. Data including demographics, mechanism of injury, Abbreviated Injury Scale (AIS), injury severity scores (ISS), prehospital and arrival variables, as well as outcomes, were then reviewed.

Each of our helicopters carries two units of low-titer (<1:200) non-leukoreduced, group O whole blood (LTO-WB), as well as two units of red blood cells (RBC) and two units of plasma. In addition, our trauma bay refrigerator has four units of LTO-WB and four units of both RBCs and plasma. While the type and amount transfused blood products were left to the discretion of prehospital and trauma bay providers, initiation of transfusion was generally guided by the Assessment of Blood Consumption (ABC) score and a 1:1:1 transfusion strategy was initially pursued.[21] Following initial resuscitation, further resuscitation was guided by coagulopathy identified on TEG. Administration of cryoprecipitate was also left to provider discretion but was often given in response to continued coagulopathy identified on TEG.

Data and definitions

Data collection was performed using the prospectively maintained blood product transfusion databases at our center. Data on all blood products were collected using records from the sole provider of blood products in our region. The primary outcome of interest was *30-day mortality*. Secondary outcomes were *blood product transfusion volumes, acute lung injury (ALI), acute renal failure, sepsis, venous thromboembolic events, overall hospital-free days, intensive care unit (ICU)-free days*, and *ventilator-free days* as defined by the Trauma Quality Improvement Program data dictionary. Cause of death was obtained from our trauma registry. Cause of death was entered into the trauma registry after being adjudicated by a panel of attending surgeons at a weekly morbidity and mortality conference.

ED blood products were defined as postarrival products while the patient remained in the ED. For those patients that were transferred directly from helipad to operating room, this was defined as those products received within the first 20 min of arrival. *Post-ED blood products* were defined as those products transfused after leaving the ED through the first 24 hours postarrival. r-TEG values consisted of the following: activated clotting time (ACT), which is increased with factor deficiency or severe hemodilution; k-time, generally increased with hypofibrinogenemia or platelet deficiency; α-angle, decreased with hypofibrinogenemia or platelet deficiency; MA, which reflects platelet contribution to clot strength and is decreased with platelet dysfunction or severe hypofibrinogenemia; and lysis at 30 min (LY30), the percent amplitude reduction at 30 min after MA, which when elevated reflects a state of hyperfibrinolysis.

Hemorrhagic shock was defined as reduced tissue perfused due to loss of blood volume, identified by arrival systolic blood pressure <90 mm Hg and arrival lactate >4 mg/dL. *Acute renal failure* was defined as a rise in serum creatinine of threefold over baseline at admission, a rise in serum creatinine over 4 mg/dL, or need for dialysis not in the setting of pre-existing end-stage renal disease. *Pneumonia* diagnosis required only entry in a clinical note with or without microbiological confirmation. *ALI* was defined as persistent arterial partial pressure of oxygen

to fraction of inspired oxygen ratio of <300 while intubated. *Systemic inflammatory response syndrome (SIRS)* was two or more criteria of the following: temperature <36°C or >38°C, pulse >90 beats per minute, respiratory rate >20 times per minute, arterial partial pressure of carbon dioxide <32 mm Hg, leukocyte count <4000 or >12 000 per μL, or >10% band forms on differential. *Sepsis* was defined as SIRS in the presence of suspected or confirmed infection and was abstracted directly from clinical notes. *Hospital-free days* were defined as days alive through 30 days and not hospitalized. Similarly, *ICU-free days* and *ventilator-free days* were defined as those days alive through 30 days and not in the ICU or on the ventilator, respectively. Those patients who died or had hospital stay exceeding 30 days received a value of 0 days for each of these three parameters.

Data analysis

Continuous data are presented as medians with 25th and 75th IQR or as means with SD. Comparisons between groups were performed using the Wilcoxon rank-sum test (Mann-Whitney U test) or Student's t-test, respectively. Categorical data are reported as proportions and, where appropriate, tested for significance using χ^2 or Fisher's exact tests. Risk factors for HYPOFIB were assessed using univariate analyses, followed by multivariable logistic regression. Additionally, the impact of HYPOFIB and early administration of cryoprecipitate (0–2 hours of admission) on outcomes were assessed with multivariate logistic regression. Included covariables were informed by the univariate analysis and included age, sex, arrival lactate and pH, scene vital signs, AIS scores, and FAST results. All statistical tests were two tailed with $p<0.05$ set as significant. STATA statistical software (V.17.0; College Station, Texas, USA) was used for univariate analyses.[22]

