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Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial

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Abstract

Background. Decreased plasma fibrinogen concentration shortly after injury is associated with higher blood transfusion needs and mortality. In North America and the UK, cryoprecipitate transfusion is the standard-of-care for fibrinogen supplementation during acute haemorrhage, which often occurs late during trauma resuscitation. Alternatively, fibrinogen concentrate (FC) can be beneficial in trauma resuscitation. However, the feasibility of its early infusion, efficacy and safety remain undetermined. The objective of this trial was to evaluate the feasibility, effect on clinical and laboratory outcomes and complications of early infusion of FC in trauma.

Methods. Fifty hypotensive (systolic arterial pressure ≤100 mm Hg) adult patients requiring blood transfusion were randomly assigned to either 6 g of FC or placebo, between Oct 2014 and Nov 2015 at a tertiary trauma centre. The primary outcome, feasibility, was assessed by the proportion of patients receiving the intervention (FC or placebo) within one h of hospital arrival. Plasma fibrinogen concentration was measured, and 28-day mortality and incidence of thromboembolic events were assessed.

Results. Overall, 96% (43/45) [95% CI 86–99%] of patients received the intervention within one h; 95% and 96% in the FC and placebo groups, respectively ($P=1.00$). Plasma fibrinogen concentrations remained higher in the FC group up to 12 h after admission with the largest difference at three h (2.9 mg dL^{-1} vs. 1.8 mg dL^{-1}; $P<0.01$). The 28-day mortality and thromboembolic complications were similar between groups.

Conclusions. Early infusion of FC is feasible and increases plasma fibrinogen concentration during trauma resuscitation. Larger trials are justified.

Key words: Fibrinogen concentrate; plasma fibrinogen; trauma coagulopathy; haemorrhage management; trauma

In trauma, haemorrhage accompanied by coagulopathy remains the leading cause of early in-hospital mortality.[1–4] Hypofibrinogenaemia is a key component of the acute traumatic coagulopathy (ATC) and is present at admission to trauma centres in haemorrhaging trauma patients[5–7] and has been associated with increased transfusion requirements and mortality.[8 9] Accordingly, nonrandomized data suggest that fibrinogen supplementation - either at higher ratios to red blood cell transfusion or based on viscoelastic testing - improves coagulation, reduces bleeding, and consequently increases survival in traumatic haemorrhage.[10–17]

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Editor's key points

- Hypofibrinogenaemia can lead to increased blood transfusion and mortality in severe trauma.
- Cryoprecipitate is used for fibrinogen supplementation in some countries, but fibrinogen concentrate has advantages that might be beneficial in acute traumatic coagulopathy.
- In this feasibility trial, fibrinogen concentrate could be administered in the first hour of hospital admission, and resulted in increased plasma fibrinogen concentrations for up to 12 h.

In North America and the UK, cryoprecipitate transfusion is the standard-of-care for fibrinogen supplementation during acute trauma resuscitation. Cryoprecipitate is a frozen product that requires thawing and pooling before use, traditionally resulting in prolonged time to infusion in ATC in clinical practice.[18 19] In Canada, pooling of single units of cryoprecipitate is performed at blood banks in hospital settings considerably prolonging preparation time, although in the setting of a clinical trial in two major trauma centres in the UK, the feasibility of early cryoprecipitate transfusion for trauma resuscitation was recently demonstrated.[20] However, as any other human plasma-derived product, it carries transfusion-related risks.[21]

Alternatively, administration of lyophilized fibrinogen concentrate (FC) is the standard-of-care for fibrinogen supplementation in many European countries.[11–17 22] Fibrinogen concentrate is a human plasma-derived product that undergoes pathogen inactivation, requires reconstitution before infusion and has standardized amounts of fibrinogen for potentially expedited use during acute trauma resuscitation. Of note, cryoprecipitate contains not only fibrinogen but also factor VIII, von Willebrand factor, factor XIII and platelet microparticles. Both products have significant quantities of fibronectin.

