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Does an early, balanced resuscitation strategy reduce the incidence of hypofibrinogenemia in hemorrhagic shock?

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ABSTRACT

Objectives Some centers have recommended including concentrated fibrinogen replacement in massive transfusion protocols (MTPs). Given our center's policy of aggressive early balanced resuscitation (1:1:1), beginning prehospital, we hypothesized that our rates of hypofibrinogenemia may be lower than those previously reported.

Methods In this retrospective cohort study, patients presenting to our trauma center November 2017 to April 2021 were reviewed. Patients were defined as hypofibrinogenemic (HYPOFIB) if admission fibrinogen <150 or rapid thrombelastography angle <60. Univariate and multivariable analyses assessed risk factors for HYPOFIB. Inverse probability of treatment weighting analyses assessed the relationship between cryoprecipitate administration and outcomes.

Results Of 29 782 patients, 6618 level 1 activations, and 1948 patients receiving emergency release blood, <1%, 2%, and 7% were HYPOFIB. HYPOFIB patients were younger, had higher head Abbreviated Injury Scale value, and had worse coagulopathy and shock. HYPOFIB had lower survival (48% vs 82%, p<0.001), shorter time to death (median 28 (7, 50) vs 36 (14, 140) hours, p=0.012), and were more likely to die from head injury (72% vs 51%, p<0.001). Risk factors for HYPOFIB included increased age (OR (95% CI) 0.98 (0.96 to 0.99), p=0.03), head injury severity (OR 1.24 (1.06 to 1.46), p=0.009), lower arrival pH (OR 0.01 (0.001 to 0.20), p=0.002), and elevated prehospital red blood cell to platelet ratio (OR 1.20 (1.02 to 1.41), p=0.03). Among HYPOFIB patients, there was no difference in survival for those that received early cryoprecipitate (within 2 hours; 40 vs 47%; p=0.630). On inverse probability of treatment weighted analysis, early cryoprecipitate did not benefit the full cohort (OR 0.52 (0.43 to 0.65), p<0.001), nor the HYPOFIB subgroup (0.28 (0.20 to 0.39), p<0.001).

Conclusions Low rates of hypofibrinogenemia were found in our center which treats hemorrhage with early, balanced resuscitation. Previously reported higher rates may be partially due to unbalanced resuscitation and/or delay in resuscitation initiation. Routine empiric inclusion of concentrated fibrinogen replacement in MTPs is not supported by the currently available data.

Level of evidence Level III.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Coagulopathy is common among trauma patients.
⇒ Some centers have recommended including concentrated fibrinogen replacement in massive transfusion protocols (MTPs) based on recent studies reporting high rates of hypofibrinogenemia (HYPOFIB) among trauma patients.
⇒ We sought to evaluate if our center's policy of balanced resuscitation (1:1:1), beginning prehospital or immediately on hospital arrival, would yield lower rates of HYPOFIB in our trauma population.

WHAT THIS STUDY ADDS

⇒ We observed substantially lower rates of arrival HYPOFIB in our trauma population compared with what has been reported in recent publications.
⇒ These lower rates may be in part due to the aggressive initiation of balanced resuscitation in the prehospital and early hospital setting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study has implications on the optimal prehospital and early hospital resuscitation strategy in trauma patients.
⇒ Early initiation of balanced resuscitation may result in lower rates of hypofibrinogenemia than previously reported, and may reduce the need for empiric concentrated fibrinogen replacement in MTPs.

BACKGROUND

Hemorrhage is the second most common cause of death in trauma patients and is the leading cause of early and preventable traumatic deaths.[1 2] Severe injuries have the potential to both initiate hemorrhage as well as induce concomitant coagulopathy that prevents hemostasis.[3] Historically, coagulopathy has been estimated to be present at admission in roughly 25% of acutely injured patients and has been found to substantially increase transfusion requirements and mortality.[4–6] Early correction of this coagulopathy via blood product resuscitation is widely recognized as a vital component of the care of bleeding patients. Multiple prior studies have informed the widespread acceptance of massive transfusion protocols (MTPs) containing high, fixed ratios of plasma and platelets (PLTs) to red blood cells (RBCs).[7–9] Although plasma contains some fibrinogen, there has recently been increased interest in defining the optimal role of concentrated fibrinogen replacement in the form of cryoprecipitate (cryo) or fibrinogen concentrates (FCs) during the initial resuscitation of trauma patients.

