Fibrinogen supplementation for the trauma patient: Should you choose fibrinogen concentrate over cryoprecipitate?

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BACKGROUND: Trauma-induced coagulopathy is frequently associated with hypofibrinogenemia. Cryoprecipitate (Cryo), and fibrinogen concentrate (FC) are both potential means of fibrinogen supplementation. The aim of this study was to compare the outcomes of traumatic hemorrhagic patients who received fibrinogen supplementation using FC versus Cryo.

METHODS: We performed a 2-year (2016–2017) retrospective cohort analysis of the American College of Surgeons Trauma Quality Improvement Program database. All adult trauma patients (≥18 years) who received FC or Cryo as an adjunct to resuscitation were included. Patients with bleeding disorders, chronic liver disease, and those on preinjury anticoagulants were excluded. Patients were stratified into those who received FC, and those who received Cryo. Propensity score matching (1:2) was performed. Outcome measures were transfusion requirements, major complications, hospital, and intensive care unit lengths of stay, and mortality.

RESULTS: A matched cohort of 255 patients who received fibrinogen supplementation (85 in FC, 170 in Cryo) was analyzed. Overall, the mean age was 41 ± 19 years, 74% were male, 74% were white and median Injury Severity Score was 26 (22–30). Compared with the Cryo group, the FC group required less units of packed red blood cells, fresh frozen plasma, and platelets, and had shorter in-hospital and intensive care unit length of stay. There were no significant differences between the two groups in terms of major in-hospital complications and mortality.

CONCLUSION: Fibrinogen supplementation in the form of FC for the traumatic hemorrhagic patient is associated with improved outcomes and reduced transfusion requirements as compared with Cryo. Further studies are required to evaluate the optimal method of fibrinogen supplementation in the resuscitation of trauma patients. (*J Trauma Acute Care Surg.* 2022;93: 453–460.

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level III.

KEY WORDS: Hemorrhagic trauma patients; fibrinogen supplementation; fibrinogen concentrate; cryoprecipitate.

Trauma remains the leading cause of death among individuals aged 1 year to 46 years old,[1] and the most common cause of early death is uncontrolled hemorrhage.[2–4] Compounding this is the development of acute coagulopathy of trauma, which occurs in up to a quarter of injured patients and is associated with a fourfold increase in mortality.[5] Acute coagulopathy of trauma is attributed to the lethal triad of acidosis, hypothermia, and loss of coagulation factors. This loss of coagulation factors is due to a combination of ongoing factor loss and dilution, endotheliopathy, consumptive coagulopathy, and hyperfibrinolysis.[6]

Fibrinogen is the final factor before formation of the stable fibrin clot, an essential component of the coagulation cascade. It is one of the earliest coagulation factors to decrease in major bleeding, and fibrin clots formed in a low fibrinogen environment are more prone to fibrinolysis.[7–9] For bleeding trauma patients receiving massive transfusion, plasma fibrinogen level below 100 mg/dL is a strong independent risk factor for death, with a stepwise increase in adjusted odds of mortality for every unit decrease in fibrinogen level on presentation.[10,11]

The principle of damage-control resuscitation mandates early and rapid replacement of coagulation factor with the use of factor concentrates in addition to hemostatic resuscitation practices. Studies show improved outcomes when fibrinogen supplementation is given as an adjunct to resuscitation in exsanguinating trauma patients.[12–16] Augmentation of fibrinogen levels for these patients is achieved with either cryoprecipitate (Cryo) or fibrinogen concentrate (FC), as fresh frozen plasma is not as effective and lacks the fibrinogen concentration necessary to achieve this goal.[17–19]

Both FC and Cryo demonstrated feasibility of use among hypofibrinogenemic trauma patients.[20,21] Although it is well studied in the cardiac surgery patient population,[22,23] there is currently only one study in the trauma patient population comparing FC and Cryo as adjuncts to resuscitation.[24] The aim of our study is to compare outcomes of bleeding trauma patients who received fibrinogen supplementation in the form of FC versus Cryo. Our primary hypothesis was that fibrinogen supplementation using FC would be associated with lower 24-hour blood product transfusion requirements as compared with using

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Cryo. Our secondary hypothesis was that FC use would be associated with a faster time to first fibrinogen supplementation as compared with Cryo.

MATERIALS AND METHODS

Study Design and Population

We performed a 2-year (2016–2017) retrospective cohort analysis of the American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) database. The TQIP database compiles more than 300 patient- and center-related variables from more than 800 trauma centers in the United States. Institutional review board granted this study exemption from approval because the TQIP database contains only deidentified data.