However, very limited evidence supports the use of FC in trauma.[23 24] Furthermore, in several countries, it is licensed only for congenital hypofibrinogenaemia.[22] Additionally, the feasibility of its early infusion, efficacy and safety remain undetermined.[23 24] Therefore, we conducted a randomized controlled trial comparing the infusion of 6 g of FC to placebo within 1h of hospital arrival. The main objectives of this trial were to evaluate the feasibility, effect on plasma fibrinogen concentration and complications of early infusion of FC in trauma patients.

Methods

Studydesign andparticipants

This is a single centre, randomized-controlled, double-blinded, feasibility trial utilizing a conventional, parallel group, two-armed design with accrual period between October 2014 and November 2015.

Adult (age >18 yr) severe trauma (blunt or penetrating) patients were eligible if they were:

i. assessed by the trauma team at our institution and
ii. identified as being at risk for significant haemorrhage as evidenced by:
   a. systolic arterial pressure ≤100 mm Hg and
   b. requiring uncrossmatched red blood cell (RBC) transfusion at any time from injury until 30 min after hospital arrival. The need for uncrossmatched RBC transfusion has good discriminatory power for prediction of significant haemorrhage in our institution.[25]

Patients were excluded if they had: received any blood or blood products before admission to our trauma centre; presented more than 6 h after injury; estimated body weight < 50 kg; had known or suspected pregnancy; catastrophic brain injury (defined as any of: Glasgow Coma Scale of three as a result of brain injury; need of immediate neurosurgery, focal signs such as anisocoria or imaging evidence of intracranial bleeding with mass effect, transcranial gunshot wound, or open skull fracture with exposure/loss of brain tissue); non-haemorrhagic shock (i.e. obstructive [cardiac tamponade, tension pneumothorax and massive pulmonary emboli], neurogenic, cardiogenic, or septic); underlying hereditary or acquired coagulopathy; known or suspected use of anticoagulant medications such as warfarin, low-molecular weight heparin, and direct thrombin and factor Xa inhibitors; or were moribund and predicted to expire in a few h.

Consent

Public endorsement for the trial was obtained as evidenced by community consultation before study commencement. As a result of the time-sensitive nature of the trial intervention, a waiver of consent was granted for patient recruitment by Sunnybrook Research Ethics Board in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Individual Medical Emergencies (Article 3.8).[26] Patients were enrolled into the study after an independent physician authorization; and participants and/or their families notified when feasible and given the opportunity to remove themselves or their family member from ongoing continuation in the trial.

Randomization and masking

In-house research assistants were responsible for verifying inclusion and exclusion criteria, and patient eligibility affirmed by a qualified investigator before randomization by the blood bank. A computerized random number generator was used to generate sequences of random numbers. Allocation was concealed with sealed opaque envelopes in the blood bank, with allocation sequence derived from blocks of four for the placebo and FC groups. Randomization was stratified by type of trauma (blunt/penetrating) to assure balanced groups.

Interventions

The study intervention (SI) was prepared by trained blood bank technologists based on predetermined standard operating procedures for FC and placebo. The aseptic reconstitution of each gram of FC as per manufacturer's instructions takes a few min. Based on bench simulations performed by our blood bank in preparation for the trial, approximately 20 min is required for reconstitution and pooling of a total dose of 6 g of FC. We, therefore, set a target of 30 min from request to randomize to infusion for the investigational product in this trial.

Fibrinogen concentrate (RiaSTAP™ CSL-Behring, King of Prussia, PA, USA) is a freeze-dried lyophilized plasma product distributed in powdered form. In Canada, RiaSTAP™ is supplied in a 1g per vial dosage form and requires reconstitution in 50 ml of sterile water. If randomized to the FC arm, six vials of

RiaSTAP™ were reconstituted and pooled with a final volume of 300 ml in a mini-bag placed in an amber cover bag to be blindly infused. The dosage of 6 g FC was selected based on a systematic review on the use of FC in trauma, which described single doses ranging from 2 g to 8 g for a total regimen of 16 g and a median dose of 6g in this population.[24] Similar dose ranges have also been used in non-trauma bleeding patients.[23 27 28]