Linked

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Fibrinogen is a vital hemostatic factor that, in the setting of tissue or vascular injury, is converted to its active form fibrin which polymerizes and links with PLTs to form a stable clot.[10] As with all coagulation factors, consumption of fibrinogen as well as fibrinolysis can lead to patients becoming hypofibrinogenemic (HYPOFIB) and coagulopathic.[11] Whereas concentrated fibrinogen replacement is commonly practiced, protocols for its use vary widely. In Europe, concentrated fibrinogen replacement is often built into the MTPs whereas in the USA it is more commonly given on an 'as needed' or 'on demand' basis, guided by fibrinogen levels or viscoelastic assays.[12 13] In an effort to elucidate the optimal practice for fibrinogen supplementation, there have recently been several small randomized trials (RCTs) in trauma patients assessing the feasibility of protocolized early concentrated fibrinogen replacement . Overall, these studies have concluded that early fibrinogen supplementation is feasible and effective at raising measured fibrinogen level, but have not been sufficiently powered to demonstrate differences in clinical outcomes.[14–18] Recent studies have reported high initial rates of HYPOFIB in trauma patients reaching up to 29%, though these results as well as the definition used for HYPOFIB are variable between studies.[19] These data have led some to call for uniform inclusion of concentrated fibrinogen replacement in MTPs.[13]

We hypothesized that, given our institution's policy of balanced 1:1:1 (plasma: PLT: RBC) or whole blood (WB) resuscitation beginning in the prehospital setting, we would see lower rates of HYPOFIB at admission to our trauma center. We also hypothesized that early cryoprecipitate administration would not show a clear clinical benefit in patients requiring MTP.

METHODS

Study setting and population

After IRB approval, we evaluated all level 1 trauma patients (16 years and older) being transported to our hospital between November 2017 and April 2021. 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 were defined as HYPOFIB if admission fibrinogen was <150 or rapid thrombelastography (r-TEG) angle was <60°. Both definitions were included as both have been used in previously published studies. Those with admission values greater than these cut points were defined as NORMAL. In-hospital resuscitation was guided by TEG values with values repeated until they were within our institution's defined normal limits (angle >60). 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. The Strengthening the Reporting in Observational Studies in Epidemiology checklist for cohort studies was followed.

Each of our helicopters carries two units of low-titer (<1:200) non-leukoreduced, group O WB (LTO-WB), as well as two units of RBCs 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. The decision to initiate prehospital transfusion is left to the discretion of our prehospital care providers. Our trauma department works closely with our prehospital care providers to train them to recognize early signs of hemorrhagic shock such as penetrating mechanism or high energy blunt mechanism with tachycardia (heart rate >120) and hypotension (systolic blood pressure (SBP) <90). Additionally, our hospital's helicopter transport service providers are trained to perform Focused Assessment with Sonography in Trauma (FAST) examinations and routinely do so when internal hemorrhage is suspected.[20] The decision to begin resuscitation in the trauma bay with WB versus component therapy is left to the discretion of the trauma faculty.

Data and definitions

Data collection was performed using the prospectively maintained blood product transfusion databases at our center. The primary outcome of interest was *30-day survival*. 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.

Prehospital transfusion ratios were calculated to assess the ratios between RBC and plasma as well as RBC and PLT. The RBC:plasma ratio was calculated by adding prehospital RBCs to prehospital WB units, then dividing that sum by the sum of prehospital plasma and prehospital WB. As our group has previously described, the RBC:PLT ratio was calculated by adding prehospital RBCs to prehospital PLT and WB units, then dividing that sum by the sum of prehospital PLT and 0.17 multiplied by prehospital WB units.[21]

ED blood products were defined as postarrival products and the patient remained in the ED. *Post-ED blood products* were defined as those products transfused after leaving the ED through the first 24 hours postarrival. *Early cryo transfusion* was defined as within 2 hours of ED arrival. R-TEG values consisted of the following: activated clotting time, k-time, α-angle (generally decreased with hypofibrinogenemia or PLT deficiency), maximum amplitude (MA) (decreased with PLT dysfunction or severe hypofibrinogenemia), and clot lysis after 30 minutes (LY-30).

