DRDC-RDDC-2016-P157

Fibrinogen in the Initial Resuscitation of Severe Trauma (FiiRST)

A Randomized Pilot Feasibility Trial

Barto Nascimento[1], Jeannie Callum[1], Homer Tien[1], Henry Peng[2], Sandro Rizoli[3], Paul Karanicolas[1], Asim Alam[1], Wei Xiong[1], Rita Selby[1], Ana Maria Garzon[1], Connie Colavecchia[1], Raymond Howald[1], Avery Nathens[1], Andrew Beckett[4]

[1] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[2] Defence Research and Development Canada, Toronto Research Center, Toronto, Ontario, Canada

[3] St Michael's Hospital, Toronto, Ontario, Canada

[4] Canadian Forces Health Services, the 1 Canadian Field Hospital, Petawawa, Ontario, and McGill University Health Centre, Montreal, Quebec, Canada

Abstract

Objectives: To evaluate the feasibility of a randomized trial, effect on outcomes and complications of early infusion of fibrinogen concentrate(FC) in trauma patients.

Background: Fibrinogen is essential for adequate primary and secondary hemostasis. Decreased plasma fibrinogen concentration shortly following injury is associated with higher transfusion needs and mortality. In North America, cryoprecipitate and/or plasma transfusion is the standard of care for fibrinogen supplementation during acute hemorrhage, which often occurs late during trauma resuscitation. Alternatively, FC, a pathogen-inactivated lyophilized product-licensed for congenital hypofibrinogenemia only in Canada and USA-may potentially be beneficial in trauma resuscitation. However, the feasibility of its early infusion, efficacy and safety remains undetermined.

Methods: Fifty hypotensive(systolic blood pressure≤100mmHg) adult trauma patients requiring blood transfusion was ordered were randomly assigned to either 6g of FC or placebo between Oct 2014 and Nov 2015 at a tertiary trauma center. The primary outcome, feasibility, was assessed by the proportion of patients receiving the intervention within 1h of hospital arrival. Plasma fibrinogen concentration was compared between study groups. Safety was measured based on 28-day mortality and thromboembolic events.

Results: Overall, 95.6%(43/45) [95%CI 86-99%] of patients received the intervention within 1h; 95.2% and 95.8% in the FC and placebo groups, respectively(*P*=1.00). Plasma fibrinogen concentrations remained higher in the FC group up to 12h of admission with the largest difference at 3h (2.9mg/dL vs. 1.8mg/dL;difference=1.1mg/dL;*P*<0.01). The 28-day mortality and thromboembolic complications were similar between the groups.

Conclusions: Early infusion of fibrinogen concentrate is feasible, improves plasma fibrinogen concentration and appears safe in trauma.

Keywords: fibrinogen concentrate, hemorrhage, cryoprecipitate, coagulopathy, trauma
(ClinicalTrials.govNCT00945542)

In trauma, hemorrhage accompanied by coagulopathy remains the leading cause of early in-hospital mortality[1-4]. Hypofibrinogenemia is a key component of the acute traumatic coagulopathy (ATC) and is present at admission to trauma centers in hemorrhaging trauma patients[5-7]. It has been associated with increased transfusion requirements and mortality[8,9]. Accordingly, non-randomized data suggest that fibrinogen supplementation improves coagulopathy, reduces bleeding, and consequently increases survival in traumatic hemorrhage[8,10-15]. Indeed, the most recent European guidelines for the management of bleeding following major trauma recommended a higher fibrinogen target of 1.5 – 2.0g/L[16].

In Canada and USA, cryoprecipitate and/or plasma transfusion is the standard of care for fibrinogen supplementation during acute trauma resuscitation. Originally developed as a concentrated source of factor VIII for the treatment of Hemophilia A, cryoprecipitate is nowadays the main source of fibrinogen for the management of acquired hypofibrinogenemia in surgery and trauma in North America. Of note, cryoprecipitate is a frozen product which requires thawing and pooling before use, traditionally resulting in prolonged time to infusion in ATC in clinical practice[17,18]. However, in a setting of a clinical trial in two major trauma centres in UK, the feasibility of early fibrinogen supplementation using cryoprecipitate for trauma resuscitation was recently demonstrated[19]. Finally, as human plasma-derived blood product, it carries transfusion-related risks, which led to its withdrawal from the market in several European countries years ago[20].

Alternatively, the administration of lyophilized fibrinogen concentrate (FC) is the standard of care for fibrinogen supplementation in many European countries[10-16]. FC is a human plasma-derived product which undergoes pathogen inactivation, requires reconstitution before infusion and has standardized amounts of fibrinogen for potentially expedited use during acute trauma resuscitation. However, very limited evidence supports its use in trauma[21,22]. Furthermore, in Canada and USA, it is licensed only for congenital hypofibrinogenemia. Additionally, the feasibility of its early infusion, efficacy and safety remains undetermined[21,22]. Therefore, we conducted a randomized controlled trial comparing the infusion of 6g 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

Study Design and Participants

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 years) 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 hemorrhage as evidenced by:

(a) having a systolic blood pressure (SBP) ≤ 100mmHg and

(b) requiring uncrossmatched red blood cell (RBC) transfusion at any time from injury until 30min following hospital arrival. The need for uncrossmatched RBC transfusion holds good discriminatory power for the prediction of significant hemorrhage in our institution[23].

