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Clinical Practice

Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial

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Abstract

Background: Low fibrinogen (Fg) concentrations in trauma haemorrhage are associated with poorer outcomes. Cryoprecipitate is the standard source for Fg administration in the UK and USA and is often given in the later stages of transfusion therapy. It is not known whether early cryoprecipitate therapy improves clinical outcomes. The primary aim of this feasibility study was to determine whether it was possible to administer cryoprecipitate, within 90 min of admission to hospital. Secondary aims were to evaluate laboratory measures of Fg and clinical outcomes including thrombotic events, organ failure, length of hospital stay and mortality.
Methods: This was an unblinded RCT, conducted at two civilian UK major trauma centres of adult trauma patients (age ≥16 yrs), with active bleeding and requiring activation of the major haemorrhage protocol. Participants were randomised to standard major haemorrhage therapy (STANDARD) (n=22), or to standard haemorrhage therapy plus two early pools of cryoprecipitate (CRYO) (n=21).
Results: 85% (95% CI: 69–100%) CRYO participants received cryoprecipitate within 90 min, median time 60 min (IQR: 57–76) compared with 108 min (67–147), CRYO and STANDARD arms respectively (P=0.002). Fg concentrations were higher in the CRYO arm and were maintained above 1.8 g litre^{-1} at all time-points during active haemorrhage. All-cause mortality at 28 days was not significantly different (P=0.14).
Conclusions: Early Fg supplementation using cryoprecipitate is feasible in trauma patients. This study supports the need for a definitive RCT to determine the effect of early Fg supplementation on mortality and other clinical outcomes.
Trial registry number: ISRCTN55509212.

Key words: cryoprecipitate; fibrinogen; haemorrhagic shock; multiple trauma

Early clinical data suggest that fibrinogen (Fg) supplementation improves outcomes for trauma haemorrhage by improving clot strength,[1] reducing blood loss[2] and increasing survival.[3] A prospective observational study of 517 patients has reported that admission Fg is an independent predictor of mortality in trauma patients,[4] and two cohort studies[5 6] have reported lower

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Editor's key points

- Trauma haemorrhage is associated with low fibrinogen, and in turn with worse outcomes.
- A feasibility study was performed to determine if fibrinogen supplementation using cryoprecipitate could be administered within 90 min of admission.
- Adult trauma patients randomised to early cryoprecipitate received cryoprecipitate significantly earlier compared with standard therapy.
- A large RCT is needed to determine the safety and efficiency of early fibrinogen supplementation in traumatic haemorrhage.

mortality for patients receiving more Fg during trauma haemorrhage. Hypofibrinogenaemia is a key component of acute traumatic coagulopathy[7] and occurs early during major blood loss.[8]

Cryoprecipitate is the standard method of Fg supplementation in UK and USA. The evidence supporting its clinical effectiveness is limited, with no randomised controlled trials (RCTs) completed.[9] A Cochrane review evaluating Fg concentrate (FgC) found limited data and reported no effect on mortality, but did find a reduction in allogeneic transfusion.[10] Early cryoprecipitate administration, could improve clinical outcomes during trauma haemorrhage, through correction of haemostasis. A major limitation to testing this hypothesis, is the need for controlled thawing of cryoprecipitate and rapid delivery to patients. RCTs evaluating transfusion in trauma are further complicated by the emergent clinical situation, availability of research personnel outside normal working hours and time pressure to administer the thawed blood product quickly. For these reasons, a feasibility design was chosen for this first study so that any potential barriers could be identified ahead of a larger, definitive efficacy trial. The primary objective of this study was to evaluate whether it was possible to deliver cryoprecipitate early (i.e. within 90 min of admission), to trauma patients with major haemorrhage.

Methods

Study design

The CRYOSTAT study was an unblinded RCT conducted at two civilian UK major trauma centres. The study was registered on www.controlled-trials.com (ISRCTN55509212).

Eligibility criteria and randomisation

Patients were eligible if they were adult trauma patients (age ≥16 yrs), were actively bleeding and required activation of the major haemorrhage protocol (MHP). MHP was activated when a patient had both on-going bleeding and signs of clinical shock. Patients were excluded if they arrived >3 h after injury; were transferred from another hospital; or if the trauma team leader deemed the patient unsuitable (i.e. injuries incompatible with life). Subjects were block-randomised by centre. The randomisation lists were prepared centrally using a computerised random number generator. Allocation was concealed using a sealed opaque envelope system and occurred within one h of hospital arrival.