Hemorrhagic shock was defined as reduced tissue perfused due to loss of blood volume, identified by arrival SBP <90 mm Hg and arrival lactate >4 mg/dL. *Acute renal failure* was defined as a threefold rise in serum creatinine during baseline at admission, a rise in serum creatinine over 4 mg/dL or new onset need for dialysis. *Pneumonia* diagnosis required only entry in a clinical note. *ALI* was defined as persistent arterial partial pressure of oxygen to fraction of inspired oxygen ratio of <300 while intubated. *Sepsis* was defined as physiologic evidence of systemic illness in the presence of suspected or confirmed infection and was abstracted 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 IQRs 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 test or Fisher's exact test. Risk factors for HYPOFIB were assessed using univariate analyses, followed by multivariable logistic regression. Additionally, the impact of HYPOFIB and early administration of cryoprecipitate and WB on outcomes were assessed with multivariate logistic regression. Covariables were chosen a priori, and included age, sex,

arrival lactate and pH, scene vital signs, AIS scores, prehospital RBC:plasma and RBC:PLT ratios, and prehospital FAST results. All statistical tests were two tailed with $p<0.05$ set as statistically significant. STATA statistical software (V.17.0; College Station, Texas, USA) was used for univariate analyses.

To assess whether early cryoprecipitate may be beneficial, inverse probability of treatment weighted analyses were conducted aiming to adjust for selection bias impacting cryoprecipitate administration. Propensity scores for receipt of cryoprecipitate were generated using a logistic regression model using variables known or thought to influence the clinical decision to give early cryoprecipitate. The following variables were selected: age, sex, blunt injury, ISS, transport from scene versus transport from an outside facility, scene SBP, scene diastolic blood pressure, scene heart rate, scene Glasgow Coma Scale (GCS) Score, need for scene intubation, arrival pH, arrival lactate, trauma activation level, and TEG values. Propensity scores were converted to inverse probability of treatment weights for each patient. Standardized mean differences compared group differences before and after weighting. Multivariable logistic regression, weighted for the inverse probability of treatment was used to assess the relationship between early cryoprecipitate use and the primary outcome, survival. Covariables included in the multivariable regression included age, ISS, sex, arrival lactate, and scene SBP.

Similar analyses weighted for inverse probability of treatment were applied separately to the secondary outcome 24-hour blood transfusion with a Poisson distribution and a log link. All associations were reported as ORs for logistic models and incidence rate ratios with robust CIs for Poisson models. Multivariable analyses were completed using R V.3.53 (R Core Team. 2013. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria). Subgroup analysis was performed to evaluate the effect of early cryoprecipitate transfusion on only those patients with a low MA value (<50) on their arrival TEG. Whereas alpha-angle assesses fibrinogen's contribution to clot kinetics or acceleration of clot formation, the TEG's maximal amplitude, or MA, assesses fibrinogen's contribution to overall clot strength, along with that of PLTs. As MA is one of the additional values where fibrinogen replacement is used, we evaluated low MA as an additional measure of our population's hypofibrinogenemia.

RESULTS

Univariate analysis

A query of the time period noted that 29 782 patients were entered into the trauma registry, 6618 were level 1 trauma activations, and 1948 patients received emergency release blood and MTP products. Of this initial query, <1%, 2%, and 7% were HYPOFIB, respectively. Among the 1948 that met inclusion for full analysis, 146 (7%) were HYPOFIB and 1802 (93%) were NORMAL. Of the 6618 level 1 trauma patients, 658 (10%) had available measured fibrinogen levels, of which 19 (3%) were <150 mg/dL. Only 234 (12%) of the 1948 patients receiving emergency release blood had a measured fibrinogen level, of which 14 (6.0%) had a level <150. All patients had available alpha angle values, and all 146 patients in the HYPOFIB group had an angle of <60. Lowering the fibrinogen level cut-off to <100 reduced the incidence of HYPOFIB to only 4% among patients receiving emergency release blood and <2% among level 1 traumas. Raising the fibrinogen level cut-off to <200 increased the incidence of HYPOFIB to 10% among patients receiving emergency release blood and 3% among level 1 traumas. Of the 1948 patients included in the study, 58% received WB either prehospital or in the ED. Among the 857 patients who received prehospital transfusion, 66% received at least one unit of WB prior to arrival. Among those 565 patients receiving prehospital WB, 68% received one unit, 30% received two units, and 2% received three units.