Patients were excluded if they received any blood or blood products prior to admission to our trauma center; presented more than 6 hours after injury; had estimated body weight under 50Kg; had known or suspected pregnancy; had a catastrophic brain injury (defined as any of: Glasgow Coma Scale of 3 due to brain injury; need of immediate neurosurgery, focal signs such as anisocoria or CT evidence of intracranial bleeding with mass effect, transcranial gunshot wound, or open skull fracture with exposure/loss of brain tissue); had non-hemorrhagic shock (i.e.: obstructive [cardiac tamponade, tension pneumothorax and massive pulmonary emboli], neurogenic, cardiogenic, or septic); had an underlying hereditary or acquired coagulopathy; had 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 few hours.

Consent

Public endorsement for the trial was obtained as evidenced by community consultation prior to study commencement. Due to 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)[24]. 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.

The utilization of community consultations and adoption of waivers of consent with independent physician authorization are established alternative consent models to ensure the ethical conduct of research, providing the necessary protection of study participants, whilst serving the legitimate requirements of time-sensitive critical care and trauma research[25-28].

Randomization and Masking

In-house research assistants were responsible for verifying inclusion and exclusion criteria, and patient eligibility affirmed by qualified investigator prior to patient 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 reconstitution of each gram of FC as per manufacturer's instructions takes few minutes. Based on bench simulations performed by our blood bank in preparation for the trial, for reconstitution and pooling of a total dose of 6g of FC, approximately 20min is required. We, therefore, set a target of 30min from request to randomize to infusion for the investigational product in this trial.

FC (RiaSTAP™) is a freeze-dried lyophilised 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. Using aseptic technique, if randomized to the FC arm, 6 vials of RiaSTAP™ were reconstituted and pooled with a final volume of 300ml in a minibag placed in an amber cover bag to be blindly infused. The dosage of 6g FC was selected based on a systematic review on the use of FC in trauma which described doses ranging from 5 grams to a total of 16 grams in this population[22]. Similar dose ranges have also been used in non-trauma bleeding patients[21,29,30]. This dose is equivalent to approximately a standard dose of 10-15 units of cryoprecipitate.

For patients randomized to the placebo arm, normal saline was pooled in similar minibags covered with an amber bag to ensure blinding and a timer set at 20min was used by the blood bank technologist to guarantee similar preparation times to FC. The 300ml blinded minibags were administered intravenously as "rapid push" over approximately 3min (1gram per 25sec) via level I automated pressure pump using Hospira Lifeshield Primary IV™ set in our pre-trial simulations. The safety of administrating 1g RiaSTAP™ in approximately 20 seconds has been described in the literature, and of up to 14 grams total dose in less than 5 minutes in cardiac and aortic surgery trials[31-34].

Outcome Measures

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

Other feasibility endpoints evaluated included: (i) proportion of patients receiving SI prior to 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 performed on admission; and at +1h, +3h, +11h, +23h & +47h following start time of SI (±30min).

Safety was measured by 28-day all-cause mortality; rates of symptomatic thromboembolic complications in both study arms (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 DVT (evidenced by leg Doppler performed at day 7 of hospital stay); incidence of acute lung injury/ acute respiratory distress syndrome (defined by the Berlin Classification of ALI) 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 due to exsanguination; mainly neurological/ due to traumatic brain injury/ withdrawal of care; or mainly due to multiple organ failure/sepsis)

Sample Size

Our institution receives approximately 220 patients with significant bleeding that requires at least 1 unit of red blood cells within 24h 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 under. A sample size of 25 patients 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 the first hour of hospital admission. Because the primary outcome is feasibility, the trial is not designed with sufficient power to exclude small but clinically significant differences in treatment effects.

Statistical analysis

Analyses for the main feasibility, safety and efficacy outcomes were performed on the per-treatment cohort for study participants for whom the SI (placebo or FC) was administered. Statistical differences in binary feasibility and safety outcomes were tested using $\chi 2$ statistics or Fisher's exact test. In consideration of relatively small sample size, we used Wilson and Jeffreys methods of binomial

confidence interval CI for the main feasibility endpoint. The times to determination of eligibility and SI infusion were depicted in minutes from admission in histogram graph form.

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 analyzed 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 were used when appropriate depending on the data distribution. All tests were two-sided and p-values less than 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. Due to the narrow window (30min) available to recruit patients in our study involving a time-sensitive intervention (30min), complete information on eligibility (exclusion criteria) was not available at the time of recruitment for few patients. This committee also advised on the "per-treatment" analysis for the feasibility, safety and efficacy data.

Data were analyzed using SAS 9.3 (SAS Institute Inc, Cary, North Carolina, USA). The trial protocol is registered at ClinicalTrial.gov, number NCT02203968.