For subjects randomized to the placebo arm, normal saline was pooled in similar mini-bags covered with an amber bag to ensure blinding and a timer set at 20 min was used by the blood bank technologist, to guarantee similar preparation times to FC. The 300 ml blinded mini-bags were administered intravenously as 'rapid push' over approximately three min (1 g per 25 sec) via level I automated pressure pump using Hospira Lifeshield Primary IV™ (San Jose, CA, USA) set in our pre-trial simulations. The safety of administering 1 g RiaSTAP™ in approximately 20 s has been described in the literature, with total doses up to 14 g administered in less than 5 min in cardiac and aortic surgery trials.[29–33]

Following the study intervention, blood product (plasma, platelet and cryoprecipitate) transfusion was ordered based on standard coagulation tests, as per our institution's massive haemorrhage protocol.[34] Our blood bank proactively prepares and issues predefined packs of blood and blood products to the bedside, that are utilized at the discretion of the treating physician.

Outcome measures

The primary outcome was feasibility evaluated by the proportion of subjects receiving SI within 1 h of hospital admission. Based on the trial's sample size of 50 subjects, feasibility was defined by 85% (96% confidence interval [CI; 72–98%]) of study participants receiving the SI within 1 h of hospital admission. According to the trial design, eligibility determination and randomization should be completed within 30 min of hospital arrival. Then, the blood bank had to randomize and prepare SI for its infusion by a bedside nurse within 30 min. Therefore, the infusion of SI had to be initiated within 1 h of trauma centre arrival.

Other feasibility endpoints evaluated included: (i) proportion of subjects receiving SI before any allogeneic blood transfusion; (ii) times to randomization, issue, and start of infusion (interval between research assistant/trauma team call to blood bank and randomization plus interval between randomization time to completion of SI issuing by blood bank, plus interval between blood bank issuing and SI infusion); (iii) duration of infusion (start and end time of mini-bag infusion); (iv) wastage of SI (SI prepared but not infused); (v) missed patients (proportion of patients who were eligible but not randomized); and (vi) randomization errors (randomized despite not meeting eligibility criteria or meeting exclusion criteria).

In order to assess the effect of FC on plasma fibrinogen concentration, blood samples were obtained and Clauss fibrinogen assay was performed on admission; and at +one h, +three h, +11 h, +23 h and +47 h after start time of SI (±30 min).

Clinical endpoints included 28-day all-cause mortality; rates of symptomatic thromboembolic complications (defined by the evidence of deep venous thrombosis, or myocardium infarction, or cerebral vascular accident, or pulmonary embolism, or arterial thrombosis at any time during hospital stay); rates of asymptomatic deep vein thrombosis (DVT) (evidenced by leg Doppler performed at day 7 of hospital stay); and incidence of acute lung injury/acute respiratory distress syndrome (defined by the Berlin Classification of acute lung injury) during hospitalization. Allergic reactions to the SI infusion were also assessed. Cause of death was blindly adjudicated by an independent physician and one of the investigators, and defined as mainly as a result of exsanguination; neurological/traumatic brain injury/withdrawal of care; or multiple organ failure/sepsis).

Sample size

Our institution receives approximately 220 patients per yr with significant bleeding that requires at least 1 unit of RBC within 24 h of hospital admission. Accounting for a missed case rate of about 10%, we expected to randomize 25 patients in each arm over a period of 15 months or less. A sample size of 25 subjects in each arm allows a precision of (13%) at 96% confidence level, assuming a baseline of 85% feasibility of study participants receiving the SI within 1 h of hospital admission.

Statistical analysis

Analyses for the main feasibility, clinical endpoints and efficacy outcomes were performed on the per-treatment cohort for study participants for whom the SI (placebo or FC) was administered. For 28-day overall mortality, both intention-to-treat and per-treatment analyses were performed. Statistical differences in binary feasibility and safety outcomes were tested using χ^2 statistics or Fisher's exact test. In consideration of a relatively small sample size, we used Wilson and Jeffreys methods of binomial CI for the main feasibility endpoint. Relative risks (RR) and 95% CI were calculated for other clinical endpoints in comparing FC with placebo. Fibrinogen concentrations were displayed using box-plots for both study arms for all time-points and their differences at each time point were analysed using Student's *t*-test. No imputation was performed for missing data. For laboratory and co-intervention data, non-parametric Wilcoxon Rank Sum test or Student's t-test was used when appropriate depending on the data distribution. All tests were two-sided and *P*-values < 0.05 were considered statistically significant.