Inclusion and Exclusion Criteria

We identified all adult (≥18 years) trauma patients who received at least one unit of packed red blood cells (PRBCs) or fresh frozen plasma (FFP) within the initial 4 hours of presentation and either FC or Cryo as an adjunct to resuscitation. We excluded patients who were dead on arrival, those with bleeding disorders or chronic liver disease, and those on preinjury anticoagulation. We also excluded patients who received both FC and Cryo transfusions.

Data Points

We extracted data points pertaining to patient demographics (age, sex, race, body mass index), emergency department (ED) vitals (systolic blood pressure [SBP], pulse rate [HR], respiratory rate [RR]. Glasgow Coma Scale [GCS]), injury characteristics (mechanism of injury, Injury Severity Score [ISS], each body region Abbreviated Injury Scale [AIS] including head and neck-AIS, chest-AIS, abdomen-AIS, and extremity-AIS), patient comorbidities (diabetes mellitus, hypertension, cerebrovascular accident, and chronic obstructive pulmonary disease [COPD]) ACS trauma center verification level, intervention for hemorrhage control (laparotomy, thoracotomy, angioembolization), intensive care unit (ICU) and hospital lengths of stay (LOS), and number of days spent on the ventilator. We also extracted data regarding the blood products transfused within 24 hours of ED presentation (including units of pRBC, FFP, and platelets) time to first fibrinogen supplementation, major in-hospital complications, and in-hospital mortality.

FC and Cryo administration were identified using *International Classification of Diseases, Tenth Revision, Procedure Coding System* (ICD-10-PCS) codes, and timing of first fibrinogen supplement administration was identified by extracting the time to procedure associated with the first administration. All procedures that trauma patients in the ACS-TQIP database undergo are provided as a separate file that contains both the individual procedure codes that patients underwent as well as the timings associated with each procedure, which can be linked with the main file using a unique patient identifier ID.

Outcome Measures

Our primary outcome measure was 24-hour blood product transfusion requirements. We also assessed the primary outcome of 24-hour blood product transfusion requirements after excluding blood product volumes received within 4 hours. Our secondary outcome measure was time to first fibrinogen supplementation. Other outcomes measured included major complications (deep venous thrombosis, pulmonary embolism, myocardial infarction, and cerebrovascular accident [CVA], acute respiratory distress syndrome, and acute kidney injury), in-hospital mortality, and survivor-only hospital and ICU LOS, and ventilator days. Length of stay was reported among survivors only, in order to minimize the risk of survival bias in this severely injured cohort of trauma patients.

Statistical Analysis

We performed descriptive statistics for the baseline characteristics of the cohort. Continuous normally distributed variables were described using a mean and a standard deviation. Continuous skewed variables were described using a median and an interquartile range. Categorical variables were described using counts and percentages. To compare baseline characteristics and outcomes between the two prematch study groups, we used the independent t test to compare the means and the Mann-Whitney U test to compare the medians. Categorical variables were compared using Pearson's χ^2 test and Fisher's exact test when expected cell counts were less than 5. Taking into account the paired nature of the postmatch data, we used the Wilcoxon paired-samples signed-rank test to compare nonparametric continuous variables, the paired sample Student's *t* test to compare parametric continuous variables, and the McNemar test to compare categorical variables among the two groups.

To control for confounding factors, we performed propensity score matching using the nearest neighbor method without replacement. Patients who received FC as an adjunct to resuscitation were matched in a 1:2 ratio to a similar cohort of patients who received Cryo as an adjunct to resuscitation. Propensity score matching was used to match both groups for demographics, ED vital signs, mechanism of injury, ISS, other body regions' AIS, comorbidities, ACS verification level of trauma centers, and hemorrhage control interventions. A logistic regression model was used to generate a propensity score for each patient based on confounding factors. Patients in each group were matched based on their propensity scores within 0.00001 of the estimated score.

Although we performed a propensity score match to adjust for intergroup confounding variable differences, we performed additional multiple linear regression analyses on the postmatch data to assess for any residual intragroup confounding bias. We performed multivariable linear regression analyses for the primary outcomes, adjusting for patient demographics (including age, sex, race), ED vitals (including SBP, HR, RR, and GCS), comorbidities (including diabetes mellitus, hypertension, COPD, and CVA), injury parameters (including penetrating injury, ISS, other body regions-AIS scores, severe abdominal injury), hemorrhage control interventions (including laparotomy, thoracotomy, sternotomy), ACS trauma center verification, and choice of fibrinogen supplementation agent.