RESULTS

Patient Characteristics and Co-interventions

One thousand sixty one trauma patients were assessed for eligibility between October 2014 and November 2015. During this period, two eligible patients did not enter the study due to the lack of timely affirmation of eligibility by the on-call investigator. Out of 1061, 50 patients were randomly assigned to placebo or FC treatment arms. Of 50 randomized patients, 5 were excluded before the SI could be administered due to unknown exclusion criteria (i.e.: non-hemorrhagic cause of shock; catastrophic traumatic brain injury; no blood transfusion ordered) at the time of determination of eligibility (Figure 1). One patient was not available for the 28-day follow-up assessment. Therefore, 45 patients were included in the analyses; with one excluded for the 28-day mortality analysis.

Apart from a difference in median age (28y in placebo vs. 48y in FC), the two study groups were balanced with respect to baseline characteristics (Table 1). Of note, hypofibrinogenemia (fibrinogen <2 g/L) on hospital admission was similar between the groups (54% in the placebo and 53% in the FC; p=1.00). However, using INR ≥ 1.3 as definition of ATC, 18% and 26% of the patients were coagulopathic at trauma center arrival in the placebo and FC groups, respectively (p=0.71).

There were no significant differences with respect to co-interventions and transfusion of blood and blood products between study groups (Table 2). The total number of RBC units transfused in 24h of hospitalization did not differ between placebo (median 3 [IQR 2-4]) and FC (median 3 [IQR2-5]) groups; p=0.41. Also, both groups had similar proportions of patients who received the SI prior to any allogeneic transfusion (12.5% in placebo vs. 14.3% in FC; p=1.00). No transfusion of plasma, platelets or cryoprecipitate occurred before SI in either group. Although numerically more patients received cryoprecipitate following the SI in the placebo arm (33% vs. 14%), no statistical significance was demonstrated (P=0.18). Finally, the median number of RBC, plasma, platelet and cryoprecipitate transfused within 24h of hospital admission were similar between the groups (Table 2).

Feasibility Outcomes

Out of 45 patients, 2 (one in each study arm) received the SI outside the 1h target feasibility for infusion (95.6% [95%CI 86-99]) (Figure 2). Both Wilson and Jeffreys CIs had lower limit >85%, which demonstrates significant evidence of feasibility of fibrinogen infusion within 1h after arrival. For the total cohort, eligibility was confirmed and infusion of the SI initiated within 17min (±9) and 51min (±8), respectively. Although the preparation time for the SI was slightly shorter in the placebo group ((23min [±4] vs. 26min [±5]; p=0.03), both times to eligibility and infusion were similar between study groups (Figure 3). The median duration of the SI infusion was 4min (3-6). Two study participants in each study arm had their SI infused exceeding 10min. The duration of the SI infusion was similar between the groups (4.5min (3-6) with placebo vs. 4min (3-10) with FC; p=0.85). The wastage rate of the SI was 10% (5/50) for the randomized patients.

Effect on Plasma Fibrinogen Concentration

Following the infusion of 6g of FC, plasma fibrinogen concentration was raised to and remained within normal range values (>2g/L) throughout resuscitation (Table 3). Higher plasma fibrinogen concentrations were measure 1h following the SI infusion until approximately 12h of hospitalization in the FC group; then no further significant differences were measured between the groups at approximately 24h and 48h of hospital admission (Figure 4). After 1h of FC infusion, the increase in plasma fibrinogen concentration was 0.93g/L (from 1.91g/L to 2.71g/L; p<0.01).

Safety Outcomes

The overall mortality rate for the 50 randomized patients was 10% (5/50). All-cause 28-day mortality was 4.2% (1/24) with placebo and 10% (2/20) with FC (RR 2.4; 95% CI 0.2-23). There were no statistically significant differences noted between the rates of deep venous thrombosis, pulmonary embolism, acute lung injury, ARDS, acute kidney injury, multiple organ failure/sepsis, and infection between the two groups (Table 4). No myocardium infarction, stroke, or allergic reactions were observed in either group.

DISCUSSION

This is the first in-hospital randomized trial evaluating the use of fibrinogen concentrate in trauma. Our data suggest that rapid and early infusion of fibrinogen concentrate (within 1h of hospital arrival) is feasible in the setting of a randomized clinical trial, improves plasma fibrinogen concentration, and was not associated with safety concerns.

In our trial, 95% of study participants received FC at a median time of 50 minutes of trauma center arrival. Traditionally, fibrinogen supplementation occurs late during trauma resuscitation. In a large prospective observational trial (PROMMTT) involving 10 US Level I trauma centers, 359 out of 1245 patients received cryoprecipitate during resuscitation for fibrinogen supplementation[18]. In this trial, the first dose of cryoprecipitate was documented at a median time from hospital arrival of 2.8 hours (IQR 1.7-4.5). In our institution, we had previously reported that cryoprecipitate was transfused at a median of 4.5h (2.9-7.5) from hospital arrival in trauma patients[17].

