Targeted fibrinogen concentrate use in severe traumatic haemorrhage

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Trauma is one of the leading causes of death worldwide, especially in the younger adult population.[1,2] Haemorrhage secondary to trauma accounts for a large proportion of this mortality as well as significant morbidity.[3] Trauma-induced coagulopathy is a disorder of blood clotting that can occur with severe haemorrhage and is associated with increased mortality and increased need for blood product transfusion.[4,5] Fibrinogen is one of the first coagulation factors to be depleted during severe haemorrhage, and hypofibrinogenaemia has been linked to poor outcomes.[6,7] After major trauma, patients' initial fibrinogen levels below normal are independently associated with higher in-hospital mortality.[8] It is hypothesised that early and rapid fibrinogen replacement may contribute to controlling haemorrhage and may therefore reduce the volume of blood products required and ultimately improve outcomes for these patients.

Three different types of fibrinogen replacement exist: fresh frozen plasma (FFP), cryoprecipitate and fibrinogen concentrate (FC). Both FFP and cryoprecipitate are reliant on donors, thus there is a resource factor involved in availability of these products. In addition, both require blood type matching to the patient receiving the transfusion, potentially delaying how quickly the trauma patient with bleeding can receive the transfusion. Cryoprecipitate is the most commonly used form of concentrated fibrinogen in Australia and New Zealand, but it can take a significant time to transfuse.[9] A 2015 randomised controlled feasibility trial demonstrated that it can take up to 90 minutes to receive cryoprecipitate as part of a trauma major haemorrhage protocol (MHP).[10] FFP also requires thawing before use and requires large volumes in order to achieve appropriate fibrinogen replacement. Large volume transfusion can result in adverse patient outcomes related to fluid overload. A recent article showed that high dose plasma transfusion does not correct trauma-induced coagulopathy and that coagulation parameters only improve with plasma, cryoprecipitate and platelet transfusion with a combined high fibrinogen load.[11]

ABSTRACT

Objective: Fibrinogen is one of the first coagulation factors to be depleted during traumatic haemorrhage, and evidence suggests hypofibrinogenaemia leads to poor outcomes. A number of fibrinogen replacement products are currently available, with no clear consensus on the ideal product to use in severe traumatic haemorrhage. We hypothesised that it will be possible to rapidly administer fibrinogen concentrate (FC) guided by rotational thromboelastometry (ROTEM) FIBTEM A5 in patients presenting with trauma haemorrhage.

Methods: We examined 36 consecutive patients with trauma admitted to a level 1 trauma centre in Australia who received FC as part of their initial resuscitation. ROTEM analysis was conducted at various time points from emergency department (ED) admission to 48 hours after admission. The primary outcome was time to administration of FC after identification of hypofibrinogenaemia using ROTEM FIBTEM A5. Data were collected on quantity and timing of product transfusion, demographics, Injury Severity Score and laboratory values of coagulation. Spearman rank order correlation was used to determine the correlation between FIBTEM A5 and Clauss fibrinogen (FibC).

Results: Thirty-six patients received FC as their initial form of fibrinogen replacement during the study. Patients were hypofibrinogenaemic by both FIBTEM A5 (6 mm) and FibC (1.7 g/L) on presentation to the ED. It took a median of 22 minutes (IQR, 17–30 minutes) from time of a FIBTEM A5 analysis to FC administration. Both parameters increased significantly ($P < 0.05$) by 24 hours after admission.

Conclusion: This study suggests that administration of FC represents a rapid and feasible method to replace fibrinogen in severe traumatic haemorrhage. However, the optimal method for replacing fibrinogen in traumatic haemorrhage is controversial and large multicentre randomised controlled trials are needed to provide further evidence. This study provided baseline data to inform the design of further clinical trials investigating fibrinogen replacement in traumatic haemorrhage.

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FC is a coagulation factor concentrate that is virally inactivated, able to be stored for up to 5 years in its lyophilised form, does not require ABO blood group compatibility testing, and is easily accessible. FC can also be transfused in low volume, increasing the speed of delivery and amount of fibrinogen in a given volume. For these reasons, it appears to have a number of potential advantages over the other two forms of fibrinogen currently available.[12] However, FC is an expensive product and its use for fibrinogen replacement in acquired hypofibrinogenaemia is currently off label.