Alpha (α) was set at 5%, and a p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (version 27; SPSS, Inc., Armonk, NY). We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies (please see supplemental digital content 1 [SDC 1, http://links.lww.com/TA/C635]

TABLE 1. Prematch Baseline Characteristics of the Study Cohort

	FC (n = 85)	Cryo (n = 6,328)	*p*
Demographics			
Age: mean ± SD, y	44 ± 19	40 ± 17	**0.039***
Age ≥65 y, n (%)	15 (17.6)	695 (11.0)	0.052
Male, n (%)	63 (74.1)	4,926 (77.8)	0.412
White race, n (%)	62 (72.9)	3,541 (56.0)	**0.002***
BMI, mean ± SD	28 ± 6	28 ± 6	0.361
ED vital signs			
SBP, mmHg, median [IQR]	108 [85–136]	110 [86–136]	0.414
HR, beats/min, median [IQR]	107 [92–128]	113 [90–132]	0.185
RR, breaths/min, median [IQR]	20 [18–24]	20 [16–26]	0.904
GCS, median [IQR]	6 [3–15]	11 [3–15]	**0.036***
SBP <90 mm Hg, n (%)	29 (34.1)	1,939 (30.6)	0.490
Injury characteristics			
Penetrating injury, n (%)	22 (25.9)	2,253 (35.6)	0.063
Head-AIS, median [IQR]	3 [0–4]	0 [0–3]	**0.007***
Chest-AIS, median [IQR]	3 [0–3]	3 [0–4]	0.327
Abdomen-AIS, median [IQR]	2 [0–3]	3 [0–4]	**0.002***
Abdomen AIS ≥3, n (%)	33 (38.8)	3,384 (53.5)	**0.007***
Extremity-AIS, median [IQR]	2 [0–3]	2 [0–3]	0.502
ISS, median [IQR]	27 [17–36]	29 [22–41]	0.061
ISS ≥16, n (%)	71 (83.5)	5,750 (90.9)	**0.020***
Comorbidities, n (%)			
Diabetes mellitus	9 (10.6)	288 (4.6)	**0.009***
Hypertension	14 (16.5)	705 (11.1)	0.122
COPD	2 (2.4)	131 (2.1)	0.856
CVA	4 (4.7)	31 (0.5)	**<0.001***
Hemorrhage control intervention, n (%)			
Laparotomy	23 (27.1)	3,252 (51.4)	**<0.001***
Thoracotomy	8 (9.4)	643 (10.2)	0.820
Angioembolization	6 (7.0)	1,550 (24.5)	**<0.001***
Intubated, n (%)	67 (38.8)	5,664 (89.5)	**0.002***
ACS trauma center verification level, n (%)			
Level I	41 (48.2)	3,383 (53.5)	**<0.001***
Level II	33 (38.8)	1,207 (19.1)	—
Others or unknown verification status	11 (13.0)	1,738 (27.5)	—

*Values of statistical significance shown in bold.
BMI, body mass index; SD, standard deviation; IQR, interquartile range.

for the full Strengthening the Reporting of Observational Studies in Epidemiology guidelines checklist).

RESULTS

We analyzed a total of 1,305,281 adult trauma patients, of which 6,413 patients met inclusion and exclusion criteria, i.e. those who received at least one unit of pRBC and FFP, and received fibrinogen supplementation in the form of either FC (n = 85) or Cryo (n = 6,328). The flow diagram of patients included in the final analysis is illustrated in SDC 2, http://links.lww.com/TA/C636 (please see supplemental digital content). The prematch demographics and baseline characteristics of our study population are summarized in Table 1. Prematch, patients in the FC group had significantly higher average age and head-AIS, and higher proportions of White patients and those with previous history of diabetes mellitus or cerebrovascular accident compared with those in the Cryo group. The Cryo group had higher average GCS and abdomen-AIS, and higher rates of laparotomy, angioembolization, and treatment at an ACS Level I trauma center.

After performing the propensity score match, we identified a cohort of 255 matched patients (FC, 85; Cryo, 170). The mean age of our study population was 41 ± 19 years, 74% of patients were male, and 74% were White. The median ISS was 26, 29% of injuries were penetrating, and 38% of patients received thoracotomy or laparotomy. The mean SBP on presentation was 102 ± 44 mm Hg, and the median GCS score was 8.[3–15] The majority of patients (57%) were treated at an ACS Level I trauma center, while 25% of patients were treated at a Level II trauma center. The overall median hospital length of stay was 8[2–21] days. The postmatch demographics and baseline characteristics of our study population are described in Table 2. There were no significant differences between the two groups postmatch.