Table 1 Baseline and demographic data comparison between HYPOFIB and NORMAL patients

	HYPOFIB (n=146)	NORMAL (n=1802)	P value
Median age, years (IQR)	30 (20, 47)	38 (25, 56)	<0.001
Male sex	85%	76%	0.013
White race	30%	38%	0.055
Blunt mechanism	71%	70%	0.799
Direct from scene	89%	88%	0.893
Helicopter transport	44%	46%	0.640
Median Head AIS	5 (2, 5)	3 (0, 4)	<0.001
Median Chest AIS	3 (0, 3)	3 (0, 3)	0.668
Median Abdomen AIS	2 (0, 3)	2 (0, 4)	0.450
Median Extremity AIS	3 (0, 4)	2 (0, 3)	0.152
Median ISS	30 (25, 44)	24 (14, 34)	<0.001

AIS, Abbreviated Injury Scale; HYPOFIB, hypofibrinogenemic; ISS, Injury Severity Score.

With respect to baseline and demographic data, HYPOFIB patients were more likely to be younger and male, but less likely to be white (table 1).

There were no differences in mechanism of injury or transport. Although truncal and extremity AIS scores were similar, HYPOFIB patients had significantly higher head AIS value, which drove a higher overall ISS as well. Field vital signs were significantly worse in the HYPOFIB cohort, with higher heart rate, lower systolic pressures, and lower GCS Score (table 2).

HYPOFIB patients were also more likely to have positive FAST examination in the field and higher prehospital transfusion volumes (median 1 unit (0, 2) compared with 0 unit (0, 1); $p=0.032$). This was primarily driven by higher WB transfusions.

HYPOFIB patients were more likely to arrive with a higher heart rate and lower GCS Score, but similar systolic pressures (table 3).

The HYPOFIB cohort also had worse lactate and base deficit, as well as lower PLT count on initial labs. The HYPOFIB patients

Table 2 Prehospital vital signs and resuscitation volumes comparison between HYPOFIB and NORMAL patients

	HYPOFIB (n=146)	NORMAL (n=1802)	P value
Median scene heart rate	116 (95, 137)	108 (84, 128)	0.002
Median scene SBP	93 (72, 129)	107 (84, 132)	0.019
Median scene GCS Score	3 (3, 14)	10 (3, 15)	<0.001
Field (+) FAST	54%	45%	0.040
Median prehospital fluid (ml)	0 (0, 250)	0 (0, 300)	0.916
Median prehospital RBC (U)	0 (0, 0)	0 (0, 0)	0.181
Median prehospital plasma (U)	0 (0, 0)	0 (0, 0)	0.538
Median prehospital WB (U)	0 (0, 1)*	0 (0, 1)	0.029

Data presented as median (IQR).
*Statistically significant defined as p<0.05.
FAST, Focused Assessment with Sonography in Trauma; GCS, Glasgow Coma Scale; HYPOFIB, hypofibrinogenemic; RBC, red blood cell; SBP, systolic blood pressure; WB, whole blood.

Table 3 Arrival vital signs, initial laboratory values, and early resuscitation volumes by HYPOFIB and NORMAL groups

	HYPOFIB (n=146)	NORMAL (n=1802)	P value
ED heart rate	112 (92, 133)	102 (80, 124)	<0.001
ED SBP	94 (77, 122)	100 (80, 124)	0.202
ED GCS Score	3 (3, 13)	9 (3, 15)	<0.001
ED (+) FAST	34%	30%	0.311
Arrival creatinine	1.26 (0.95, 1.51)	1.23 (0.99, 1.51)	0.733
Arrival base excess	−7 (−12, −2)	−4 (−8, −1)	<0.001
Arrival lactate	5.4 (3.4, 9.0)	3.9 (2.5, 6.0)	<0.001
Arrival hemoglobin	12.4 (10.1, 14.0)	12.4 (10.8, 13.8)	0.928
Arrival PLT count	138 (105, 200)	218 (162, 271)	<0.001
Arrival rTEG-ACT	136 (121, 167)	113 (105, 121)	<0.001
Arrival r-TEG K-time	3.7 (3.1, 5.1)	1.5 (1.1, 1.9)	<0.001
Arrival r-TEG angle	53 (45, 57)	73 (69, 76)	<0.001
Arrival r-TEG MA	45 (38, 52)	63 (59, 68)	<0.001
Arrival r-TEG LY-30	1 (0, 2)	0 (0, 18)	0.302
ED RBC	1 (0, 4)	1 (0, 3)	0.008
ED plasma	2 (0, 5)	1 (0, 3)	<0.001
ED PLTs	0 (0, 1)	0 (0, 0)	<0.001
ED WB	0 (0, 1)*	0 (0, 1)	0.013
Post-ED RBC	3 (0, 9)	1 (0, 5)	0.002
Post-ED plasma	2 (0, 6)	0 (0, 3)	<0.001
Post-ED PLTs	1 (0, 2)	0 (0, 1)	<0.001