RESULTS

Hypofibrinogenemia status analysis

During the study period, 4169 patients under the age of 18 years were entered into the trauma registry, with 926 level 1 trauma activations, of which 186 patients received emergency-release blood products during this time; 1%, 3%, and 10% were HYPOFIB, respectively. Of the 186 patients of interest, 18 were HYPOFIB and 168 were NORMAL. HYPOFIB patients were younger and, therefore, had lower body weight. However, there were no differences in sex, race, or blood type (table 1). In addition, there were no differences in injury mechanism, scene versus transfer, or method of transport. While overall ISS was higher in the HYPOFIB group, this was driven by significantly higher head injury scores. While there were only a small number of patients that received Clauss fibrinogen assays in the trauma bay (n=6), these values correlated with our TEG definition of hypofibrinogenemia at 100%.

Table 1 Demographics and baseline data

	HYPOFIB (n=18)	NORMAL (n=168)	P value
Age, years	11 (3, 14)	14 (9, 16)	0.058
Weight, kg	32 (24, 63)	59 (34, 70)	0.037
Male sex	68%	65%	0.781
White race	38%	29%	0.412
Group O blood type	31%	45%	0.217
Blunt mechanism	69%	68%	0.954
Scene transport	76%	77%	0.910
Helicopter transport	25%	31%	0.645
Isolated head	27%	11%	0.008
Head AIS	5 (5, 5)	3 (0, 5)	0.001
Chest AIS	2 (0, 3)	3 (0, 3)	0.753
Abdomen AIS	0 (0, 2)	3 (0, 4)	0.029
ISS	30 (27, 38)	28 (17, 38)	0.038

Continuous values presented as medians with 25th and 75th IQR.
AIS, Abbreviated Injury Scale; HYPOFIB, hypofibrinogenemic; ISS, injury severity score.

Table 2 Scene and field vital signs and resuscitation data

	HYPOFIB (n=18)	NORMAL (n=168)	P value
Scene heart rate	122 (116, 153)	122 (90, 146)	0.531
Scene SBP	79 (59, 119)	103 (83, 125)	0.093
Scene GCS	3 (3, 3)	5 (3, 15)	0.028
Shock (defined by SIPA)	93%	64%	0.016
Field RBC, mL/kg	0.0 (0.0, 0.0)	0 (0, 0.01)	0.808
Field plasma, mL/kg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.241
Field whole blood, mL/kg	3.0 (0.0, 13.0)	0.0 (0.0, 7.0)	0.047
Field total blood, mL/kg	7.0 (0.0, 14.0)	0.03 (0.0, 9.0)	0.203

Continuous values presented as medians with 25th and 75th IQR.
GCS, Glasgow Coma Scale; HYPOFIB, hypofibrinogenemic; RBC, red blood cell; SBP, systolic blood pressure; SIPA, Shock Index Pediatric Age-Adjusted.

Consistent with their greater head AIS, HYPOFIB patients had lower field GCS (table 2). Although overall field transfusion volumes were similar, HYPOFIB received greater whole blood as part of their resuscitation. Keeping with greater head AIS and lower field GCS, arrival GCS with HYPOFIB patients were significantly lower (table 3). Also consistent with greater abdominal AIS, NORMAL patients had higher positive FAST exams on arrival. HYPOFIB patients had uniformly more coagulopathic r-TEG values on arrival as well as greater evidence of shock by admission lactate levels, although their Shock Index Pediatric Age-Adjusted levels were not more likely to be positive.

HYPOFIB patients received greater transfusion volumes both in the ED and after leaving the ED (table 4). This was consistent across all blood components with the exception of whole blood. HYPOFIB patients received more post-ED cryoprecipitate than NORMAL patients (0.0 mL/kg (0.0, 3.0) vs 0.0 mL/kg (0.0, 0.0; $p<0.001$). ICU admission fibrinogen levels were lower in the HYPOFIB group (134 (89, 173) vs 210 (150, 284); $p<0.001$), as were ICU admission r-TEG alpha-angle values (56 (46, 73) vs 68 (63, 75); $p=0.015$).