TABLE 2. Postmatch Baseline Characteristics of the Study Cohort

	FC (n = 85)	Cryo (n = 170)	*p*
Demographics			
Age: mean ± SD, y	44 ± 19	45 ± 19	0.156
Age ≥65 y, n (%)	15 (17.6)	31 (18.2)	0.718
Male, n (%)	63 (74.1)	125 (73.5)	0.617
White race, n (%)	62 (72.9)	126 (74.1)	0.628
BMI, mean ± SD	28 ± 6	27 ± 6	0.110
ED vital signs			
SBP: median [IQR], mm Hg	108 [85–136]	102 [78–132]	0.731
HR: median [IQR], beats/min	107 [92–128]	108 [84–127]	0.974
RR: median [IQR], breaths/min	20 [18–24]	20 [17–25]	0.413
GCS, median [IQR]	6 [3–15]	9 [3–15]	0.360
SBP <90 mm Hg, n (%)	29 (34.1)	63 (37.1)	1.000
Injury characteristics			
Penetrating injury, n (%)	22 (25.9)	51 (30.0)	0.493
Head-AIS, median [IQR]	3 [0–4]	2 [0–4]	0.378
Chest-AIS, median [IQR]	3 [0–3]	3 [0–3]	0.418
Abdomen-AIS, median [IQR]	2 [0–3]	2 [0–3]	0.766
Abdomen-AIS ≥3, n (%)	33 (38.8)	62 (36.5)	0.678
Extremity-AIS, median [IQR]	2 [0–3]	2 [0–3]	0.938
ISS, median [IQR]	27 [17–36]	26 [17–34]	0.291
ISS ≥16, n (%)	71 (83.5)	150 (88.2)	0.189
Comorbidities, n (%)			
Diabetes mellitus	9 (10.6)	20 (11.8)	0.607
Hypertension	14 (16.5)	25 (14.7)	1.000
COPD	2 (2.4)	4 (2.4)	1.000
CVA	4 (4.7)	2 (1.2)	0.375
Hemorrhage control intervention, n (%)			
Laparotomy	23 (27.1)	46 (27.1)	1.000
Thoracotomy	8 (9.4)	19 (11.2)	0.581
Angioembolization	6 (7.0)	13 (7.4)	0.847
Intubated, n (%)	67 (78.8)	153 (90.0)	0.170
ACS trauma center verification level, n (%)			
Level I	41 (48.2)	84 (49.7)	0.371
Level II	33 (38.8)	59 (34.2)	—
Others or unknown verification status	11 (13.0)	27 (16.1)	—

TABLE 3. Outcomes of the Postmatch Study Cohort

Outcomes	FC (n = 85)	Cryo (n = 170)	*p*
Primary outcome			
24-h Transfusion requirements (including 4-h transfusions)			
pRBC, median [IQR]	4 [3–9]	10 [6–20]	**<0.01***
FFP, median [IQR]	3 [1–6]	8 [4–14]	**<0.01***
Platelets, median [IQR]	1 [0–2]	2 [1–4]	**<0.01***
24-h Transfusion requirements (excluding 4-h transfusions)			
pRBC, median [IQR]	1 [0–1]	3 [1–5]	**<0.01***
FFP, median [IQR]	1 [0–1]	2 [1–3]	**<0.01***
Platelets, median [IQR]	0 [0–1]	1 [0–2]	**<0.01***
Secondary outcome			
Mins to 1st fibrinogen supplement, median [IQR]	43 [45–120]	64 [59–153]	**0.038***
Other outcomes			
In-hospital complications, n (%)			
Thromboembolic complications**	8 (9)	21 (12)	0.38
Deep venous thrombosis	3 (4)	9 (5)	0.63
Pulmonary embolism	4 (5)	6 (4)	0.69
Myocardial infarction	0 (0)	1 (1)	1.00
Cerebrovascular Accident	1 (1)	6 (4)	0.63
Acute respiratory distress syndrome	8 (5)	4 (5)	1.00
Acute kidney injury	6 (4)	3 (4)	1.00
In-hospital LOS, days, median [IQR]	6 [1–16]	9 [2–23]	**0.04***
ICU LOS: median [IQR], d	4 [1–9]	5 [2–12]	**0.04***
Total ventilator days, median [IQR]	2 [1–6]	3 [2–9]	0.10
Mortality, n (%)	37 (43)	72 (42)	0.63

*Values of statistical significance shown in bold.
**Thromboembolic complications were defined as deep venous thrombosis, pulmonary embolism, myocardial infarction, or cerebrovascular accident.
Mins, minutes.

The primary and secondary outcomes are summarized in Table 3. In terms of primary outcomes, patients in the FC group had significantly lower 24-hour requirements of pRBC, FFP, and platelets, and results were similar when 24-hour transfusion requirements were assessed after excluding 4-hour transfusion volumes received. In terms of secondary outcomes, patients in the FC group had earlier time to first fibrinogen supplementation as compared with the Cryo group. In terms of the remaining outcomes, there were no differences between the two groups in terms of in-hospital complications. Patients in the FC group had significantly shorter hospital and ICU LOS but no difference in ventilator days among survivors compared with patients in the Cryo group. There was no difference between the two groups in terms of in-hospital mortality. Table 4 describes the outcomes comparison between the prematch FC and Cryo groups.