Data presented as median (IQR).
*Statistically significant defined as p<0.05.
ACT, activated clotting time; ED, emergency department; FAST, Focused Assessment with Sonography in Trauma; GCS, Glasgow Coma Scale; HYPOFIB, hypofibrinogenemic; LY-30, Clot lysis after 30 minutes; MA, maximum amplitude; PLT, platelet; RBC, red blood cell; r-TEG, rapid thromboelastography; SBP, systolic blood pressure; WB, whole blood.

were uniformly more coagulopathic on presentation, with the exception of fibrinolysis. Consistent with worse coagulopathy and shock on arrival, early transfusion volumes were significantly higher in the HYPOFIB patients (table 4).

Table 4 Complications, outcomes, and resource utilization comparison between HYPOFIB and NORMAL patients

	HYPOFIB (n=146)	NORMAL (n=1802)	P value
TRALI	<1%	<1%	0.620
TACO	<1%	<1%	0.774
Acute renal failure	20%	9%	<0.001
Pneumonia	16%	19%	0.324
Sepsis	18%	25%	0.058
Venous thromboembolism	6%	5%	0.866
Acute lung injury	34%	29%	0.202
Hospital-free days	0 (0, 12)	14 (0, 23)	<0.001
ICU-free days	0 (0, 23)	24 (0, 29)	<0.001
Ventilator-free days	0 (0, 28)	28 (0, 30)	<0.001
30-day survival	48%	82%	<0.001
Death from TBI	72%	51%	<0.001
Time to death, hours	28 (7, 50)	36 (14, 140)	0.012

Data presented as median (IQR).
HYPOFIB, hypofibrinogenemic; ICU, intensive care unit; TACO, transfusion-associated circulatory overload; TBI, traumatic brain injury; TRALI, transfusion-related acute lung injury.

Table 5 Risk factors for arrival hypofibrinogenemia

	OR	95% CI	P value
Age, per year	0.98	0.96 to 0.99	0.03
Male sex	1.08	0.54 to 2.25	0.83
Arrival lactate	0.95	0.87 to 1.04	0.28
Scene SBP, per mm Hg	0.99	0.98 to 1.01	0.42
Head AIS	1.24	1.06 to 1.46	0.009
Abdomen AIS	0.91	0.75 to 1.10	0.33
Chest AIS	0.87	0.71 to 1.06	0.16
External AIS	0.82	0.49 to 1.34	0.45
Extremity AIS	1.10	0.89 to 1.36	0.35
Face AIS	0.86	0.66 to 1.10	0.25
Scene heart rate, beats per minute	1.00	0.99 to 1.01	0.50
Scene DBP, per mm Hg	0.99	0.97 to 1.01	0.23
Scene Glasgow Coma Scale Score	1.00	0.95 to 1.07	0.93
Arrival pH	0.01	0.001 to 0.20	0.002
Prehospital RBC:FFP	1.14	0.77 to 1.62	0.48
Prehospital RBC:PLT	1.20	1.02 to 1.41	0.03
Positive prehospital FAST	0.85	0.46 to 1.54	0.61
Pre-hospital WB	0.34	0.23 to 0.50	<0.001
ED WB	1.28	0.94 to 1.75	0.12

AIS, Abbreviated Injury Scale; DBP, diastolic blood pressure; ED, emergency department; FAST, Focused Assessment with Sonography in Trauma; FFP, fresh frozen plasma; PLT, platelets; RBC, red blood cells; SBP, systolic blood pressure; WB, whole blood.