Consent

Written informed consent was sought on admission, but where this was not possible the emergency care research process was used. A senior trauma team leader, not involved in the trial, was able to decide whether an eligible trauma patient could be entered into the study. Written informed agreement from a personal consultee or from the participant, was subsequently sought as soon as possible after study entry. The protocol was approved by NRES Committee South Central - Oxford C (12/SC/0145).

Intervention

Subjects were randomised into two equal study arms. Patients randomised to the intervention (CRYO arm) received standard major haemorrhage therapy with additional receipt of two early pools of cryoprecipitate, given within 90 min of admission (chosen as a significantly different timeframe to UK standard practice). We conducted a prospective, multi-centre, observational study of admissions with severe traumatic injuries, recruiting at 22 hospitals in the UK, including both major trauma centres and trauma units. Time to first transfusion of cryoprecipitate for major haemorrhage was a median of 184 min (personal communication, Stanworth & Brohi, 2014). No changes were made to the MHP or to cryoprecipitate thawing methods for this study. One pool of cryoprecipitate in the UK equates to 5 single units pooled with a volume of 150–200 ml and mean Fg content of 2.0 g.[11]

The dose of cryoprecipitate was chosen using results from *ex vivo* ROTEM® data. 19 coagulopathic trauma blood samples were spiked with increasing doses of Fg (range: 3 g to 12 g).[4] A 4 g dose of Fg resulted in an increase in ROTEM clot strength values (EXTEM and FIBTEM Maximum Clot Firmness) that might indicate clinical efficacy, and therefore two pools of cryoprecipitate were chosen.

Standard therapy

In the STANDARD arm, subjects received major haemorrhage therapy alone. The two hospitals shared a common MHP based on delivery of an empiric 'MHP pack (6 units red blood cells (RBC) and 4 units fresh frozen plasma (FFP)). Tranexamic acid (TXA)(1 g i.v. bolus, 1 g 8-h infusion) was part of the MHP protocol.[12] If haemorrhage continued after completion of MHP pack 1, MHP pack 2 was transfused (6 units RBC, 4 units FFP, 2 pools cryoprecipitate and 1 adult pool of platelets (4 pooled buffy coat platelets or 1 single apheresis unit)). During active bleeding the targets for MHP therapy (using standard laboratory tests) were: PTr≤1.5; Clauss Fg≥1.5 g litre^{-1}; platelet count >100×10^{-9} litre; haemoglobin 8–10 g dl^{-1}. FFP and cryoprecipitate took on average 17 min to thaw. Limited amounts of pre-thawed FFP were available at one participating centre. The MHP protocol was used throughout the duration of active bleeding. The order of transfusion of blood components within each pack was according to clinical discretion. Additional components could be ordered to maintain MHP laboratory targets, where necessary. Transfusion of blood components during in-patient stay followed local hospital guidelines.

Outcomes

The primary outcome was feasibility, defined by the percentage of subjects randomised to the intervention (CRYO) arm (according to Intention to Treat (ITT) criteria) in receipt of cryoprecipitate within 90 min. For this trial to be successful, it was pre-specified that this should be ≥90%. The protocol was deemed to have been followed if the first cryoprecipitate pool was started within 90 min. An additional primary outcome was recruitment rate,

calculated by: number of subjects enrolled as a proportion of total number of eligible patients, presenting to the two centres.

Secondary outcomes were clinical and laboratory measures of efficacy and safety. Safety was measured by symptomatic thrombotic events: arterial (e.g. myocardial infarction (MI), stroke) and venous (e.g. pulmonary embolism (PE), deep venous thrombosis (DVT)) during hospital stay and up to three months after admission. Other clinical outcomes included: 28-day all-cause mortality; transfusion requirements (RBC, FFP, platelets, cryoprecipitate) at 6 h, 24 h and 28 days; non-acute and acute transfusion reactions related to cryoprecipitate infusion to day 28; presence of single or multiple organ failure (MOF), and acute respiratory distress syndrome (ARDS) to day 28 (determined by sequential organ failure assessment scores) and length of hospital stay. We compared actual mortality rates with predicted mortality using the PS12 prediction model (Probability of Survival model: based on Injury Severity Scores (ISS), Glasgow Coma Scale (GCS), intubation status, gender and age).[13] Laboratory measures included: Clauss Fg, ROTEM EXTEM and FIBTEM at 3 pre-specified points during active bleeding (immediately after transfusion of 4 units, 8 units and 12 units RBC) and at 24 h and 72 h from randomisation. Clauss Fg concentrations were measured at days 7, 14, 21 and 28. The EXTEM and FIBTEM measurements of interest were CA5 (clot amplitude at 5 min) and MCF (maximum clot firmness).