An independent data safety and monitoring board blinded to the randomization data, monitored the results of the study and ensured the safety of study participants. This committee adjudicated on the validity of excluding patients who were randomized in error and did not receive the SI. As a result of the narrow window (30 min) available to recruit patients in our study involving a time-sensitive intervention (30 min), complete information on eligibility (exclusion criteria) was not available at the time of recruitment for a few patients. Data were analysed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). The trial protocol is registered at ClinicalTrial.gov, number NCT02203968.

Results

Patient characteristics and co-interventions

During the study period, 50 patients were randomized and analysed; one was excluded for the 28-day follow-up assessment. Detailed patient flow through the trial is depicted in Figure 1. Of note, five subjects inadvertently randomized did not receive the SI and were excluded post randomization. Out of these 5 subjects, the only one randomized to placebo sustained an unsalvageable traumatic brain injury. Out of the remaining four subjects randomized to FC, two had no blood transfusion order, one had a tension pneumothorax, and one progressed

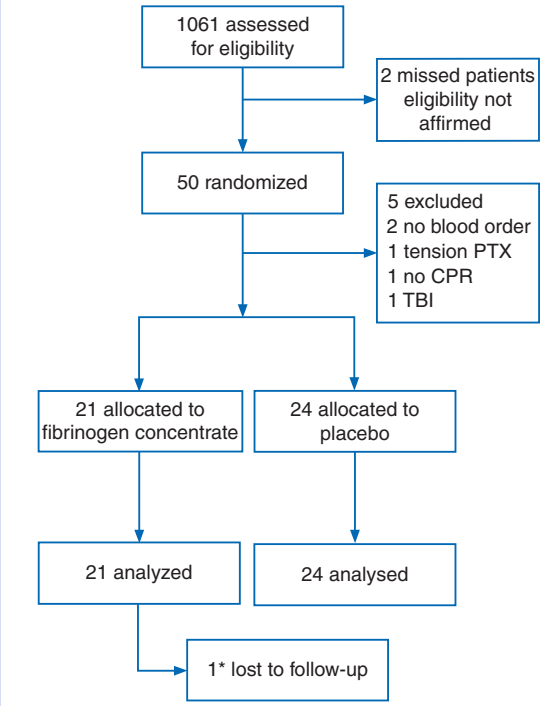

Fig 1 Flow of patients through the rial.
*Lost to follow-up and excluded from outcome at 28 days
CPR, cardio-pulmonary resucitation; PTX, pneumothorax; TBI, traumatic brain injury

into cardiac arrest shortly after admission and had resuscitative efforts withdrawn because of a "do not resuscitate" advance healthcare directive communicated by the substitute decision maker.

Apart from a difference in median age (28 yr in placebo vs. 48 yr in FC), the two study groups were balanced with respect to baseline characteristics (Table 1). There were no significant differences with respect to co-interventions and transfusion of blood and blood products between study groups (Table 2). No transfusion of plasma, platelets or cryoprecipitate occurred before SI in either group. Although numerically more subjects received cryoprecipitate after the SI in the placebo arm (33% vs. 14%), no statistical significance was demonstrated (P=0.18).

Feasibility outcomes

Out of 45 subjects, 43 received the SI within the one h target feasibility for infusion (95.6% [95% CI 86–99]). Both Wilson and Jeffreys CIs had lower limit >85%, which demonstrates significant evidence of feasibility. For the total cohort, eligibility was confirmed and infusion of the SI initiated within 17 min (9) and 51 min (8), respectively. Although preparation time for the SI was slightly shorter in the placebo group (23 [4] min vs 26 [5] min; P=0.03), both times to eligibility (17 [9] min in the placebo vs 16 [8] min in the FC; P=0.6) and infusion (51 [9] min in the placebo vs 50 [8] min in the FC; P=0.6) were similar between study groups. The median duration of SI infusion was 4 (3–6) min. Two study participants in each study arm had SI infusion time > 10 min. Duration of SI infusion was similar between groups (4.5 (3–6) min with placebo vs 4 (3–10) min with FC; P=0.85). The wastage rate of the SI was 10% (5/50) for the randomized subjects.