HYPOFIB patients had lower survival, shorter time to death, and were significantly more likely to die from head injury (table 4). Although renal failure was higher in the HYPOFIB cohort, the incidence of sepsis was lower. This may reflect the lower likelihood of developing sepsis with higher mortality and shorter time to death. The hospital, ICU, and ventilator-free days were significantly lower among the HYPOFIB patients.

We then evaluated only those patients in the HYPOFIB group. Among these patients, only 10% received early cryoprecipitate (within 2 hours of ED arrival). There was no difference in survival for those that received early cryoprecipitate (40% vs 47%; p=0.630). HYPOFIB patients that died had markedly higher head AIS value (5 vs 3) and overall ISS value (38 vs 26), but no difference in arrival vitals or evidence of shock.

Multivariable and weighted analyses

HYPOFIB patients had a higher prehospital RBC:PLT ratio than normal patients (4.4 (2.1, 5.9) vs 5.2 (4.9, 5.9); p=0.010). On multivariable analysis, lower age, higher head Injury Severity Scale Score, lower pH, and higher prehospital RBC:PLT ratio were associated with HYPOFIB. Prehospital WB administration was associated with decreased odds of hypofibrinogenemia (OR 0.34, CI 0.23 to 0.50, p<0.001). Receipt of WB in the ER was not associated with hypofibrinogenemia (OR 1.28, CI 0.94 to 1.75, p=0.12) (table 5).

On weighted, multivariable analysis, early cryoprecipitate was associated with decreased likelihood of survival (table 6).

Subgroup analyses

To evaluate the impact of prehospital transfusion on our findings, we evaluated those who did and did not receive prehospital transfusions. Of the 1948 patients included, 44% (857) received prehospital blood products (either WB or 1:1). These patients had an 8% incidence of HYPOFIB versus 6% in the no prehospital blood group (p=0.065). The prehospital blood

Table 6 Weighted inverse probability analysis evaluating the relationship between early cryoprecipitate administration and survival

30-day survival			
	OR	95% CI	P value
Age, per year	0.97	0.96 to 0.97	<0.001
Injury Severity Score, per point	0.93	0.92 to 0.94	<0.001
Early cryoprecipitate	0.52	0.43 to 0.65	<0.001
Hypofibrinogenemia	0.28	0.20 to 0.39	<0.001
Male sex	0.97	0.78 to 1.22	0.80
Scene SBP, per mm Hg	0.90	0.88 to 0.93	<0.001
Arrival lactate, per mmol/L	1.00	1.00 to 1.01	0.04

SBP, systolic blood pressure.

group was more likely to receive early cryoprecipitate than the no prehospital blood cohort (6% vs 4%; p=0.064). Although not statistically significant, the survival rate was lower in the prehospital blood group (78 vs 83%; p=0.059). These findings are consistent with the prehospital group being more severely injured (median ISS 26 (17, 38) vs 24 (14, 34); p=0.001)), with worse Field Shock Index (1.13 (0.87, 1.52) vs 84 (67, 1.08); p<0.001), and higher lactate on arrival (4.2 (2.9, 6.5) vs 3.7 (2.3, 6.0); p=0.002).

To better define the impact of prehospital resuscitation on arrival incidence of HYPOFIB and subsequent outcomes, we further evaluated only those who received prehospital blood products. Of the 857 who received prehospital blood, 565 received prehospital WB and 292 received 1:1 component therapy. The incidence of HYPOFIB in those receiving prehospital WB was 8%, compared with 5% in those receiving balanced resuscitation through component therapy (p=0.071). There was no difference in early cryoprecipitate transfusion between groups (p=0.367). There was also no difference in survival between the two prehospital cohorts (77 vs 82%; p=0.149). However, the WB cohort was significantly more severely injured (median ISS 27 (17, 41) vs 22 (13, 33); p<0.001), with worse Field Shock Index (1.16 (0.90, 1.51) vs 1.05 (0.80, 1.43); p=0.019), and higher lactate on arrival (4.5 (3.1, 6.9) vs 3.7 (2.4, 6.0); p<0.001).