In a systematic review comparing the efficacy and safety of FC and cryoprecipitate, the authors found limited evidence and were unable to recommend one product over the other.[13] Another review of cryoprecipitate and FC indicated that neither product was superior, with the main differences between the two being infection risk and cost.[14] Cryoprecipitate undergoes viral testing and donor screening at the initial time of blood donation; however, no further viral reduction steps are taken.[14]

In recent years, there has been an increasing use of viscoelastic haemostatic assays and subsequent use of targeted product administration.[15] This approach is supported by current European guidelines for the management of major bleeding and coagulopathy following trauma.[16] The rotational thromboelastometry (ROTEM) assay FIBTEM is predictive of massive transfusion in trauma and it has the benefit of providing a more rapid result than Clauss fibrinogen (FibC).[17] Compared with standard laboratory tests, viscoelastic haemostatic assays provide a result that reflects that of whole blood rather than just the plasma component and the turnaround for results is faster. There are obvious theoretical benefits for the FIBTEM-guided use of FC in severe trauma, but there is currently inadequate high level evidence to support this use.[18]

The primary objective of this observational study was to determine the time to FC transfusion from a FIBTEM A5 and the relationship between FIBTEM A5 results and FibC in bleeding patients. We hypothesised that it will be possible to rapidly administer

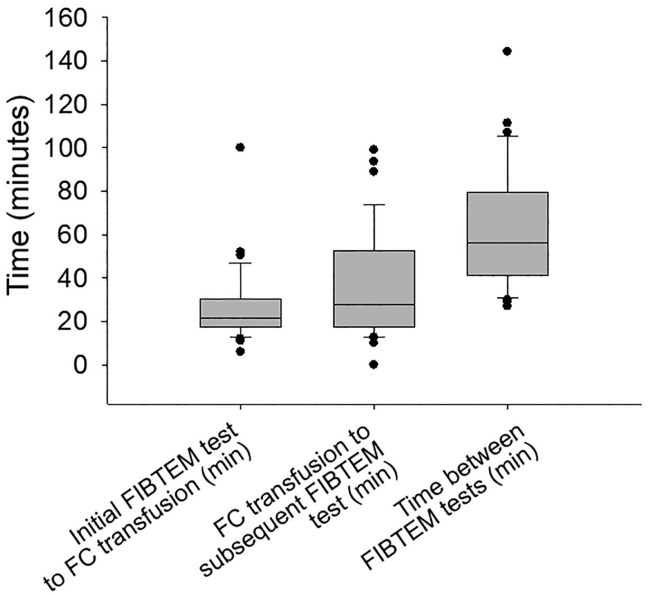
Table 1. Patient demographics and blood product transfusion distribution*

Variables	Result
Total number of patients	36
Sex	
Male	28 (78%)
Female	8 (22%)
Age (years), median (IQR)	32 (19.5–43.0)
ISS, median (IQR)	33 (25.0–49.0)
ISS ≥ 15	33 (92%)
ISS ≥ 25	28 (78%)
Mechanism of injury	
Blunt	27 (75%)
Penetrating	9 (25%)
Surgical and/or interventional radiological intervention	31 (86%)
Mechanical ventilation (h), median (IQR)	79 (32–303)
ICU length of stay (h), median (IQR)	135 (51–341)
Venous thromboembolic events	4 (11%)
ICU mortality	12 (33%)
Hospital mortality	12 (33%)
PRBC (units), median (IQR)	7.5 (3.5–11)
Transfusion of < 4 PRBC	9 (25%)
Transfusion of ≥ 4–9 PRBC	14 (39%)
Transfusion of ≥ 10 PRBC	13 (36%)
Initial FC dose (g), median (IQR)	4 (4–4)
Additional FC	5 (14%)
Cryoprecipitate (units), median (IQR)	10 (0–30)
Total additional fibrinogen (g), median (IQR)	3 (0–9.5)
Total fibrinogen (g)	7 (14%)
FFP	12 (33%)
FFP (units)†, median (IQR)	0 (0–2)
FFP (units)‡, median (IQR)	3 (2–4)
Platelets	17 (47%)
Platelets (units)†, median (IQR)	0 (0–2)
Platelets (units)‡, median (IQR)	2 (1–3)
Prothrombinex (Seqirus)	4 (11%)
Prothrombinex (Seqirus) (IU)†, median (IQR)	0 (0–0)
Prothrombinex (Seqirus) (IU)‡, median (IQR)	1000 (750–1500)