On multivariate analyses of the postmatch data, fibrinogen supplementation with FC was independently associated with lower 24-hour PRBC (β, −6.9; 95% confidence interval [CI], −3.8 to −10.0; $p < 0.001$; Durbin-Watson statistic 1.92) (Table 5), FFP (β −5.1; 95% CI, −3.1 to −7.1; $p < 0.001$; Durbin Watson statistic, 1.88) (Table 6), and platelet transfusion requirements (β −1.2 [95% CI -0.4 to −2.1], $p = 0.006$, Durbin-Watson statistic 2.00) (Table 7, Supplemental Digital Content 3 [SDC 3, http://links.lww.com/TA/C637]). We also performed multivariate analyses for the primary outcome measures after excluding the 4-hour blood product transfusion volumes. The results were qualitatively similar when compared with the multivariate analyses for the primary outcome measures after including the 4-hour blood transfusion volumes.

DISCUSSION

Our study is the largest to date comparing FC and Cryo for use in the trauma patient population in terms of clinical outcomes. The results show that fibrinogen supplementation for the bleeding trauma patient in the form of FC is associated with lower overall transfusion requirements at 24 hours, earlier time to first fibrinogen administration, and shorter LOS as compared with Cryo, with no associated differences in terms of mortality and major complications. These findings bear important implications as the ideal massive transfusion protocol remains to be elucidated, and the important role of fibrinogen supplementation in damage-control resuscitation efforts is continually being investigated and highlighted, without consensus on the ideal fibrinogen supplementation agent.

Although fibrinogen supplementation for bleeding trauma patients is beginning to be widely accepted due to increasing recognition and evidence, there is continued controversy over the ideal agent for this task. Cryo is regularly administered for fibrinogen replacement in acquired bleeding disorders in the

TABLE 4. Outcomes of the Prematch Study Cohort

Outcomes	FC (n = 85)	Cryo (n = 6,328)	*p*
Primary Outcome			
24-h Transfusion requirements (including 4-h transfusions)			
pRBC, median [IQR]	4 [3–8]	13 [7–24]	**<0.01***
FFP, median [IQR]	3 [1–5]	9 [4–18]	**<0.01***
Platelets, median [IQR]	1 [0–2]	2 [1–4]	**<0.01***
24-h Transfusion requirements (excluding 4-h transfusions)			
pRBC, median [IQR]	1 [0–1]	3 [1–6]	**<0.01***
FFP, median [IQR]	1 [0–1]	2 [1–4]	**<0.01***
Platelets, median [IQR]	0 [0–1]	1 [0–2]	**<0.01***
Secondary outcome			
Mins to 1st fibrinogen supplement, median [IQR]	45 [43–120]	184 [126–236]	**<0.001***
Other outcomes			
In-hospital complications, n (%)			
Thromboembolic complications**	8 (9)	711 (11)	0.596
Deep venous thrombosis	3 (4)	431 (7)	0.232
Pulmonary embolism	4 (5)	166 (3)	0.235
Myocardial infarction	0 (0)	46 (1)	0.430
Cerebrovascular accident	1 (1)	124 (2)	0.604
Acute respiratory distress syndrome	8 (5)	280 (4)	0.900
Acute kidney injury	6 (4)	570 (9)	0.079
In-hospital LOS: median [IQR], d	6 [1–16]	10 [2–24]	**0.011***
ICU LOS: median [IQR], d	4 [1–9]	5 [2–14]	**0.006***
Total ventilator days, median [IQR]	2 [1–6]	3 [1–9]	**0.010***
Mortality, n (%)	37 (43)	2,632 (42)	0.719

*Values of statistical significance shown in bold.
**Thromboembolic complications were defined as deep venous thrombosis, pulmonary embolism, myocardial infarction, or cerebrovascular accident.

TABLE 5. Multiple Linear Regression-Predictors of 24-h PRBC Transfusion Requirements

	β	95% CI	*p*
Demographics			
Age, every year increase	+0.01	−0.08 to +0.11	0.783
Male sex	−0.11	−3.69 to +3.46	0.951
White race	−0.078	−3.71 to +3.55	0.966
ED vitals			
SBP <90 mm Hg	+5.27	+1.92 to +8.63	**0.002**
HR, every bpm increase	+0.05	0.00 to +0.10	0.049
RR, every bpm increase	+0.02	−0.21 to +0.24	0.892
GCS score, every point increase	+0.28	−0.06 to +0.62	0.108
Intubation	+1.14	−3.42 to +5.72	0.624
Comorbidities			
Diabetes mellitus	+1.06	−4.37 to +6.49	0.701
Hypertension	−3.11	−8.41 to +2.18	0.247
COPD	+6.52	−4.80 to +17.13	0.227
CVA	+3.74	−6.45 to +13.49	0.470
Operative interventions			
Thoracotomy	+8.77	+3.22 to +14.31	**0.002**
Laparotomy	+3.77	−0.38 to +7.93	0.075
Sternotomy	+7.22	−4.67 to +19.12	0.233
Injury parameters			
ISS, every unit increase	−0.07	−0.28 to +0.14	0.523
Penetrating injury	+2.96	−1.31 to +7.24	0.174
Severe abdominal injury	+4.35	−0.87 to +9.56	0.102
Head AIS, every unit increase	+1.59	+0.37 to +2.82	**0.011**
Chest AIS, every unit increase	+0.69	−0.64 to +2.02	0.308
ACS Level I trauma center	−3.28	−6.34 to −0.22	**0.036**
FC administration	−6.91	−3.82 to −10.03	**<0.001**

Values of statistical significance shown in bold.