Sample and data collection

Blood samples were drawn from the femoral vein or antecubital fossa, immediately upon admission to ED. Blood for ROTEM analysis and Fg determination was drawn into 2.7 ml citrated tubes (0.109 M, 3.2%, Becton-Dickinson, Plymouth, UK). Patient characteristics, severity of injury and admission physiology were collected using the GCS, Abbreviated Injury Scale (AIS) and the ISS. Data were collected on fluid and transfusion requirements to day 28. Timing of transfusions was collected from randomisation to end of first active bleed. A three-month follow-up telephone questionnaire was completed evaluating safety (symptomatic thromboembolic events (arterial and venous), as pre-specified in the study protocol).

Sample analysis

ROTEM samples were processed within 2 h of blood draw, with a ROTEM delta instrument (TEM International, Munich, Germany).[14] Clauss Fg concentrations (STA Fibrinogen [Stago, Asnières sur Seine, France] or Siemens Thrombin [Sysmex UK, Milton Keynes, UK] reagents) were determined with the STA-R evolution (Stago) or the Sysmex CS2100i (Sysmex UK) analysers.

Sample size and data analysis

If the proportion of the intervention group who received cryoprecipitate within 90 min from admission was 90%, a sample size of 20 would yield a 95% confidence interval for this estimate of between 69 and 99%. Therefore, the trial target was 40 subjects (20 per arm). Replacements were sought for any subject who withdrew consent or who was randomised incorrectly. Primary analysis for the feasibility outcome was performed on the ITT population. ITT was defined as randomised subjects who gave informed consent and for whom the primary outcome of cryoprecipitate administered within 90 min was recorded. A per-treatment (P-T) analysis was also performed for secondary outcomes. All analyses used data from the ITT population, unless otherwise stated.

Key patient characteristics and clinical condition of the patients were compared using Fisher's exact test or Mann-Whitney *U*-test for categorical or continuous data, as appropriate. Fg concentrations were analysed using two-way ANOVA, with repeated measures and mean values are given when comparing these values. Numbers of transfused units pre- and post-randomisation were compared using a quasi-Poisson regression model. All-cause mortality and hospital stay were estimated using the Kaplan-Meier method and compared using the log-rank test.

Sensitivity analyses were conducted for the primary outcome by assuming all missing data related to either administration >90 min or ≤90 min accordingly. Similarly, missing data for the number of units of RBC transfused at 6 h and 24 h and Clauss Fg at 24 h and 72 h, were assumed equal to the 25th or 75th centiles, derived from the complete patient data for each arm in sensitivity analyses. All analyses were unadjusted for other risk factors, and there was no adjustment for multiple testing. All significance tests were two-sided, and the significance level was 5%. All analyses were undertaken using the SAS/STAT software version 9 (SAS Institute Inc., Cary, NC USA).

An Independent Data Monitoring Committee (IDMC) monitored all safety events throughout the study. The study manuscript was produced according to CONSORT recommendations for the reporting of RCT's.[15]

Results

Recruitment and baseline characteristics

202 trauma patients with major blood loss were admitted between July 2012 and October 2013. 138 met eligibility criteria and 44 were randomised. Three patients were not included in the analysis: 1 was randomised in error; in 1 there was lack of information to determine whether cryoprecipitate had been given within 90 min; and one withdrew consent.

Of 21 subjects allocated to CRYO and 22 allocated to STANDARD, 13 and 14 subjects respectively completed the study to 3 month follow-up. The ITT group included 20 in CRYO and 21 in STANDARD (Fig. 1). Per-treatment analysis included 23 receiving cryoprecipitate within 90 min (17 CRYO, 6 STANDARD– received as part of MHP pack 2), and 18 in the comparator arm.