FC = fibrinogen concentrate; FFP = fresh frozen plasma; ICU = intensive care unit; ISS = Injury Severity Score; PRBC = packed red blood cells. * Demographic and distribution of blood products transfused to patients receiving fibrinogen concentrate, *n* = 36. Total additional fibrinogen represents all fibrinogen products administered after the initial dose of fibrinogen concentrate. Total fibrinogen represents the sum of all fibrinogen products transfused. Data are presented as *n* (%) and median values with 25–75% interquartile ranges (IQRs). Requirement for additional FC, platelet and prothrombinex (Seqirus) transfusion is presented as a percentage of patients. † Median (IQR, 25–75%) of the whole cohort. ‡ Median (IQR, 25–75%) of patients receiving a transfusion.

Figure 1. Timing between FIBTEM analysis and fibrinogen concentrate transfusion*

Variables	Result
Initial FIBTEM test to FC transfusion (min)	22.0 (17.5–30.3)
FC transfusion to subsequent FIBTEM test (min)	28.0 (17.6–52.5)
Time between FIBTEM tests (min)	56.5 (42.0–78.0)



* Data are presented as median values with interquartile ranges; error bars represent minimum and maximum values; *n* = 36.

Table 2. Laboratory parameters at emergency department (ED) admission and 24 hours after ED admission

Variables	ED admission* Median (IQR)	24 h after ED admission* Median (IQR)	*P*†
FIBTEM A5 (mm)	6 (4–11)	15 (12–17)	< 0.001
FibC (g/L)	1.7 (1.3–2.2)	3.5 (2.8–4)	< 0.001
INR	1.4 (1.1–1.9)	1.3 (1.2–1.4)	ns
Platelets (x10^9/L)	192 (143–248)	115 (84–136)	< 0.001
Haemoglobin (g/L)	129 (107–144)	95 (87–112)	< 0.001
pH	7.18 (7.05–7.29)	7.37 (7.33–7.40)	< 0.001
Base excess (mmol/L)	–9.15 (–16.6 to –7.00)	–2.7 (–5.80 to –1.23)	< 0.001
Lactate (mmol/L)	5.6 (3.2–8.1)	1.7 (1.4–2.8)	< 0.001

FibC = Clauss fibrinogen; INR = international normalised ratio; ns = not significant.
* Data are presented as median values with 25–75% interquartile ranges. † *P* values are derived from the Student *t* test or Mann–Whitney rank sum test; significance level $P < 0.001$.

FC guided by FIBTEM A5 results in the setting of severe traumatic haemorrhage.

Methods

This retrospective observational study was conducted at a 750-bed tertiary health service with a level 1 trauma centre in Queensland, Australia. Ethics approval was obtained through the Gold Coast Hospital and Health Service Human Research and Ethics Committee (HREC/14/QGC/17).

A ROTEM-guided trauma MHP was implemented in our institution in 2014. The majority of severely injured patients with trauma are managed using this approach in conjunction with damage control resuscitation and rapid surgical control of haemorrhage. Fibrinogen replacement is guided by ROTEM FIBTEM analysis. A FIBTEM A5 of less than 10 mm in the setting of significant haemorrhage triggers fibrinogen replacement with FC or cryoprecipitate.[19] FIBTEM A5 amplitude of 10 mm has been shown to detect hypofibrinogenaemia with 70% sensitivity.[20] FC was reconstituted in the emergency department (ED) according to manufacturer's instructions and administered as an intravenous bolus. The duration of intravenous bolus is about 30 seconds per gram of FC.

This study included consecutive patients with trauma who received FC as part of their initial resuscitation (between December 2014 and December 2016). Patients were excluded if they received cryoprecipitate before FC.