United States, United Kingdom, and Australia.[25,26] However, many European countries have largely replaced Cryo with FC due to safety and logistical concerns. This divergence in practice has important implications as FC and Cryo are two distinct coagulation factor concentrate products. Both are coagulation factor concentrates derived from pooled plasma, however FC is lyophilized, whereas Cryo is not. There are perceived advantages to using FC over Cryo: it has a higher, more standardized fibrinogen concentration; viral inactivation; no need for ABO compatibility matching; and ease of reconstitution and administration. Cryo must be stored at −25 degrees Celsius and requires ABO compatibility matching and thawing before administration. Cryo also contains coagulation factors in addition to fibrinogen, namely FVIII, vWF, FXIII, fibronectin, antithrombin, and alphas-2 antiplasmin, unlike FC.[27] Considering the important logistical and hemostatic profile differences between agents, it is worthwhile to compare their performance in terms of clinical outcomes.

Our findings show that FC use is associated with earlier time to fibrinogen supplementation in trauma patients. The median time to first fibrinogen supplement in our study cohort was 45 minutes for patients in the FC group and 64 minutes for those in the Cryo group. These findings are in line with those of the FEISTY trial, a prospective multicenter controlled pilot trial comparing the time to fibrinogen replacement with FC versus with Cryo for bleeding hypofibrinogenemic trauma patients.[24] The investigators found that FC was administered earlier on average at 29 minutes versus 60 minutes for Cryo. Restoration of fibrinogen levels was achieved in both arms of the study. The reason behind this earlier administration time observed in both our study and the FEISTY trial may pertain to the lyophilized nature of FC, allowing it to be stored on the shelf at the hospital or indeed even in the ambulance for long periods of time. This allows for rapid reconstitution and administration without need for thawing or crossmatching beforehand, in stark contrast to Cryo. However, our results, and those of the Fibrinogen Early In Severe Trauma studY and CRYOSTAT-1 trials also showed that Cryo may be administered faster than previously thought possible.[21] For now, the data implies that FC use is associated with faster fibrinogen supplementation compared with Cryo. Future large-scale prospective studies may be able to better guide us on which exact factors can be optimized during administration of either fibrinogen supplementation agent.

The results of the FEISTY trial did, however, differ from ours in that their median time to FC administration was shorter (29 minutes vs. 45 minutes). The reasons behind this may be attributed to the prospective, randomized, and well-coordinated nature of the FEISTY trial, and the difference in trauma systems between Australia and the United States. It is possible that simply participating in a clinical trial would have led to clinical and research teams exhibiting increased efforts to administer either

TABLE 6. Multiple Linear Regression-Predictors of 24-h FFP Transfusion Requirements

	β	95% CI	*p*
Demographics			
Age, every year increase	+0.01	−0.05 to +0.07	0.734
Male sex	−0.01	−2.34 to +2.34	0.995
White race	−0.39	−2.76 to +1.97	0.743
ED vitals			
SBP <90 mm Hg	+3.56	+1.42 to +5.78	**0.001**
HR, every bpm increase	+0.02	−0.01 to +0.06	0.130
RR, every bpm increase	+0.01	−0,14 to +0.15	0.899
GCS score, every point increase	+0.10	−0.12 to +0.32	0.380
Intubation	+1.12	−1.86 to +4.10	0.459
Comorbidities			
Diabetes mellitus	+2.11	−1.43 to +5.66	0.067
Hypertension	−3.57	−6.97 to −0.06	0.241
COPD	+3.52	−3.40 to +10.45	**0.046**
CVA	+4.37	−2.28 to +11.27	0.317
Operative interventions			
Thoracotomy	+6.23	+2.61 to +9.85	**0.001**
Laparotomy	+2.50	−0.217 to +5.71	0.071
Sternotomy	+7.24	−0.52 to +15.01	0.061
Injury parameters			
ISS, every unit increase	−0.05	−0.19 to +0.09	0.486
Penetrating injury	+2.91	+0.12 to +5.71	**0.041**
Severe abdominal injury	+2.73	−0.68 to +6.15	0.116
Head AIS, every unit increase	+0.81	+0.02 to +1.62	**0.045**
Chest AIS, every unit increase	+0.32	−0.55 to +1.19	0.472
ACS Level I trauma center	−2.35	−4.35 to −0.35	**0.021**
FC administration	−5.13	−3.14 to −7.12	**<0.001**