Recently, early cryoprecipitate transfusion for major hemorrhage was evaluated in a feasibility non-blinded randomized trial[19]. The primary objective of transfusion of cryoprecipitate within 90 minutes of arrival was achieved in 85% (95%CI 69-100) of 21 trauma patients requiring activation of major hemorrhage protocol. Half of the intervention group received cryoprecipitate after 60min 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 to the time to FC infusion in our trial (95% of participants received FC within <60min of arrival) illustrated the challenges of rapidly transfusing cryoprecipitate, which requires thawing before being delivered to bedside. In Canada and Australia, cryoprecipitate is a pooled product and therefore its preparation and time to infusion in our jurisdiction would be even longer.

Decreased plasma fibrinogen concentration at hospital admission is common in bleeding trauma patients and has been implicated in increased bleeding and mortality in trauma[8,9]. Recently, several retrospective studies have documented improvements in coagulopathy either by conventional or viscoelastic testing measurements; reduction of transfusion volumes; and improvements in survival rates associated with the use of fibrinogen concentrate in isolation or combined with prothrombin complex concentrate in trauma[10-15]. The utility of fibrinogen concentrate in reducing blood product requirements in other clinical settings has also been reported[21,22,29,30].

Accordingly, in 2015, the Canadian Armed Forces (CAF) adopted Fibrinogen Concentrate (RiaSTAP™, CSL Behring) to start damage control resuscitation for bleeding patients in the austere far forward combat setting. This was due to RiaSTAP's long shelf life (5 years) and the ability to rapidly reconstitute the product after storage at room temperature.

The infusion of 6g of FC led to improved plasma fibrinogen concentrations (>2.0g/L) as compared to placebo during active hemorrhage. Four patients (19%) in the FC group dropped fibrinogen concentration to <2.0g/L after baseline time point as oppose to 67% in the placebo group ($p<0.01$). This finding is in keeping with the recent randomized trial on early cryoprecipitate transfusion (4g of fibrinogen) where plasma fibrinogen concentrations were higher (>1.8g/L) than placebo throughout resuscitation[19]. The dose utilized in our study resulted in similar increase in plasma fibrinogen levels (0.93g/L) previously reported[13,15,36,37].

Although not powered to detect differences in complications between study groups, no major concerns were observed with FC use in our trial. FC is a human-derived product that is subjected to viral inactivation step (pasteurisation-heat treatment at +60°C for 20 hours) during manufacturing to mitigate transmission risks. A comprehensive systematic review evaluating FC use in the perioperative setting concluded that there was no significant increase in thrombotic events in FC treated patients[38]. Furthermore, based on 27 years of pharmacosurveillance data and comprehensive literature review, an incidence of 4.3 thromboembolic events per 10^5 treatment episodes (calculated from 28 cases reporting a possible thromboembolic event regardless of their definitive relationship to fibrinogen concentrate use) has been recently estimated[39].

Limitations

This is a small feasibility trial; thus prone to significant differences between study groups (i.e. age, admission coagulopathy and crystalloid utilization). This was also apparent in the wide 95% CIs around the relative risks generated. Although some rates of complications differed between the groups, no definitive conclusions can be drawn due to the small sample size. Therefore, one should exercise caution when interpreting clinical measures in this small trial which are presented as safety data only.

Five patients who did not receive the SI were excluded post-randomization. This is a well-recognized issue in emergency research testing time-sensitive interventions where there is a narrow window to determine eligibility[40]. However, the 95% CI interval for the trial's primary outcome remained within the acceptable limit with 45 patients. Future trials should account for a minimum of 10% post-randomization exclusions when determining sample size.

Due to the nature of our trial population – bleeding trauma patients in hemorrhage shock – admission research blood samples were not obtained timely for 7% of patients due to inability of establishing adequate vascular access. This should be considered when designing clinical trials involving similar populations with laboratory endpoints.

CONCLUSIONS

Our trial demonstrated that infusion of 6 grams of fibrinogen concentrate within 1 hour of arrival to our trauma center is feasible, improves plasma fibrinogen concentration by approximately 1g/L and appears safe in a population of trauma patients at risk of significant hemorrhage. This trial also suggests that fibrinogen concentrate might be a faster and safer alternative to cryoprecipitate transfusion for fibrinogen supplementation in hemorrhaging trauma patients. Finally, these data will inform the design of larger trials in order to definitively evaluate the efficacy and safety of fibrinogen concentrate in trauma resuscitation.

Funding: Supported by grants from the Canadian Forces Health Services; Defense Research and Development Canada; and CSL Behring.

Role of funding agencies: Funding agencies had no participation or role in study design, data collection, data analysis, data interpretation, writing of manuscript, or the decision to submit study findings for publication.

Additional Contributions: The authors would like to acknowledge the fundamental support of the blood bank team for the conduct of this trial. We would like to thank the trauma registry personnel for the invaluable help with the trauma registry data. The authors also acknowledge all research assistants and coordinators of the Tory Regional Trauma Centre for the excellent help with data collection and entry.