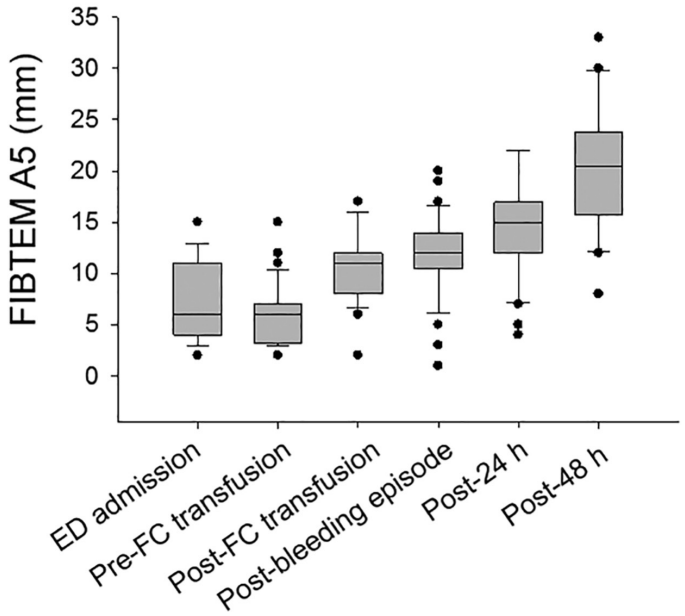
Data collected included patient demographics (age, gender), length of hospital and intensive care unit stay and Injury Severity Score (ISS). Quantity and timing of blood product transfusion were collected for packed red blood cells, FC, cryoprecipitate, FFP, platelets and prothrombin complex concentrate. ROTEM analysis was collected at various time points from ED admission to 48 hours after admission. Further laboratory blood tests were collected as per standard care of the patient with trauma: international normalised ratio (INR) (reference interval [RI], 0.9–1.2), FibC (RI, 1.7–4.5 g/L), platelets (RI, 400–4000 x10^9/L), haemoglobin (RI, 110–165 g/L), lactate (RI, 0.5–2.2 mmol/L), base excess (RI, –2.0 to –3.0 mmol/L) — RIs as per ranges at the Gold Coast University Hospital.

Statistical analysis

For all parameters, normality and equality of variance was tested using the Kolmogorov–Smirnov test. Data were expressed as median and

Figure 2. FIBTEM and Clauss fibrinogen (FibC) changes over time from emergency department (ED) admission*

Time point	FIBTEM A5 (mm)	FibC (g/L)
ED admission	6 (4–11)	1.7 (1.3 – 2.2)
Pre-FC transfusion	6 (3.5–7)	-
Post-FC transfusion	11 (8–12)	-
Post-bleeding episode	12 (11–14)	-
Post-24 h	15 (12–17)	3.5 (2.8 – 4.0)
Post-48 h	21 (17–24)	4.9 (4.2 – 6.0)



* Data are presented as median values with 25–75% interquartile ranges; error bars represent minimum and maximum values. Statistical significance was established between pre- and post-administration of fibrinogen concentrate using the Mann–Whitney rank sum test; significance level $P < 0.001$.

interquartile range (IQR) (25th–75th percentile), with most datasets lacking normal distribution. Spearman rank order correlation was used to determine the correlation between FIBTEM and FibC concentrations. Changes within groups between time points were assessed using Student *t* test or Mann–Whitney rank sum tests. No correction was performed for multiple analyses. Statistical analysis was performed using SigmaPlot version 11.0 (SYSTAT Software, Chicago, Ill, USA). A $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Thirty-six patients with trauma received FC as their initial form of fibrinogen replacement during the study period (Table 1). The majority of patients were male, had a median age of 32 years (IQR, 19.5–43.0 years) and had blunt trauma. This cohort of patients was significantly injured, with a median ISS 33 (IQR, 25.0–49.0), and 33% of patients died. Median packed red blood cells transfusion requirement was 7.5 units (IQR, 3.5–11 units), the majority of patients required a significant transfusion (≥ 4 units in 24 hours) and 36% received a massive transfusion (≥ 10 units in 24 hours). The initial FC dose transfused was 4 g. A number of patients required additional fibrinogen replacement using either FC or cryoprecipitate. In patients requiring cryoprecipitate the median transfusion requirement was 10 units (IQR, 0–30 units). Thirty-three per cent of patients received FFP as part of their resuscitation, with a median of 3 units (IQR, 2–4 units). Nearly half the patients received platelets (median 2 units; IQR, 1–3 units), this would be expected utilising our ROTEM-guided trauma MHP. Only a minority of patients received prothrombin complex concentrate.

Time from FIBTEM to fibrinogen concentrate transfusion

It took a median of 22 minutes (IQR, 17.5–30.3 minutes) to administer FC after each patient's initial FIBTEM analysis (Figure 1). Subsequent testing to assess response of FC transfusion took place a median of 28 minutes later (IQR, 17.6–52.5 minutes). In under one hour, hypofibrinogenaemia could be identified, a treatment given (FC transfusion), and efficacy of intervention assessed.