Effect on plasma fibrinogen concentration

After infusion of 6 g of FC, plasma fibrinogen concentration increased to and remained within normal range values (>2 g L^{-1}) throughout resuscitation (Fig. 2). Higher plasma fibrinogen concentrations were measured 1 h after SI infusion until approximately 12 h of hospitalization in the FC group; then no further significant differences were measured between groups at 24 h and 48 h of hospital admission (Fig. 2). After 1 h of FC infusion, the increase in plasma fibrinogen concentration was 0.93 g L^{-1} (increasing from 1.91 g L^{-1} at admission to 2.71 g L^{-1}; P<0.01).

Clinical endpoints

Overall mortality rate for the 50 randomized subjects was 10% (5/50). The intention-to-treat analysis for 28-day mortality showed no differences between study groups (placebo 2/25 [8%] vs FC 3/24 [12.5%]; P=0.67). On the per-treatment analysis, all-cause mortality and deaths by exsanguination were also statistically similar between study arms (Table 3). There were no statistically significant differences noted between rates of DVT, pulmonary embolism, acute lung injury, acute respiratory distress syndrome, acute kidney injury, multiple organ failure/sepsis, and infection between the two groups (Table 3). No myocardial infarction, stroke, or allergic reactions were observed in either group.

Discussion

This is the first in-hospital randomized trial evaluating use of FC in trauma. Our data suggest that rapid and early infusion of FC (within one h of hospital arrival) is feasible in the setting of a randomized clinical trial, and FC increases plasma fibrinogen concentration.

In our trial, 95% of study participants received FC at a median time of 50 min of trauma centre arrival. Traditionally, fibrinogen supplementation occurs late during trauma resuscitation. In a large prospective observational trial (PROMMTT) involving 10 US Level I trauma centres, 359 out of 1245 patients received cryoprecipitate during resuscitation for fibrinogen supplementation.[19] In this trial, the first dose of cryoprecipitate was documented at a median time from hospital arrival of 2.8 h (IQR 1.7–4.5). In our institution, we had previously reported that cryoprecipitate was transfused at a median of 4.5 h (2.9–7.5) from hospital arrival in trauma.[18]

Recently, early cryoprecipitate transfusion for major haemorrhage was evaluated in a feasibility non-blinded randomized trial.[20] The primary objective of transfusion of cryoprecipitate within 90 min of arrival was achieved in 85% (95% CI 69–100) of 21 trauma patients requiring activation of the major haemorrhage protocol. Half of the intervention group received cryoprecipitate after 60 min of hospital arrival. This trial demonstrated that cryoprecipitate can also be transfused early during trauma resuscitation. However, the longer time to fibrinogen replacement with cryoprecipitate as compared with the time to FC infusion in our trial (95% of participants received FC < 1 h of arrival) illustrated the challenges of rapidly transfusing cryoprecipitate, which requires thawing before being delivered to bedside. In

Table 1 Subject characteristics. N values represent the number of subjects in each group in whom the measured parameter is available. [1]Age difference, P=0.05 (non-parametric Wilcoxon Rank Sum Test used); [2]Acute Traumatic Coagulopathy defined by INR ≥1.3. FC, fibrinogen concentrate; %, percentage of occurrence; IQR, interquartile ranges; SD, standard deviation