Values of statistical significance shown in bold.

arm of the intervention since the time to administration was the primary outcome of the study. This is in contrast to the retrospective nature of our study, and also the fact that the trauma centers administering fibrinogen supplementation were not coordinating with one another. The Australian trauma system is distinct form the US trauma system,[28] with an increased physician presence during the prehospital phase of management, which may influence the timing of decision making and administration of fibrinogen supplementation. At this point, it is pertinent to mention that our results and those of the FEISTY trial both fall in line with the literature regarding average time to FC supplementation. The FiiRST-1 trial found that 95% of trauma patients received FC within 60 minutes, and the E-FIT-1 trial found 69% of trauma patients received FC within 45 minutes.[20,29]

We found that FC use was associated with lower blood product transfusion requirements at 24 hours compared with Cryo. This was in contrast to the findings of the FEISTY trial, which found that both blood product and crystalloid transfusions at 24 hours were similar between the two groups. We think that this discrepancy may be due to the much larger sample size in our study (n = 255) compared with the FEISTY trial (n = 62), being adequately powered to detect a difference in transfusion requirements. The FC group in the FEISTY trial also had a significantly higher rate of operative intervention compared with the Cryo group, indicating that these patients may have been more severely injured than the Cryo group, possibly counteracting any benefit of FC administration in reducing transfusion requirements. It is also interesting to note that in the FEISTY trial, the majority of patients did not receive FFP or platelets during their resuscitation. Indeed the average ratio of PRBC: FFP: Platelets in the FEISTY trial was 5:0:0. It is possible that the appropriate timing of fibrinogen supplementation in the form of FC or Cryo guided by ROTEM FIBTEM A5 testing led to prevention or earlier correction of traumatic coagulopathy, which may have meant that the majority of patients did not require further FFP or platelet transfusions. This may be one plausible explanation for the lack of differences in transfusion requirements seen between the two groups in the FEISTY trial. Regarding the reasons behind the reductions in PRBC, FFP, and platelets among our FC group, it is possible that the earlier administration and higher average fibrinogen concentrations of FC was associated with earlier correction of plasma fibrinogen levels, earlier formation of stable fibrin clots, and subsequently earlier correction of trauma-induced coagulopathy, leading to earlier hemostasis and reduced transfusion requirements. However, this is merely a hypothesis as we do not have available the time to achieving definitive hemostasis, viscoelastic testing results, nor the reasoning behind the administration of fibrinogen supplements to either group. Interestingly, in the FEISTY trial, FC use was associated with a higher increase in FIBTEM A5 values compared to the Cryo arm. Nevertheless, these findings are important as the clinical implications of the choice of fibrinogen supplementation in the bleeding hypofibrinogenemic trauma patient are currently still being elucidated.

Venous thromboembolic (VTE) complications are an important consideration in all coagulation factor concentrates, including FC and Cryo, as they are all inherently procoagulant therapies. Due to the previously mentioned differences in coagulation factor concentrations and hemostatic profile between FC and Cryo, concerns of a dissimilar effect of the two agents on VTE rates are justified. We found no associated difference in terms of VTE complications between the two groups, and this is aligned with the results of the FEISTY and FIBERS trial[22] comparing FC to Cryo in the cardiac surgery patient population. The overall VTE rate in our study was 11%, comparable to the 9% rate found in the FIBERS trial. These findings suggest that there should be no concerns about increased VTE risk when using FC in lieu of Cryo in the trauma patient. In addition, we also found no associated difference in in-hospital mortality between the two groups. Our overall mortality rate (42%) was higher than that reported by the FEISTY trial (15%), indicating the severely injured nature of our cohort. The FEISTY trial reported deaths to be higher in the FC group (24% vs. 6%) compared with the Cryo group, in contrast to our findings. However, on subanalysis of these deaths, it was found that approximately half were related to traumatic brain injuries and not hemorrhage. We were unable to describe the cause of death in our patient cohort, and future prospective large-scale clinical studies with an emphasis on assessing survival benefits of FC versus Cryo are warranted.

Although it was not our aim to assess differences in cost between the two agents, it is worth mentioning that an economic analysis found FC to be at least twice as expensive as Cryo, even after adjusting for any Cryo wastage that may occur.[30] The authors concluded that for FC to be competitive with Cryo, it must be demonstrated that FC is associated with a reduction of at least 0.25 to 0.66 ICU days. Interestingly, both our study and the FEISTY trial demonstrated reductions in ICU and hospital LOS among patients who received FC compared with Cryo. In addition, the economic analysis also surveyed 30 US transfusion centers and found that 97% did not use FC for acquired bleeding and that the major reasons for this were prohibitive cost and off-label usage with insufficient evidence. We think that the US reliance on Cryo as the sole fibrinogen supplement for trauma patients should be revisited in light of our findings as well as those of the FEISTY trial, especially as increasing evidence mounts in favor of FC and a potential exists for reducing the cost of FC production.