Laboratory parameters

FIBTEM A5 and laboratory parameters of coagulation are shown in Table 2. Patients were hypofibrinogenaemic by both FIBTEM A5 (6 mm) and FibC (1.7 g/L) on presentation to the ED. Both parameters improved incrementally by 24 hours after admission (Figure 2). The INR was elevated at 1.4 at ED presentation. Both the platelet count and haemoglobin level were within normal range on admission and had dropped significantly by 24 hours. This cohort of significantly injured patients (ISS, 33) had markedly abnormal blood gas analysis on admission: pH 7.18 (IQR, 7.05–7.29), base excess –9.15 (IQR, –16.6 to –7.00) and lactate 5.6 mmol/L (IQR, 3.2–8.1 mmol/L), which had normalised by 24 hours (Table 2).

Table 3. FIBTEM and Clauss fibrinogen (FibC) increment at various time points

FIBTEM and FibC increment*	Result† Median (IQR)	Unit
FIBTEM A5 pre- to post-FC transfusion	4.0 (3.0–5.5)	mm
	1.3 (0.8–1.6)	mm/g FC
FIBTEM A5 pre-FC transfusion to post-bleeding episode	5.0 (3.0–8.5)	mm
	0.7 (0.3–1.1)	mm/g of fibrinogen
FIBTEM A5 pre-FC transfusion to post-24 h	9.0 (5.0–12.0)	mm
	1.1 (0.5–1.8)	mm/g of fibrinogen
FIBTEM A5 ED admission to post-24 h	6.5 (4.0–11.0)	mm
	0.8 (0.3–1.5)	mm/g of fibrinogen
FibC ED admission to post-24 h	1.6 (1.1–2.1)	g/L
	0.2 (0.1–0.4)	g/L/g of fibrinogen

ED = emergency department; FC = fibrinogen concentrate. * FIBTEM A5 results are reported in units of mm and mm/g of total fibrinogen transfused. FibC results are reported in units of g/L and g/L/g of fibrinogen transfused. † Data are presented as median values with 25–75% interquartile ranges.

Fibrinogen increment during resuscitation

FIBTEM A5 and FibC increments during various time points are shown in Table 3. FIBTEM A5 increased from pre-FC transfusion to all recorded time points (post-FC transfusion, post-bleeding episode and 24 h after initial transfusion). One gram of FC raised FIBTEM amplitude by about 1 mm. FIBTEM A5 was also increased along with FibC from ED admission to 24 hours later. The greatest FIBTEM A5 increment observed was from pre-FC transfusion to 24 hours after transfusion (9 mm or 1.1 mm/g of fibrinogen). Total fibrinogen dose of 7 g over the 24-hour period (FC combined with cryoprecipitate and FFP) increased FIBTEM A5 by about 1 mm/g fibrinogen and FibC by 0.2 g/L per gram of fibrinogen.

FIBTEM A5 and Clauss fibrinogen correlation

The correlation between FIBTEM A5 and FibC at three different time points (at ED presentation, at 24 hours and at 48 hours) is shown in Figure 3. At each time point, there was a statistically significant ($P = 0.001$) moderate to strong correlation ($r = 0.7–0.8$) between these two values.