REFERENCES

1. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: areassessment. *J Trauma*. 1995 Feb; 38(2):185-93.

2. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg*. 1998 May; 186(5):528-33.

3. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. *J Trauma*. 2003; 55: 39-44.

4. Tisherman SA1, Schmicker RH, Brasel KJ, et al. Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. *Ann Surg*. 2015 Mar;261(3):586-90. doi: 10.1097/SLA.0000000000000837.

5. Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. *Br J Anaesth.* 2010; 105: 116-21.

6. Levy JH, Szlam F, Tanaka KA, et al. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg.* 2012; 114: 261-74.

7. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. *J Trauma*. 2008; 65(4):748-54.

8. Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma.* 2008; 64: S79-85.

9. Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost.* 2012; 10: 1342-51.

10. Nienaber U1, Innerhofer P, Westermann I, et al. The impact of fresh frozen plasma vs coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury. 2011 Jul;42(7):697-701. doi: 10.1016/j. *Injury*.2010.12.015. Epub 2011 Mar 9.

11. Schöchl H1, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care. 2010;14(2):R55. doi: 10.1186/cc8948. Epub 2010 Apr 7.

12. Schöchl H1, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care*. 2011;15(2):R83. doi: 10.1186/cc10078. Epub 2011 Mar 4.

13. Weiss G1, Lison S, Glaser M, et al. Observational study of fibrinogen concentrate in massive hemorrhage: evaluation of a multicenter register. *Blood Coagul Fibrinolysis*. 2011 Dec;22(8):727-34. doi: 10.1097/MBC.0b013e32834cb343.

14. Wafaisade A1, Lefering R, Maegele M, et al. Trauma Registry of DGU. Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. J Trauma Acute Care Surg. 2013 Feb;74(2):387-3; discussion 393-5. doi: 10.1097/TA.0b013e31827e2410.

15. Schlimp CJ1, Voelckel W, Inaba K, et al. Impact of fibrinogen concentrate alone or with prothrombin complex concentrate (+/- fresh frozen plasma) on plasma fibrinogen level and fibrin-based clot strength (FIBTEM) in major trauma: a retrospective study. *Scand J Trauma Resusc Emerg Med*. 2013 Oct 8;21:74. doi: 10.1186/1757-7241-21-74.

16. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013; 17: R76.

17. Nascimento B, Rizoli S, Rubenfeld G, et al. Cryoprecipitate transfusion: assessing appropriateness and dosing in trauma. *Transfus Med*. 2011 Dec;21(6):394-401. doi: 10.1111/j.1365-3148.2011.01098.x. Epub 2011 Aug 18.

18. Holcomb JB, Fox EE, Zhang X, et al. Cryoprecipitate use in the PROMMTT study. *J Trauma Acute Care Surg*. 2013; 75: S31-9

19. Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. Br J Anaesth. 2015 Jul;115(1):76-83. doi: 10.1093/bja/aev134. Epub 2015 May 19.

20. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. *Br J Anaesth*. 2014 Dec;113(6):922-34. doi: 10.1093/bja/aeu158. Epub 2014 Jun 27.

21. Kozek-Langenecker S, Sørensen B, Hess JR, et al. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care*. 2011; 15(5): R239.

22. Aubron C, Reade MC, Fraser JF, et al. Efficacy and safety of fibrinogen concentrate in trauma patients—a systematic review. *J Critical Care*, 2013 Dec 30; doi:10.1016/j.jcrc.2013.12.011. Epub ahead of print.

23. Nascimento B, Rizoli S, Rubenfeld G, et al. Design and preliminary results of a pilot randomized controlled trial on a 1:1:1 transfusion strategy: the trauma formula-driven versus laboratory-guided study. *J Trauma*. 2011 Nov;71(5 Suppl 1):S418-26. doi: 10.1097/TA.0b013e318232e591.

24. Tri-Council Policy Working Party on Ethics: Draft 2nd Edition of the Tri-Council Policy Statement: Ethical Conduct for ResearchInvolvingHumans.December2010;Article3.8.http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf

25. Annane D, Outin H, Fisch C, Bellissant E. The effect of waiving consent on enrollment in a sepsis trial. *Intensive Care Med*. 2004 Feb;30(2):321-4. Epub 2004 Jan 9.

26. Clifton GL, Knudson P, McDonald M. Waiver of consent in studies of acute brain injury. *J Neurotrauma*. 2002 Oct;19(10):1121-6.

27. CRASH Trial management group: Research in Emergency Situations: with or without relatives consent. *Emer Med J*. 2004 Nov;21(6):703.

28. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. Crit Care Med. 2009 Jan;37(1 Suppl):S65-8. doi: 0.1097/CCM.0b013e3181920851.

29. Warmuth M., Mad P. Wild C. Systematic review of the efficacy and safety of fibrinogen concentrate substitution in adults. *Acta Anaesthesiologica Scandinavica*. 2012 56: 539–548. doi: 10.1111/j.1399-6576.2011.02586.x.