Patients who arrived with a low MA value were also independently evaluated. Of 133 patients in the cohort, only 18 received early cryoprecipitate. Baseline characteristics of patients with low MA who did and did not receive early cryoprecipitate were similar. Survival was also similar between those who did and did not receive early cryoprecipitate (44% vs 48%, respectively, p=1). However, patients who received early cryoprecipitate required more transfusions in the first 24 hours after injury: median RBC 27 (IQR 8–48) vs 4 (1–9), PLT 27 (9–46) vs 4 (2–10), PLT 27 (8–47) vs 4 (1–9).

DISCUSSION

In this study, we report a low incidence of admission hypofibrinogenemia among our institution's trauma population. We found that patients that present with HYPOFIB are seriously injured, particularly with severe traumatic brain injury and profound shock. Early use of cryoprecipitate was not associated with improved survival, regardless of arrival fibrinogen status. Early plasma and/or WB resuscitation, however, was associated with an increased time to death but no change in outcomes.

We found a much lower rate of admission HYPOFIB in our patients compared with those that have recently been reported in the literature. In an article published by Meizoso *et al*[13] in 2022, the authors report a HYPOFIB rate of 15% among 476 patients meeting the highest-level trauma activation criteria. In contrast, we found a HYPOFIB rate of only 2% among 6618 level 1 trauma activations and only 7% among patients requiring emergency release blood and MTP activation. Both studies used a fibrinogen level <150 mg/dL to define HYPOFIB with our study also considering patients with r-TEG angle value of <60° as HYPOFIB. Similarly, McQuilten *et al*[19] report 29.3% of 469 trauma patients requiring massive transfusion had an earliest measured fibrinogen level of <100 mg/dL. Additionally, in the recent FEISTY (Fibrinogen Early In Severe Trauma studY) RCT, Winearls *et al* report 62 of 98 trauma patients judged by the treating physician to have significant hemorrhage or with an assessment of blood consumption score ≥2 were HYPOFIB as defined by a rotational thromboelastometry (ROTEM) fibrinogen assay (FIBTEM A5) value of ≤10. It is not entirely clear why there is such high variation in the reported rates of HYPOFIB, and disparity in the criteria used to define HYPOFIB makes comparison between studies more difficult. Meizoso *et al*[13] report a 2:1: MTP protocol with no reported prehospital administration of blood products and Winearls *et al*[18] and McQuilten[19] *et al* are multicenter studies with variable MTPs. We suspect that our institution's standardized initiation of balanced 1:1 and/or WB resuscitation in the prehospital and early hospital setting is primarily responsible for our low rate of HYPOFIB as plasma and WB both contain fibrinogen.

The recently published CRYOSTAT-2 (Early Cryoprecipitate in Major Trauma Hemorrhage) Study randomized patients to standard resuscitation practices or standard practices plus empiric cryoprecipitate transfusion.[22] In this trial, no clinical benefit was seen in patients randomized to empiric transfusion. It is noteworthy that the median time from admission to first administration of cryoprecipitate was 68 min, with less than 70% of the intervention arm patients receiving cryoprecipitate within the study goal of 90 minutes from admission. Of even more interest for planning future studies, whereas blunt injured patients had a non-significant trend towards benefit (p=0.16), penetrating patients had a 74% increased mortality. Whether this reflects a greater degree of hypofibrinogenemia in blunt injured patients (particularly head injuries) remains to be elucidated. However, the CROSTAT-2 Trial did not report their rates of HYPOFIB as these data were not available for all patients.[22]

If early, balanced resuscitation is able to reduce the incidence of arrival HYPOFIB to the levels we observed in our patient population, then addition of concentrated fibrinogen replacement to MTPs would add additional cost and complexity although only benefitting a small percentage of patients. Furthermore, viscoelastic assays such as r-TEG and ROTEM provide rapid results and have been shown to accurately and reliably diagnose HYPOFIB and lead to more efficient and precise correction of coagulopathy.[10 23–25] This was demonstrated in the FEISTY Trial[18] in which patients were screened for HYPOFIB using ROTEM prior to administration of either cryo or FC. In this study, Winearls *et al* found that the median time from ROTEM blood draw to commencement of first cryo administration was 60 minutes and time to FC administration was only 29 minutes.