Discussion

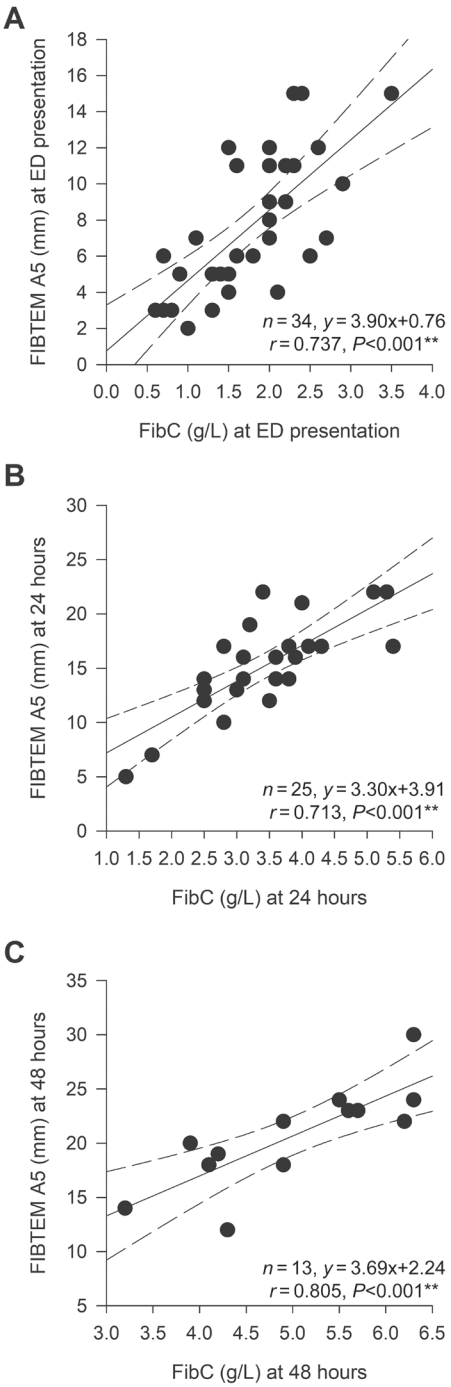
In this observational study, the primary outcome examined was time to administration of FC following ROTEM FIBTEM A5 assay performed on arrival to ED. The median time from initial FIBTEM A5 test to administration of FC was 22 minutes. This time frame suggests that rapid administration with FC is feasible, especially when comparing it with the time to transfusion of other products in the literature. The CRYOSTAT trial published in 2015 concluded that using cryoprecipitate early in major haemorrhage was feasible; however, there was a median time to cryoprecipitate transfusion of 60 minutes.[10] In a large cohort study of bleeding patients from a variety of contexts, the time to cryoprecipitate issue in those with trauma was 1.7 hours.[9] The difference in time to fibrinogen administration seen between FC and cryoprecipitate is likely due to the need to retrieve cryoprecipitate from the blood bank before use, thaw it and have it delivered to another area of the hospital. A major advantage of FC is its rapid time of reconstitution and its easy storage in the ED. Another recently published study, the FiiRST trial reported that early FC use in patients with hypotension requiring blood transfusions was feasible and increased fibrinogen levels during traumatic haemorrhage.[21] However, in a multicentre randomised controlled trial in the United Kingdom, the E-FIT 1 trial, the administration of FC to patients within 45 minutes of their admission was not feasible.[22] The E-FIT results differ to those of our observational study, which suggest FC can be delivered in about 20 minutes. It is possible that the time to delivery of FC in E-FIT was longer due to the constraints of a double-blinded randomised controlled trial, with the study drug being reconstituted in a blinded fashion, whereas our study was an observational study of clinical practice.

To assess the effectiveness of FC administration, follow-up FIBTEM testing was performed about 30 minutes after the initial transfused dose (median time, 28 min; IQR, 17.6–52.5 minutes). Median time between FIBTEM tests was 56.5 minutes (IQR, 42.0–78.0 minutes). In under one hour, hypofibrinogenaemia could be identified, a treatment given (FC transfusion) and efficacy of intervention assessed.

Our study showed that for each gram of fibrinogen administered, the FIBTEM A5 was increased by about 1 mm. This is similar to the result that was obtained in a prospective multicentre study on bleeding patients with trauma, for whom a mean dose of 3.8 g (SD, 1.2 g) fibrinogen produced a 5.1 mm increment in FIBTEM A5 (1 g fibrinogen, resulting in 1.3 mm FIBTEM increment).[23]

There was a statistically significant ($P < 0.001$) increase in FibC concentrations and FIBTEM A5 amplitude from ED admission to 24 hours after admission. When FIBTEM A5 and FibC values were correlated, they were statistically significant at all three time points (ED admission, 24 h and 48 h after admission), with moderate to strong correlations

Figure 3. FIBTEM A5 and Clauss fibrinogen (FibC) correlation



n = number of patients with available data. Correlation analysis determined the association at between FIBTEM A5 (mm) and FibC (g/L) at different time points (**A**, **B** and **C**). The association between the two parameters was significant ($P < 0.001$) at all three time points (emergency department admission, 24 h and 48 h post-admission), with moderate to strong correlations ($r = 0.7–0.8$) noted. Data are presented as linear relationship and 95% confidence intervals. † $P < 0.001$.