Several baseline imbalances were seen between CRYO and STANDARD arms (Table 1). In the STANDARD arm, subjects were older, more severely injured and had a greater number of head injuries. These differences were reflected in admission physiology (Table 1). The median Fg at admission was 1.6 g litre^{-1} (IQR: 1.4–2.1 g litre^{-1}) and 1.6 g litre^{-1} (IQR: 1.4–2.2 g litre^{-1}), CRYO and STANDARD respectively. All but one subject received TXA (STANDARD arm), and minimal volumes of fluid were administered pre-randomisation; median 50 ml (CRYO arm) *vs* 250 ml (STANDARD arm). Similar volumes of blood were transfused pre-randomisation.

Feasibility outcomes

The primary outcome for this study was achieved in 85% (95% CI: 69–100%). Reasons for cryoprecipitate not being administered included: two subjects no longer had active bleeding; the third situation related to clinical delay, whilst establishing whether the patient had ongoing bleeding. Six (29%; 95% CI 24–33%) of patients in the STANDARD arm received cryoprecipitate early; comparative odds of receiving cryoprecipitate early in the CRYO arm was 13 (95% CI 2.5, 96). Sensitivity analysis confirmed these results were robust. Median time to administration

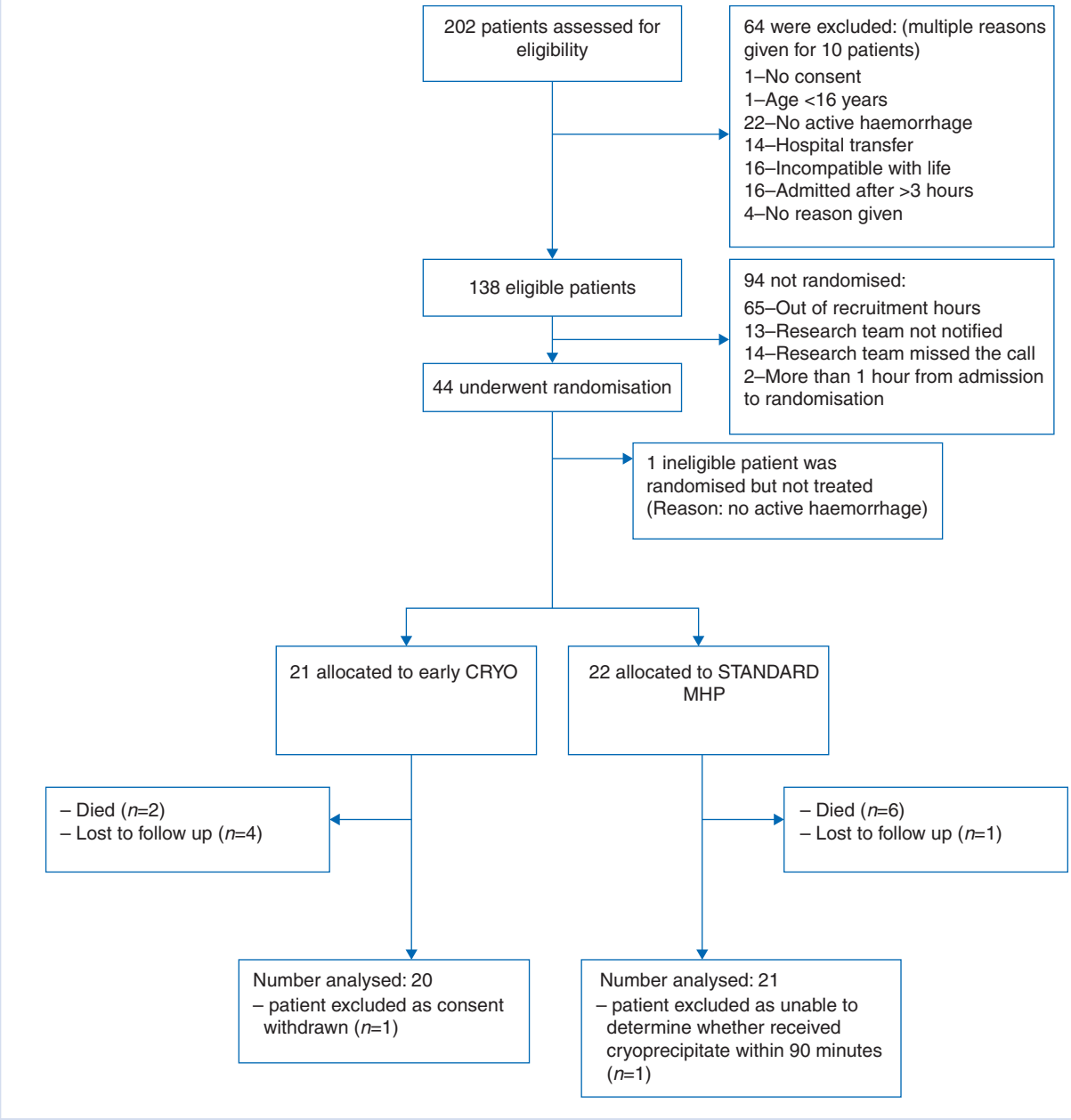

Fig 1 CONSORT Diagram.

of cryoprecipitate was 60 min (IQR: 57–76) compared with 108 min (67–147), CRYO and STANDARD arms, respectively (P=0.002).

Sixty eight per cent (138 out of 202, 95% CI: 62–75%) of trauma patients admitted with major blood loss, met the eligibility criteria. Recruitment rate was 27% at centre A and 33% at centre B. In total, 32% of eligible patients (44 out of 138) were enrolled. Reasons for not randomising eligible patients included: out of formal recruitment hours (n=65, 69%); research team not notified (n=13, 14%); research team missed/unable to attend (n=14, 15%) and >1 h from admission to randomisation (n=2, 2%). All 41 subjects were randomised within 60 min of admission.