While complications were similar between the two groups, hospital-free, ventilator-free, and ICU-free days were all lower in the HYPOFIB group (table 5). We did not observe a difference in mortality at 24 hours between the HYPOFIB group and the NORMAL group (19% vs 21%, $p=0.84$). Thirty-day mortality was significantly greater in the HYPOFIB group, with nearly 80% attributed to head injury. Consistent with the majority of deaths from head injury, HYPOFIB patients had longer time to death compared with NORMAL patients who had almost 20% of deaths due to hemorrhage. All deaths not attributed to either traumatic brain injury or hemorrhage in our dataset were attributed to multiorgan failure. Controlling for age, prehospital GCS, arrival lactate, and ED resuscitation volumes, HYPOFIB was associated with lower 30-day survival (OR 0.09, 95% CI 0.008 to 0.892, $p=0.040$).

Table 3 Arrival vital signs and initial laboratory data

	HYPOFIB (n=18)	NORMAL (n=168)	P value
Arrival heart rate	118 (102, 146)	120 (94, 138)	0.508
Arrival SBP	91 (75, 108)	106 (82, 122)	0.301
Arrival GCS	3 (3, 3)	3 (3, 15)	0.029
Shock (defined by SIPA)	63%	66%	0.781
Arrival temperature, °C	36.1 (33.7, 37.1)	36.6 (36.0, 37.0)	0.215
Arrival FAST (+)	14%	40%	0.030
ED hemoglobin, g/dL	12.4 (10.5, 14.0)	12.1 (10.8, 13.3)	0.521
ED platelets, $\times 10^3$	139 (100, 210)	237 (184, 302)	0.001
ED base deficit	9 (–14 to –3)	5 (–9 to –2)	0.124
ED lactate	6.5 (4.0, 10.3)	3.9 (2.5, 6.0)	0.004
ED r-TEG ACT, s	183 (156, 206)	113 (105, 121)	<0.001
ED r-TEG k-time, min	4.4 (3.5, 6.0)	1.6 (1.2, 2.2)	<0.001
ED r-TEG angle, degree	47 (36, 52)	72 (66, 75)	<0.001
ED r-TEG MA, mm	41 (35, 45)	62 (56, 67)	<0.001
ED r-TEG LY30	0.2 (0.0, 43)	0.5 (0.1, 1.9)	0.733

Continuous values presented as medians with 25th and 75th IQR.
ACT, activated clotting time; ED, emergency department; FAST, focused assessment for the sonography of trauma; GCS, Glasgow Coma Scale; HYPOFIB, hypofibrinogenemic; LY30, lysis at 30 min; MA, maximum amplitude; r-TEG, rapid thrombelastography; SBP, systolic blood pressure; SIPA, Shock Index Pediatric Age-Adjusted.

Early cryoprecipitate analysis

Next, we looked at patients who received early cryoprecipitate (within the first 2 hours) of arrival. Of the 186 patients, 12% received early cryoprecipitate. With the exception of race, there were no differences in baseline data between those who received early cryoprecipitate and those who did not; all p>0.05. Patients who received early cryoprecipitate were more likely to be Hispanic (45% vs 24%; p=0.047). The overall ISS was greater in those receiving early cryoprecipitate (35 (26, 43) vs 26 (17, 35); p=0.02), with a trend toward higher head AIS scores (5 (3, 5) vs 3 (0, 5); p=0.093). Field physiology and resuscitation volumes were similar between groups; all p>0.05.

While arrival heart rate and blood pressures were similar, arrival ED GCS was lower in those who received early cryoprecipitate (3 (3, 3) vs 3 (3, 15); p=0.024). Arrival r-TEG values were more coagulopathic by ACT (136 (121, 183) vs 113 (105, 128); p<0.001), alpha-angle (59 (51, 65) vs 71 (65, 75); p<0.001), and MA (50 (42, 55) vs 62 (56, 67); p<0.001). In addition, early cryoprecipitate patients presented with more evidence of shock by ED lactate values (5.9 (4.2, 8.5) vs 3.7 (2.5, 6.3); p=0.018). ED resuscitation volumes of RBCs (42 mL/kg (22, 55) vs 5 mL/kg (0, 15); p<0.001), plasma (26 mL/kg (17, 33); p<0.001), and platelets (0 mL/kg (0, 6) vs 0 mL/kg (0, 0); p<0.001) were greater in the early cryoprecipitate patients.