(r = 0.7–0.8) noted. The strong correlation between FIBTEM A5 and FibC levels at all three time points suggests that FIBTEM A5 could be used to assess fibrinogen levels. Clinically, this is very important, since the FIBTEM A5 can provide a much faster result compared with FibC. This is important in traumatic haemorrhage, given that timely results will likely result in more timely administration of appropriate products. The use of FIBTEM A5 has previously been shown to correlate well with standard laboratory tests.[24] There is increasing evidence for its use in guiding therapy and management of bleeding and coagulopathy.[25,26]

Current literature suggests that the use of FC may have a beneficial effect in reducing the total amount of blood products transfused. In a Cochrane Review of six randomised controlled trials assessing the effects of FC compared with usual transfusion practices in bleeding patients, the use of FC appeared to decrease overall transfusion requirements.[27] In another study investigating thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy, FC decreased the exposure of patients to allogenic blood products.[28] Since our study was observational and did not have a control group, we were unable to assess this potential benefit of FC.

It is well documented that hypofibrinogenaemia results in reduced clot strength, leading to increased blood loss and subsequently increased transfusion requirements and poorer outcomes.[29,30] Fibrinogen can be replaced via different products; however, there is currently no strong evidence to support the use of one approach or transfusion product over another. Although cryoprecipitate has traditionally been used for fibrinogen replacement in trauma, a review suggests there is currently no clear consensus regarding the overall benefit of cryoprecipitate over FC.[31] The ideal method, dose, and timing of fibrinogen supplementation remains unclear, despite increasing recognition and evidence of its important role in the management of haemorrhage.[19]

Notwithstanding the options for fibrinogen replacement, there is an increasing trend towards use of FC over FFP or cryoprecipitate. An international multicentre study reported no consistent correction of any measure of clot function or increases in procoagulant levels with high dose FFP therapy when used in traumatic haemorrhage.[11] Cryoprecipitate has been widely accepted as a fibrinogen supplement in acquired coagulopathy, but there is a lack of level 1 evidence to support its use.[32] The CRYOSTAT-2 trial (ISRCTN 4998314) is currently recruiting in all

major trauma centres in the United Kingdom. This large multicentre randomised controlled trial will recruit over 1500 severely injured patients with trauma who will be randomly allocated to standard MHP or standard MHP plus early empiric delivery of cryoprecipitate. This trial will hopefully add to the evidence base surrounding early fibrinogen replacement in severe traumatic haemorrhage. However, two key questions will remain: what is the optimum product for fibrinogen replacement? and, should fibrinogen replacement be empiric or targeted to patients with haemorrhage and hypofibrinogenaemia? For reasons already outlined, the results of our study support ongoing investigation and trials of FC versus cryoprecipitate in traumatic haemorrhage.

Although this study suggests that rapid administration of FC for patients with severe traumatic haemorrhage is feasible in the acute setting, we are aware of its limitations. This is an observational study at a single centre with a relatively small cohort of patients. Almost all patients in this cohort received other products in addition to FC. These included a median of 7.5 units (IQR, 3.5–11 units) of packed red blood cells, and 60% of the patients received a median of 10 units (IQR, 0–30 units) of cryoprecipitate. Since a number of patients were transfused with cryoprecipitate and/or FFP in addition to FC, we were unable to determine exactly how efficacious FC is in increasing fibrinogen levels when used alone, nor were we able to compare it directly with other products.

This observational study formed the platform for future trials, including Fibrinogen Early in Severe Trauma Study (FEISTY).[33] This pilot randomised controlled trial compared time to administration of either cryoprecipitate or FC in patients with traumatic haemorrhage and has recently been presented but not yet published. There has been increasing use of FC in traumatic haemorrhage without a sound evidence base. There is an urgent need for a multicentre randomised controlled trial comparing cryoprecipitate with FC in terms of safety, efficacy and economic implications. Future trials should have patient-centred clinical outcomes and target a specific group of severely injured patients with trauma with major haemorrhage and evidence of hypofibrinogenaemia.

Conclusion

There is currently a lack of high level evidence to support the use of early fibrinogen as a key player in the management of severe traumatic haemorrhage. This study has demonstrated that it is feasible to rapidly replace fibrinogen in severe traumatic haemorrhage using FC guided by FIBTEM A5. However, further multicentre randomised controlled trials comparing cryoprecipitate with FC are urgently needed.

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Competing interests

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Author contribution statement

JW, DC, MW and EW conceived the study design. DH, EC and KW performed data input and checking. JS and JW performed the literature review. AB performed statistical analysis and prepared figures and table. JS and JW wrote the initial manuscript draft. All authors reviewed and contributed to the final manuscript.