30. Wikkelsø A, Lunde J, Johansen M, et al. Fibrinogen concentrate in bleeding patients (Review). *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD008864. DOI: 10.1002/14651858.CD008864.pub2.

31. Solomon C, Pichlmaier U, Schoechl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth.* 2010, 104:555-562.

32. Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of Fibrinogen Concentrate as First-line Therapy during Major Aortic Replacement Surgery: A Randomized, Placebo-controlled Trial. *Anesthesiology*, Jan 2013; Vol118 (1): 40–50. doi: 10.1097/ALN.0b013e3182715d4d

33. Rahe-Meyer N, Alexander Hanke, Dirk S, et al. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: Results from a randomized, placebo-controlled trial. *Journal of Thoracic and Cardiovascular Surgery*. Mar 2013 Vol 145, Issue 3, Supplement , S178-S185.

34. Solomon C, Hagl C, Rahe-Meyer N. Time course of haemostatic effects of fibrinogen concentrate administration in aortic surgery. *Br J Anaesth*. 2013 Jun;110(6):947-56

35. Danés AF, Cuenca LG, Bueno SR, et al. Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. *Vox Sang*. 2008 Apr;94(3):221-6. doi: 10.1111/j.1423-0410.2007.01024.x. Epub 2008 Jan 2.

36. Gollop ND, Chilcott J, Benton A, et al. National audit of the use of fibrinogen concentrate to correct hypofibrinogenaemia. *Transfus Med*. 2012 Oct;22(5):350-5. doi: 10.1111/j.1365-3148.2012.01168.x. Epub 2012 Jun 14.

37. Innerhofer P, Westermann I, Tauber H, et al. The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Injury. 2013 Feb;44(2):209-16. doi: 10.1016/j.injury.2012.08.047. Epub 2012 Sep 20.

38. Lin DM, Murphy LS, Tran MH. (2013) Use of prothrombin complex concentrates and fibrinogen concentrates in the preoperative setting: a systematic review. Transfusion Medicine Reviews, 27, 91-104.

39. Solomon C, Gröner A, Ye J, et al. Safety of fibrinogen concentrate: analysis of more than 27 years of pharmacovigilance data. Thromb Haemost. 2015 Apr;113(4):759-71. doi: 10.1160/TH14-06-0514. Epub 2014 Dec 11.

40. Fergusson D, Aaron SD, Guyatt G, et al. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ. 2002;325:652– 654.

TABLE 1. Demographics and Baseline Characteristics

	N	Placebo	N	FC
Age, year	24	28 (24-41)	21	48 (30-58)
Sex, male	24	87	21	77
Penetrating type of trauma	24	54	21	52
Time from injury to hospital, min	24	43 (33-55)	21	44 (30-59)
Injury Severity Score	24	23 (18-29)	21	25 (19-29)
Glasgow Coma Scale	24	15 (12-15)	21	15 (14-15)
Systolic Blood Pressure, mmHg	24	99 (82-99)	21	106 (80-144)
Temperature, ºC	15	35 (0.7)	13	35 (1.4)
pH	15	7.2 (0.2)	14	7.2 (0.1)
Lactate, g/L	20	5 (4-8)	20	5 (3-9)
International Normalized Ratio	22	1.1 (0.2)	19	1.2 (0.3)
Fibrinogen, g/L	22	1.9 (1.7-2.4)	19	1.9 (1.6-2.3)
Platelet x 10^9/L	22	254 (200-282)	20	269 (242-314)
Hemoglobin, g/L	22	122 (112-144)	20	118 (105-125)
Troponin, g/L	19	7 (5-12)	15	8 (5-25)
Acute Traumatic Coagulopathy*	22	18	19	26
Fibrinogen <2, g/L	22	54	19	53

Data are presented as means (standard deviation), median (interquartile ranges) or percentage of occurrence. N values represent the number of patients in each group in whom the measured parameter is available. FC indicates fibrinogen concentrate. *Acute Traumatic Coagulopathy defined by INR ≥1.3.

TABLE 2. Co-interventions and Transfusion within 24 hour

	Placebo (24)	FC (21)	P
Tranexamic Acid, %	96	100	1.00
Vasopressor, %	54	67	0.39
Urgent Trauma Laparotomy, %	42	52	0.47
Orthopedic Operation, %	42	38	0.81
Angioembolization, %	4	9	0.59
Chemical DVT Prophylaxis, %	83	95	0.35
Pre-SI RBC	1.96 (1.7-2.4)	1.91 (1.6-2.3)	0.68
Post-SI RBC	1.73 (1.3-2.0)	2.71 (2.2-3.4)	0.20
Plasma	1.75 (1.4-2)	2.73 (2.4-3.6)	0.72
Platelets	2.32 (1.9-2.7)	2.81 (2.5-3.6)	0.53
Cryoprecipitate	3.5 (2.9-4)	4.0 (3.1-4.6)	0.18
Crystalloid, ml	8050 (6000-9700)	5112 (3412-7287)	0.03