Despite receiving early cryoprecipitate, this group presented to the ICU with lower fibrinogen levels (115 (89, 185) vs 210 (156, 284); p=0.001). However, early cryoprecipitate patients had similar r-TEG alpha-angle values on presentation to the ICU compared with the control group (74 (72, 76) vs 67 (61, 74); p=0.226). Patients who received early cryoprecipitate (0–2 hours) had higher mortality by univariate analysis (55% vs 31%, p=0.045). However, after controlling for age, race, ISS, and ED transfusion volumes, no difference was noted on multivariate analysis for early cryoprecipitate (OR 0.36, 95% CI 0.07 to 1.81, p=0.221).

Table 4 Hospital transfusion data

	HYPOFIB (n=18)	NORMAL (n=168)	P value
ED RBCs, mL/kg	35.1 (6.5, 54.2)	5.4 (0.0, 17.3)	0.002
ED plasma, mL/kg	19.0 (6.3, 34.6)	3.8 (0.0, 12.0)	0.002
ED platelets, mL/kg	0.0 (0.0, 5.9)	0.0 (0.0, 0.0)	0.003
ED whole blood, mL/kg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.898
ED total blood, mL/kg	61.4 (24.6, 85.7)	12.4 (0.0, 32.8)	<0.001
Post-ED RBCs, mL/kg	27.7 (16.1, 48,1)	7.2 (0.0, 24.3)	<0.001
Post-ED plasma, mL/kg	18.2 (10.3, 42.7)	0.0 (0.0, 11.2)	0.001
Post-ED platelets, mL/kg	6.2 (0.0, 15.0)	0.0 (0.0, 2.1)	<0.001
Post-ED whole blood, mL/kg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.000
Post-ED total blood, mL/kg	44.1 (30.2, 101.3)	9.5 (0.0, 38.5)	<0.001

ED, emergency department; HYPOFIB, hypofibrinogenemic; RBC, red blood cell.

Table 5 Complications and mortality data

	HYPOFIB (n=18)	NORMAL (n=168)	P value
Acute renal failure	12.5%	3.5%	0.075
Sepsis	6.3%	16.7%	0.249
Venous thromboembolism	0%	5%	0.331
Acute respiratory distress syndrome	12.5%	5.6%	0.250
Hospital-free days	0 (0, 0)	11 (0, 21)	<0.001
Ventilator-free days	0 (0, 0)	27 (0, 30)	<0.001
ICU-free days	0 (0, 0)	22 (0, 28)	<0.001
PaO_2/FiO_2 at 24 hours	189 (68, 482)	415 (270, 522)	0.040
PaO_2/FiO_2 at 48 hours	376 (283, 424)	382 (291, 482)	0.565
PaO_2/FiO_2 at 72 hours	338 (285, 420)	360 (255, 450)	0.862
24-hour mortality	19%	21%	0.81
30-day mortality	82%	28%	<0.001
Cause of death, TBI	79%	62%	0.083
Cause of death, hemorrhage	0%	18%	0.049
Time to death, hours	36 (31, 47)	12 (0.2, 35)	0.014

HYPOFIB, hypofibrinogenemic; ICU, intensive care unit; TBI, traumatic brain injury.

DISCUSSION

This single-center study evaluating the role of hypofibrinogenemia in pediatric patients requiring emergency-release blood products represents one of the few studies to investigate the topic. In our study, we demonstrated an association between hypofibrinogenemia and mortality at 30 days (82% vs 31%, p<0.001). We also demonstrated that the majority of patients with HYPOFIB died as a result of their traumatic brain injuries as opposed to hemorrhage. While several studies have demonstrated an association between hypofibrinogenemia and mortality in adults, the evidence is inconsistent in traumatically injured pediatric patients.[5 6 23] Reed *et al* found a similar association between mortality and hypofibrinogenemia in patients aged 13 years or younger.[24] In other studies, there has been no association between hypofibrinogenemia and mortality in pediatric patients.[25 26] Fibrinogen levels have been shown to vary as a function of time from injury as a result of initial hyperfibrinolysis followed by fibrinolysis shutdown. This is especially true in those with traumatic brain injuries.[27] The methods and timing of hypofibrinogenemia diagnosis may play a role in the inconsistent results seen in these studies.