References

1 Alberdi F, García I, Atutxa L, Zabarte M; Trauma and Neurointensive Care Work Group of the SEMICYUC. Epidemiology of severe trauma. *Med Intensiva* 2014; 38: 580-8.
2 Norton R, Kobusingye O. Injuries. *N Engl J Med* 2013; 368: 1723-30.

3 Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. *Crit Care* 2005; 9 (Suppl): S1-9.

4 Hunt H, Stanworth S, Curry N, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. *Cochrane Database Syst Rev* 2015; (2): CD010438.

5 Holcomb JB. What is new in the treatment of trauma induced coagulopathy? *Expert Rev Hematol* 2015; 8: 703-5.

6 Thorarinsdottir HR, Sigurbjornsson FT, Hreinsson K, et al. Effects of fibrinogen concentrate administration during severe hemorrhage. *Acta Anaesthesiol Scand* 2010; 54: 1077-82.

7 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.

8 McQuilten ZK, Wood EM, Bailey M, et al. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. *Injury* 2017; 48: 1074-81.

9 McQuilten ZK, Bailey M, Cameron PA, et al. Fibrinogen concentration and use of fibrinogen supplementation with cryoprecipitate in patients with critical bleeding receiving massive transfusion: a bi-national cohort study. *Br J Haematol* 2017; 179: 131-41.

10 Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. *Br J Anaesth* 2015; 115: 76-83.

11 Khan S, Davenport R, Raza I, et al. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. *Intensive Care Med* 2015; 41: 239-47

12 Aubron C, Reade MC, Fraser JF, Cooper DJ. Efficacy and safety of fibrinogen concentrate in trauma patients — a systematic review. *J Crit Care* 2014; 29: 471.e11-7.

13 Jensen NHL, Stensballe J, Afshari A. Comparing efficacy and safety of fibrinogen concentrate to cryoprecipitate in bleeding patients: a systematic review. *Acta Anaesthesiol Scand* 2016; 60: 1033-42.

14 Wong H, Curry N. Do we need cryoprecipitate in the era of fibrinogen concentrate and other specific factor replacement options? *ISBT Science Series* 2018; 13: 23-8.

15 Solomon C, Asmis LM, Spahn DR. Is viscoelastic coagulation monitoring with ROTEM or TEG validated? *Scand J Clin Lab Invest* 2016; 76: 503-7.

16 Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care* 2016; 20: 100.

17 Schöchl H, Cotton B, Inaba K, et al. FIBTEM provides early prediction of massive transfusion in trauma. *Crit Care* 2011; 15: R265.

18 Spahn DR. TEG®- or ROTEM®-based individualized goal-directed coagulation algorithms: don't wait — act now! *Crit Care* 2014; 18: 637.

19 Winearls J, Reade M, Miles H, et al. Targeted coagulation management in severe trauma: the controversies and the evidence. *Anesth Analg* 2016; 123: 910-24.

20 Baksaas-Aasen K, Van Dieren S, Balvers K, et al. Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage: a prospective observational multicenter study. *Ann Surg* 2018. doi: 10.1097/SLA.0000000000002825. [Epub ahead of print]

21 Nascimento B, Callum J, Tien H, et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. *Br J Anaesth* 2016; 117: 775-82.

22 Curry N, Foley C, Wong H, et al. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Crit Care* 2018; 22: 164.

23 Juffermans NP, Wirtz MR, Balvers K, et al. Towards patient-specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry. *J Thromb Haemost* 2019; 17: 441-8.

24 Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. *Crit Care* 2015; 19: 97.

25 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.

26 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* 2015; 122: 241-75.

27 Wikkelsø A, Lunde J, Johansen M, et al. Fibrinogen concentrate in bleeding patients. *Cochrane Database Syst Rev* 2013; (8): CD008864.

28 Schöchl H, 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: R83.

29 Inaba K, Karamanos E, Lustenberger T, et al. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg* 2013; 216: 290-7.

30 Hagemo JS, Stanworth S, Juffermans NP, et al. Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. *Crit Care* 2014; 18: R52.

31 Novak A, Stanworth SJ, Curry N. Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage — how do they compare? *Expert Rev Hematol* 2018; 11: 351-60.

32 Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. *Br J Anaesth* 2014; 113: 922-34.

33 Winearls J, Wullschleger M, Wake E, et al. Fibrinogen Early in Severe Trauma Study (FEISTY): study protocol for a randomised controlled trial. *Trials* 2017; 18: 241.