	N	Placebo	N	FC
Age[1], yr, median (range)	24	28 (19–88)	21	48 (19–78)
Sex, male (%)	24	87	21	77
Penetrating type of trauma (%)	24	54	21	52
Time from injury to hospital, min, median (IQR)	24	43 (33–55)	21	44 (30–59)
Injury Severity Score, median (IQR)	24	23 (18–29)	21	25 (19–29)
Glasgow Coma Scale, median (IQR)	24	15 (12–15)	21	15 (14–15)
Systolic Arterial Pressure, mm Hg, median (IQR)	24	99 (82–99)	21	106 (80–144)
Temperature, °C, mean (SD)	15	35 (0.7)	13	35 (1.4)
pH, mean (SD)	15	7.2 (0.2)	14	7.2 (0.1)
Lactate, g L^{-1}, median (IQR)	20	5 (4–8)	20	5 (3–9)
International Normalized Ratio, mean (SD)	22	1.1 (0.2)	19	1.2 (0.3)
Fibrinogen, g L^{-1}, median (IQR)	22	1.9 (1.7–2.4)	19	1.9 (1.6–2.3)
Platelet × 10^9 L^{-1}, median (IQR)	22	254 (200–282)	20	269 (242–314)
Haemoglobin, g L^{-1}, median (IQR)	22	122 (112–144)	20	118 (105–125)
Troponin, g L^{-1}, median (IQR)	19	7 (5–12)	15	8 (5–25)
Acute Traumatic Coagulopathy[2] (%)	22	18	19	26
Fibrinogen <2 g L^{-1} (%)	22	54	19	53

Table 2 Co-interventions and transfusion[1]. Transfusion and crystalloid data are presented as median (interquartile ranges). [1]For the transfusion data, numbers represent units transfused for each product. In our institution, platelets are issued in pools of 4 units (random donor method) or 5 units (apheresis method); and cryoprecipitate is issued in pools of 10 units per adult dose. DVT, deep venous thrombosis; FC, fibrinogen concentrate; RBC, red blood cells; SI, study intervention

	Placebo (N=24)	FC (N=21)	P
Tranexamic Acid, %	96	100	1.00
Vasopressor, %	54	67	0.39
Urgent Trauma Laparotomy, %	42	52	0.47
Orthopaedic Operation, %	42	38	0.81
Angioembolization, %	4	9	0.59
Chemical DVT Prophylaxis, %	83	95	0.35
SI before RBC Transfusion, %	12.5	14.3	1.00
Pre-SI RBC Transfusion	1.96 (1.7–2.4)	1.91 (1.6–2.3)	0.68
Post-SI RBC Transfusion	1.73 (1.3–2.0)	2.71 (2.2–3.4)	0.20
24 h RBC Transfusion	3 (2–4)	3 (2–5)	0.41
24 h Plasma Transfusion	1.75 (1.4–2)	2.73 (2.4–3.6)	0.72
24 h Platelet Transfusion	2.32 (1.9–2.7)	2.81 (2.5–3.6)	0.53
24 h Cryoprecipitate Transfusion	3.5 (2.9–4)	4.0 (3.1–4.6)	0.18

Canada and Australia, cryoprecipitate is pooled after thawing on demand in blood banks; therefore its preparation and time to infusion would be even longer.

In trauma, several retrospective studies have documented improvements in coagulation; reduction in transfusion volumes; and increased survival rates with use of FC.[11–16] The utility of FC in reducing blood product requirements has also been demonstrated in other clinical settings.[23 24 27 28] Accordingly, in 2015, the Canadian Armed Forces (CAF) adopted FC (RiaSTAP™, CSL Behring) to start damage control resuscitation for bleeding patients in the austere far forward combat setting.

Infusion of 6 g of FC led to increased plasma fibrinogen concentrations (>2.0 g L^{-1}) compared with placebo during active haemorrhage. This finding is in keeping with the recent randomized trial on early cryoprecipitate transfusion (4 g of fibrinogen), where plasma fibrinogen concentrations were higher (>1.8 g L^{-1}) than placebo throughout resuscitation.[20] The dose utilized in our study, equivalent to approximately 15 units of cryoprecipitate, resulted in a similar increase in plasma fibrinogen concentrations (0.93 g L^{-1}).[14 16 35 36] Finally, we observed that plasma fibrinogen concentrations equilibrate at 24 h and 48 h between study groups. This fibrinogen response to traumatic haemorrhage and supplementation suggests an inherent and effective regulation of fibrinogen concentrations that might be protective against late thrombosis. Similar 24 h plasma fibrinogen concentrations have also been documented between controls and patients who had supplementation of exogenous fibrinogen, irrespectively of dosage in other clinical settings and in an animal model of traumatic hemorrhage.[16 32 37–39] Collectively, early replacement of fibrinogen with a dose of 6 g of FC might not be required; lower initial single doses could be considered when designing future trials in a population of trauma patients at risk of significant haemorrhage.