In our study, patients with hypofibrinogenemia were more likely to have lower weights, higher lactates, lower GCS scores, and higher head and overall AIS scores. Additionally, they were

more coagulopathic in general with significant differences in all TEG measurements outside of LY30. While those patients with hypofibrinogenemia received more blood products, both while in the ED and in their following hospital course, there were no deaths attributed to hemorrhage in this group. Significantly more patients in the normal fibrinogen group died of hemorrhage in comparison (0% vs 18%, p=0.04). These results are likely related to the higher abdominal AIS scores and positive FAST rates in the NORMAL group. This highlights the role that traumatic head injury likely played in the increased mortality seen in the hypofibrinogenemia group. Patients with hypofibrinogenemia died predominantly as a result of their traumatic brain injuries, with those without hypofibrinogenemia died predominantly from hemorrhage. Several studies have found an association between traumatic brain injury and hypofibrinogenemia. This includes an increased risk of progression of head bleeds and death from traumatic brain injury in those with hypofibrinogenemia.[27–29]

While there was an unadjusted increase in mortality in those patients receiving cryoprecipitate, this difference was not sustained on multivariate analysis. Cryoprecipitate was administered at physician discretion and was likely given in response to abnormal physiology and coagulopathy demonstrated on TEG. This makes it unsurprising that these patients had lower fibrinogen levels and greater coagulopathy on admission to the PICU. The data regarding the use of cryoprecipitate, or other fibrin replacement products, in the early resuscitation of traumatically injured patients are limited. Stinger *et al* demonstrated that in traumatically injured combat patients receiving massive transfusion, those that received transfusion products with higher levels of fibrinogen had improved mortality.[30] Rourke *et al* observed improved mortality at 24 hours in adult patients undergoing massive transfusion who received cryoprecipitate.[31] Tama *et al* observed improved 24-hour survival in pediatric patients undergoing massive transfusion that received cryoprecipitate.[32] The improvement in survival seen in these studies was not replicated in our paper, although our study is limited by the small number of patients with hypofibrinogenemia. While the number of patients with HYPOFIB is limited, we believed it was telling that none of the HYPOFIB patients in our study died because of hemorrhage. It is unlikely that early inclusion of cryoprecipitate to correct their trauma-induced coagulopathy would have had a significant impact on mortality. Additionally, there is no evidence that early use of cryoprecipitate can positively impact outcomes in patients with traumatic brain injuries, which those with HYPOFIB were more likely to succumb to.

The timing and indications for fibrin replacement product administration also remains a topic of investigation. No patients in our study with hypofibrinogenemia died of hemorrhage. Rather, most of them died as a result of traumatic brain injury. The ability of fibrin replacement products to augment outcomes in patients with traumatic brain injuries has not been investigated. Given this it is unclear what role the empiric administration of fibrin concentrated products early in the administration of a massive transfusion should play. In the study by Rourke *et al* that demonstrated an association between improved survival and cryoprecipitate administration, cryoprecipitate was given on average at 103 min after admission.[31] This time period indicates that there may be enough time to give cryoprecipitate in response to abnormal viscoelastic assays or fibrinogen results and still see clinical benefit. In other words, there is time to give cryoprecipitate as an on-demand product, as opposed to empirically during the initial resuscitative phase, and still see a benefit. A recommendation for the empiric administration of fibrin concentrated products in patients with severe traumatic brain injuries would require further investigations demonstrating an ability for these products to positively change outcomes in patients with traumatic brain injuries. Given that this evidence does not exist, our findings would support leaving cryoprecipitate as an on-demand product and not include its use in the initial administration of massive transfusion.

Our study had several limitations. The small number of patients with hypofibrinogenemia meant that our study may have been insufficiently powered to find significant findings for several outcomes, including a mortality benefit in those patients receiving cryoprecipitate. The patients with hypofibrinogenemia also presented with more severe injury patterns and deranged physiology. This made it difficult to identify which outcomes were a product of deranged fibrinogen levels as opposed to greater traumatic burden. Additionally, while a majority of the HYPOFIB patients succumbed to head injuries, we do not have long-term neurological outcome available for these patients in our retrospective database. Another limitation of this study is that some patients received blood products prior to arriving to the trauma bay and having their initial TEG drawn. This may have affected our initial TEG findings. We chose to include these patients in our study to provide a practical evaluation of patients arriving to the trauma bay with HYPOFIB. Further investigations are needed to understand the timing and indications for fibrin replacement products, especially in those with traumatic brain injuries.

Contributors JG: study design, literature review, dataset development, data analysis, manuscript creation, manuscript review. J-MVG: study design, data analysis, manuscript creation, manuscript review. JC: study design, dataset development, manuscript review. CG: study design, dataset development, manuscript review. DEM: study design, manuscript review. CC: study design, manuscript review. CEW: study design, manuscript review. BAC: study design, literature review, dataset development, data analysis, manuscript creation, manuscript review, guarantor.

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