Transfusion and crystalloid data are presented as median (interquartile ranges). FC indicates fibrinogen concentrate; DVT indicates deep venous thrombosis; SI indicates study intervention; RBC indicates red blood cells

TABLE 3. Plasma Fibrinogen Concentration (g/L)

Time points (hours of admission)	N	Placebo	N	Fibrinogen Concentrate	P
Admission	22	1.96 (1.7-2.4)	19	1.91 (1.6-2.3)	0.75
2h	20	1.73 (1.3-2.0)	18	2.71 (2.2-3.4)	<0.01
4h	21	1.75 (1.4-2)	16	2.73 (2.4-3.6)	<0.01
12h	19	2.32 (1.9-2.7)	19	2.81 (2.5-3.6)	<0.01
24h	19	3.5 (2.9-4)	18	4.0 (3.1-4.6)	0.07
48h	14	4.63 (4.2-6.7)	14	6.13 (4.3-7.4)	0.32

Data are presented as median (interquartile ranges).

TABLE 4. Safety Outcomes

	Placebo	FC	Relative Risk	95% CI
All-cause 28-day mortality[y]	1/24 (4.2)	2/20* (10)	2.4	-0.2 to 23
Death by exsanguination	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
Myocardium 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

Data are presented as number of positive outcomes over total number of cases assessed per study group, and percentages. Placebo considered reference standard for relative risk calculation. [y] One patient in the FC group died nine days following hospital admission due to worsening brain injury; in the placebo group, the single death was mostly related to anoxic brain injury following cardiac arrests due to initial traumatic bleeding. *One study participant lost to follow-up at day 28.
CI indicates confidence interval.

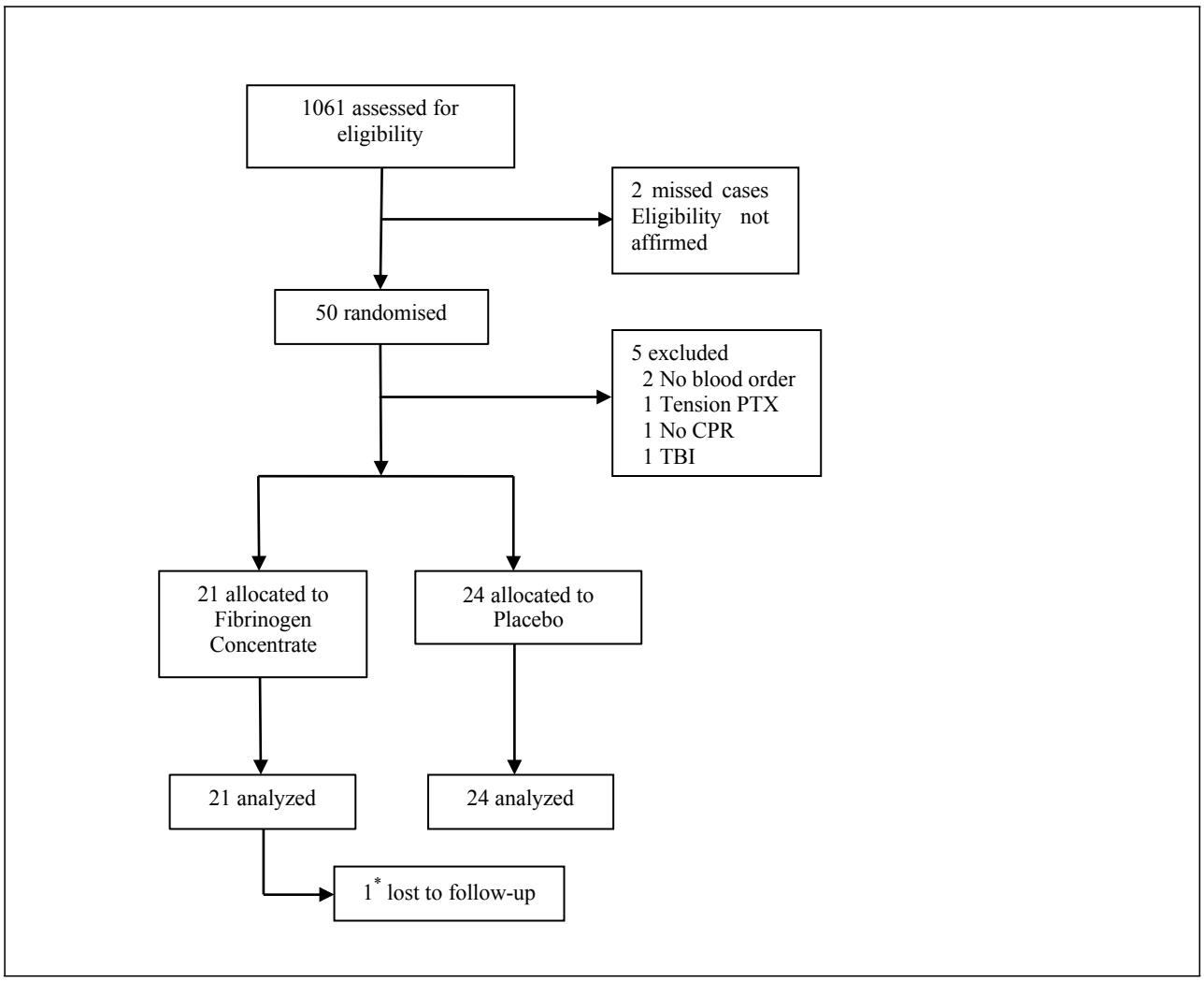

FIGURE 1. Flow of Patients through the trial.