Aside from this difference in the rate of HYPOFIB, our results are largely in agreement with those reported by prior studies. As observed previously, we found that patients presenting with HYPOFIB had significantly higher ISS, head AIS Score with lower GCS Score, higher rates of shock and coagulopathy, and higher transfusion requirements and mortality.[13 26] Among our 146 HYPOFIB patients, we observed no difference in mortality in those that received early cryo compared with those that did not. Although there is some retrospective evidence that early

cryo administration may be associated with reduced mortality,[27 28] our results are consistent with the available RCT data that have demonstrated no difference in clinical outcomes.[14–18 22] In our study, we did observe that among HYPOFIB patients, early WB or plasma transfusion was significantly associated with an increased time to death and there was a trend towards association with survival as well, though this relationship was not significant. These results provide further evidence that earlier initiation of balanced resuscitation may provide greater clinical benefit than inclusion of concentrated fibrinogen replacement in MTPs.

Ideally, balanced resuscitation of hemorrhaging patients begins immediately in the prehospital setting. This has previously been shown to be feasible multiple times,[29 30] and most notably in the 2018 PAMPer (Prehospital Air Medical Plasma) Trial,[31] patient's receiving prehospital plasma transfusion were found to have a lower 30-day mortality. In this study, we found that patients severely enough injured to be HYPOFIB on arrival to the ED were significantly more likely to have received prehospital WB. We speculate that prehospital administration of blood products to our most severely injured patients likely contributed to the low rates of HYPOFIB observed in this patient population. Of note, a relatively high proportion of the CRYOSTAT-2 participants (43%) received prehospital blood product transfusion, and we speculate this may have contributed to the lack of clinical benefit seen with empiric transfusion.[22] Only one RCT, the FlinTIC (Fibrinogen in Trauma-Induced Coagulopathy) Trial,[16] has assessed the effect of prehospital concentrated fibrinogen replacement. They report improved early hospital FIBTEM values and higher fibrinogen concentrations in the patients who received prehospital FC, but this study was likely underpowered to demonstrate any difference in clinical outcomes. Although prehospital concentrated fibrinogen replacement may not be necessary if balanced prehospital resuscitation can be initiated, further research is warranted to discover the optimal prehospital resuscitation protocol.

Our study has limitations that must be considered during its interpretation. Despite our large sample size, this article includes patients from only one center and therefore limits our ability to generalize our findings to other institutions. All of our patient population was assessed for HYPOFIB using TEG values on arrival, but only 12% had measured Clauss fibrinogen levels. This limits our ability to compare our results to studies defining HYPOFIB purely based on measured fibrinogen level. Additionally, PLTs are not available in the prehospital setting for the majority of patients and therefore, interpretation of the prehospital RBC:PLT ratio should be done cautiously. Few patients (5%) in our cohort received early cryoprecipitate, which limits the interpretation of our findings. To identify an increase in survival from 84% to 89% (α 0.1, β 0.2), over 6000 patients would be needed. Therefore, a benefit of cryoprecipitate may exist but be undetected in our data set. Lastly, although clinical variables were prospectively recorded into the study registry, these variables were retrospectively analyzed for the purposes of this study. This study design allows us to observe associations with clinical outcomes but restricts our ability to demonstrate causality. Further research will be necessary to support our hypothesis that balanced resuscitation may be responsible for the low HYPOFIB rates observed in our center.

In this study, we demonstrated substantially lower rates of hypofibrinogenemia among trauma patients than what have recently been reported in the literature. We hypothesize that this may be at least in part due to our center's practice of early initiation of balanced resuscitation. If the rates of hypofibrinogenemia found in our patient population can be achieved in other centers using a similar resuscitation strategy, it would suggest empiric inclusion of concentrated fibrinogen replacement in MTPs may not be warranted. Although these results simply reflect the practice of a single center and from a retrospective data set, they are in agreement with the results of the available RCT data. Further research is needed to define the optimal role of concentrated fibrinogen replacement in the care of severely injured patients.

Media summary

We found a substantially lower rate of hypofibrinogenemia among severely injured patients compared with what has recently been reported. This may be due to our center's early initiation of balanced resuscitation.

Contributors KMM, JC, CEW, and BAC designed the study; DL, KMM, JBB, MS performed data collection; KMM, GEH, and JC performed data analysis; KMM, GEH, JC, CEW, and BAC interpreted the data; DL, KMM, GEH, JBB, MS, JC, CEW, and BAC wrote the article. BAC is the guarantor for this article.

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