Although not powered to detect differences in complications between study groups, mortality rates were not different between groups. However, the small sample size with only three deaths on per-treatment analysis produces highly unstable estimates; thus no definitive conclusion can be drawn. Furthermore, as described in Table 3, all deaths in this trial can be considered unavoidable.

Fibrinogen concentrate is a human-derived product that is subjected to viral inactivation step (pasteurisation at 60 °C for 20 h) during manufacturing to mitigate potential infectious agent transmission risks. A comprehensive systematic review evaluating FC use in the perioperative setting and 27 yr of

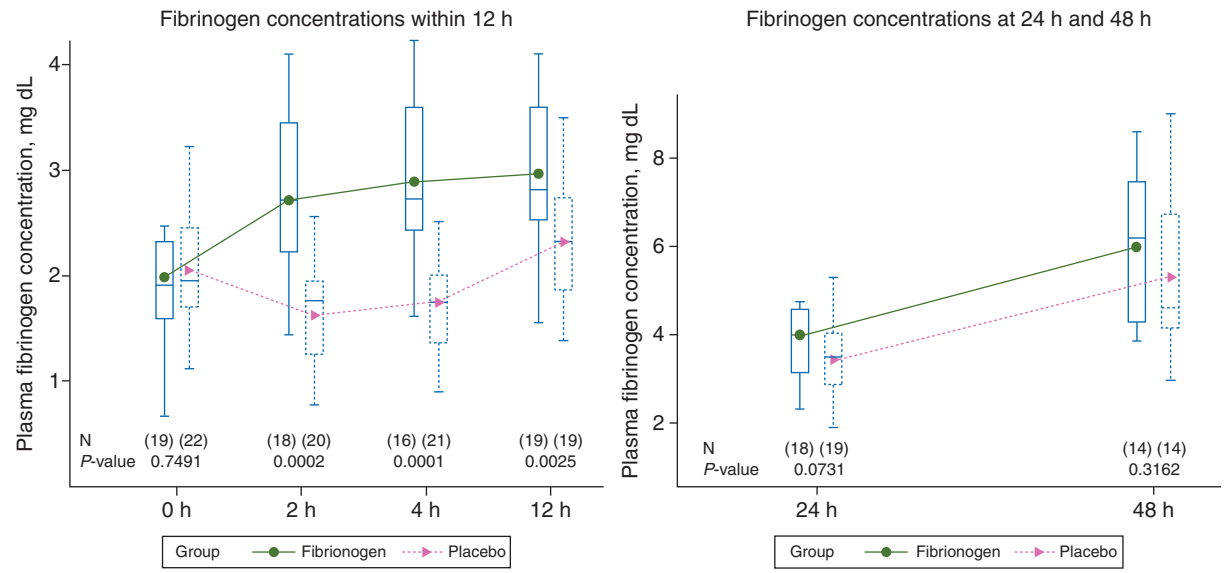

Fig 2 Plasma Fibrinogen Concentrations throughout 48 h of Hospitalization.
Data are presented as means (standard deviation) or median (interquartile ranges)
FC, fibrinogen concentrate