Our finding of reduced blood product transfusion requirements in the FC group compared with the Cryo group may have both individual-level as well as system-level implications. For the individual trauma patient, a decreased requirement of conventional blood products would be associated with reduced donor exposure, which is cumulative based on the number of total blood product units received. Although the risks of unnecessary donor exposure associated with blood product transfusions have considerably reduced over time because of improved donor screening and blood processing techniques, this exposure may become especially significant for massively transfused patients, correlated with the risks of sepsis, transfusion overload, and increased exposure to biological response modifiers.[31] Furthermore, the United States is currently facing a shortage of blood products as blood donation came to a halt due to the COVID-19 pandemic.[32] For the trauma system, such decreases in blood product transfusion requirements for bleeding patients may translate into reduced system-wide strain due to the current high demand but low supply for blood products.

Our study has several limitations. First, due to the study design utilizing a national database, we rely on propensity score matching to provide adequate retrospective control of confounding

variables. We did, however, assess for both intergroup as well as intragroup confounding bias. We performed multiple linear regression analyses after the propensity match, and found fibrinogen supplementation with FC to be independently associated with lower 24-hour blood product transfusion requirements. Further, we were limited by which variables we could assess. Notably, we could not provide information regarding the crystalloid or colloid fluid resuscitation practices, coagulation test parameters including viscoelastic testing results, or plasma fibrinogen levels for our study cohort. We could not provide information regarding the decision-making process behind fibrinogen supplementation in our study cohort, nor whether the target fibrinogen level was achieved. Further, we could only assess short-term outcomes such as 24-hour transfusion requirements and in-hospital mortality, as no information on long-term outcomes of patients beyond the hospital discharge was available. However, given that hemorrhage-related mortalities tend to occur early, these short-term endpoints remain highly relevant.

We performed power analyses, and for a power of 80%, beta error rate of 20% and alpha significance level of 5%, we found the minimum detectable effect size for complications to be 0.46, and for mortality to be 0.39. According to Cohen's conventions, a minimum detectable effect size of between 0.2 and 0.5 is considered as "medium." Thus, although we found that there were no statistically significant differences between the two groups in terms of mortality and major complications, our study may not have been adequately powered to detect small differences in effect size in terms of these outcome measures. Future prospective studies that are appropriately powered to detect these differences are warranted. In addition, although the results of our study have been compared with those of the FEISTY trial, the retrospective observational nature of our study must be kept in mind compared with the prospective randomized interventional nature of the FEISTY study. Finally, this study took place in US trauma centers, where prehospital and in-hospital resuscitation practices and resource availability may differ from those employed in different trauma systems. As such, these findings may not be generalizable to all trauma systems. Future prospective randomized controlled trials on the impact of choice of fibrinogen supplement for bleeding hypofibrinogenemic trauma patients are warranted to address these limitations. The FEISTY-II trial is currently ongoing to build on the previous pilot trial. This Phase III trial intends to enroll more than 900 severely injured bleeding patients randomized to receiving either FC or Cryo, and compare clinical outcomes with a primary focus on days alive out of hospital at 90 days. Future research directions should also include an investigation of the optimal volume and composition of reconstitution fluid that should be used when administering FC to bleeding trauma patients.

CONCLUSION

Fibrinogen supplementation in the form of FC for the hemorrhaging trauma patient is associated with reduced transfusion requirements, faster fibrinogen supplementation, and shorter LOS as compared with Cryo. These findings indicate that the choice of method of fibrinogen supplementation has a significant effect on clinical outcomes and further prospective studies are warranted to evaluate the optimal method of fibrinogen supplementation in the resuscitation of bleeding trauma patients. Our findings, coupled with the superior storage characteristics of FC, may provide further supporting evidence for the prehospital use of FC, as well as in rural and/or critical access facilities with limited resources. Further, the findings of reduced LOS associated with FC use may offset some of the high costs associated with this factor concentrate. However, these findings must be investigated further and confirmed in large-scale prospective studies with robust cost analyses.

AUTHORSHIP

O.O., T.A., R.R., M.D., and B.J. designed this study. A.N., C.S., R.F., L.G., O.O., and B.J. searched the literature. O.O., L.G., R.R., M.D., and B.J. collected the data. A.N., T.A., C.S., O.O., R.F., Mo.D., and B.J. analyzed the data. All authors participated in data interpretation and article preparation.

DISCLOSURE

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