* Lost to follow-up and excluded from outcome at 28 days. PTX=Pneumothorax; CPR=cardio-pulmonary resuscitation; TBI=traumatic brain injury

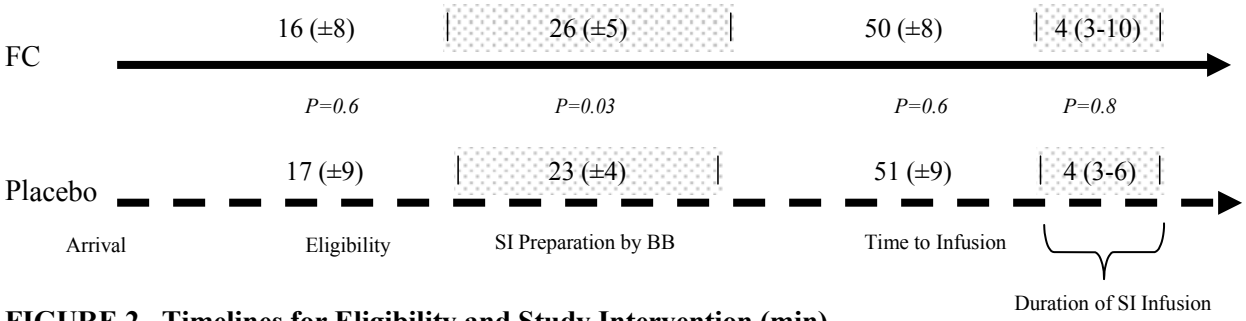

FIGURE 2. Timelines for Eligibility and Study Intervention (min).

Data are presented as means (standard deviation) or median (interquartile ranges). FC=fibrinogen concentrate; SI=study intervention; BB=blood bank

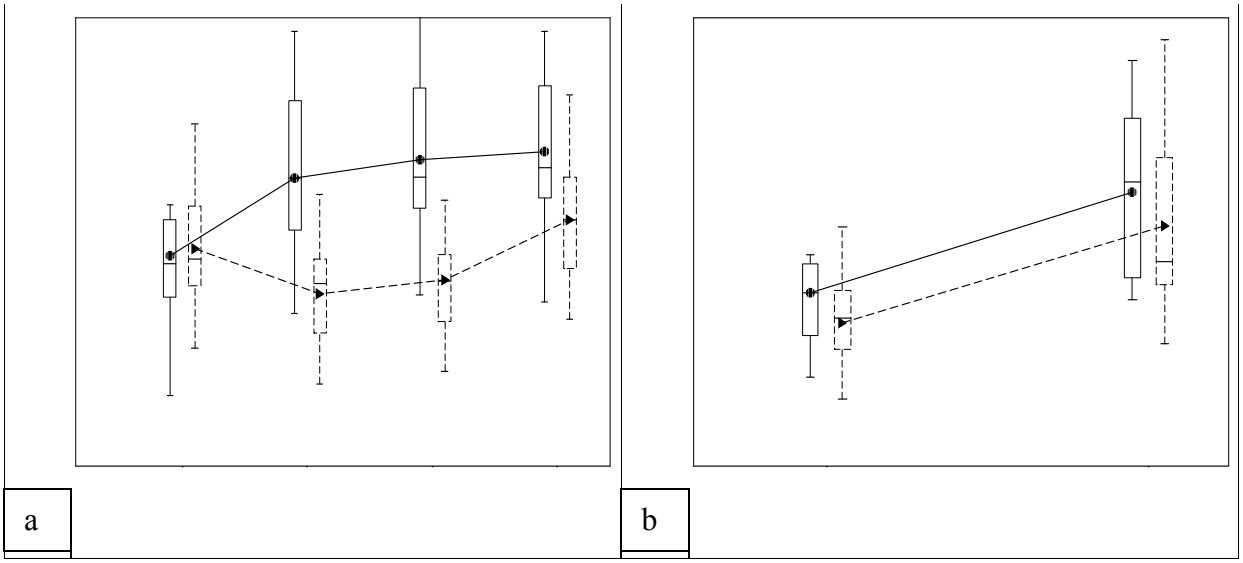

FIGURE 3. Plasma Fibrinogen Concentrations throughout 48h of Hospitalization; figure 3a. fibrinogen concentrations within 12h; figure 3b. fibrinogen concentrations at 24h and 48h.

Data are presented as means (standard deviation) or median (interquartile ranges). FC=fibrinogen concentrate