Table 3 Clinical endpoints. Data are presented as number of positive outcomes over total number of patients assessed per study group, and percentages. Placebo considered reference standard for relative risk calculation. [1]One subject in the FC group died nine days after hospital admission as a result of worsening severe brain injury; in the placebo group, the single death was mostly related to anoxic brain injury after cardiac arrests as a result of initial traumatic bleeding. [2]One study participant was lost to follow-up at day 28. [3]The only death in the trial (in the FC group) that was classified as being mainly as a result of exsanguination occurred in a 61 year-old female with a history of two previous myocardial infarctions. It happened in less than 2 h of hospital arrival after prehospital and in-hospital cardiac arrests after resuscitative efforts were discontinued because of futility. CI, confidence interval; FC, fibrinogen concentrate

	Placebo	FC	Relative Risk	95% CI
All-cause 28-day mortality[1]	1/24 (4.2)	2/20[2] (10)	2.4	−0.2 to 23
Death by exsanguination[3]	0	1/21 (4.8)	NA	NA
Symptomatic Deep Venous Thrombosis	0	0	NA	NA
Deep Venous Thrombosis on Leg Doppler	3/14 (21.4)	2/15 (13.3)	0.62	−0.1 to 3.2
Pulmonary Embolism	1/24 (4.2)	2/21 (9.5)	2.3	−0.2 to 23.4
Myocardial Infarction	0	0	NA	NA
Stroke	0	0	NA	NA
Acute Lung Injury	2/24 (8.3)	0	NA	NA
Acute Respiratory Distress Syndrome	2/24 (8.3)	0	NA	NA
Acute Kidney Injury	2/24 (8.3)	3/21 (14.3)	1.7	−0.3 to 9.3
Multiple Organ Failure	2/24 (8.3)	2/21 (9.5)	1.1	−0.2 to 7.4
Infection	8/24 (33.3)	5/21 (23.8)	0.7	−0.3 to 1.8

pharmacosurveillance concluded that there was no significant increase in thrombotic events associated with FC.[40 41]

Limitations

This is a small feasibility trial not powered to exclude differences in treatment effects. Therefore, one should exercise caution when interpreting clinical measures in this small trial, which are presented to inform the design of larger studies. Although not statistically significant, a clinically important age difference between study groups was observed. As a result of the small sample size, several older subjects in the FC arm skewed the group's median resulting in higher median age compared with the placebo group. Accordingly, 21% of subjects in

the placebo group were older than 50 years whereas 48% of fibrinogen group subjects were > 50 years of age. Older patients in the FC group might have influenced its rates of complications. It is known that the geriatric trauma population is at increased risks of complications.[42]

Five subjects who did not receive the SI were excluded post-randomization. This is a well-recognized issue in emergency research testing time-sensitive interventions.[43] However, the 95% CI for the trial's primary outcome remained within the acceptable limit with 45 subjects. Future trials should account for a minimum of 10% post-randomization exclusions when determining sample size.

Conclusions

Infusion of 6 g of FC within one h of arrival to our trauma centre is feasible and improves plasma fibrinogen concentration by approximately 1 g L^{-1} in a population of trauma patients at risk of significant haemorrhage. This trial suggests that FC might be a faster alternative to cryoprecipitate transfusion for fibrinogen supplementation in haemorrhaging trauma patients. Finally, these data will inform the design of larger trials, in order to definitively evaluate the efficacy and safety of FC in trauma resuscitation.

Authors' contributions

Study design/planning: B.N., J.C., H.T., H.P., S.R., P.K., A.A., W.X., R.S., A.M.G., C.C., R.H., A.N., A.B.

Study conduct: B.N., J.C., H.T., H.P., S.R., P.K., A.A., W.X., R.S., A.M.G., C.C., R.H., A.N., A.B.

Data analysis: B.N., J.C., H.T., H.P., S.R., P.K., A.A., W.X., R.S., A.M.G., C.C., R.H., A.N., A.B.

Writing paper: B.N., J.C., H.T., W.X., A.B.

Revising paper: all authors

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Declaration of interest

B.N. received speaker honoraria and a research grant from CSL Behring, the manufacturer of RiaSTAP™. S.R. received unrestricted educational grants for a Consensus Conference on ROTEM™ from CSL Behring and TEM International. H.T. was part of the Canadian Armed Forces during the time this trial was conducted. H.P. is a scientist at the Defence Research and Development Canada and Canadian Forces Health Services.

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