Other outcomes including safety

At admission, mean Clauss Fg was the same in both arms: 1.8 g litre^{-1}. During active haemorrhage mean Fg concentrations were higher in the CRYO arm: 2.5 g litre^{-1} compared with 1.7 g litre^{-1} ; 2.1 g litre^{-1} compared with 0.9 g litre^{-1} ; and 2.0 g litre^{-1} compared with 1.3 g litre^{-1} at the 4, 8 and 12 unit time points, respectively (Fig. 2). Small numbers of samples, limited statistical comparison between groups during active haemorrhage (Fig. 2). Fibrinogen values remained >1.8 g litre^{-1} at all times in the CRYO arm (compared with a nadir of 0.6 g litre^{-1} in the STANDARD arm).

Table 1 Patient characteristics and injury characteristics at baseline (ITT population). Values are median (IQR) or *n* (%), except for age which is median (range). *No subject received platelets or cryoprecipitate before randomisation. †Data not reported for one subject in STANDARD arm, data for *n*=20. ITT, intention to treat

	CRYO	STANDARD
SUBJECTS		
N	20	21
Age	31 (16–83)	50 (16–85)
Male	17 (85)	15 (71.4)
TIMELINES		
Injury to Hospital (min)	95 (76–119)	96 (75–106)
INJURIES & PHYSIOLOGY		
Blunt	18 (90)	15 (71)
ISS	28 (22–42)	41 (29–45)
Systolic arterial pressure (mm Hg)	84 (56–104)	79 (65–90)
HR (per min)	124 (91–160)	113 (102–130)
GCS	13 (5–15)	8 (3–15)
Lactate (mEq litre^{-1})	5.0 (3.9–6.0)	6.9 (3.6–12.3)
Base Excess (mEq litre^{-1})	−9.0 (−12.7–6.9)	−14.5 (−20.0–7.1)
Fibrinogen (g litre^{-1})	1.6 (1.43–2.14)	1.55 (1.43–2.24)
PT (sec)	12.6 (11.1–13.4)	13.2 (11.8–15.8)
PRE RANDOMISATION		
TXA administered	20 (100)	19 (95)†
RBC (units)	3 (2–4)	2 (1–3)
FFP (units)	0 (0–0)	0 (0–0)
Platelets (pools)*	0 (0–0)	0 (0–0)
Cryoprecipitate (pools)*	0 (0–0)	0 (0–0)
Crystalloid (ml)	50 (0–500)	250 (0–500)

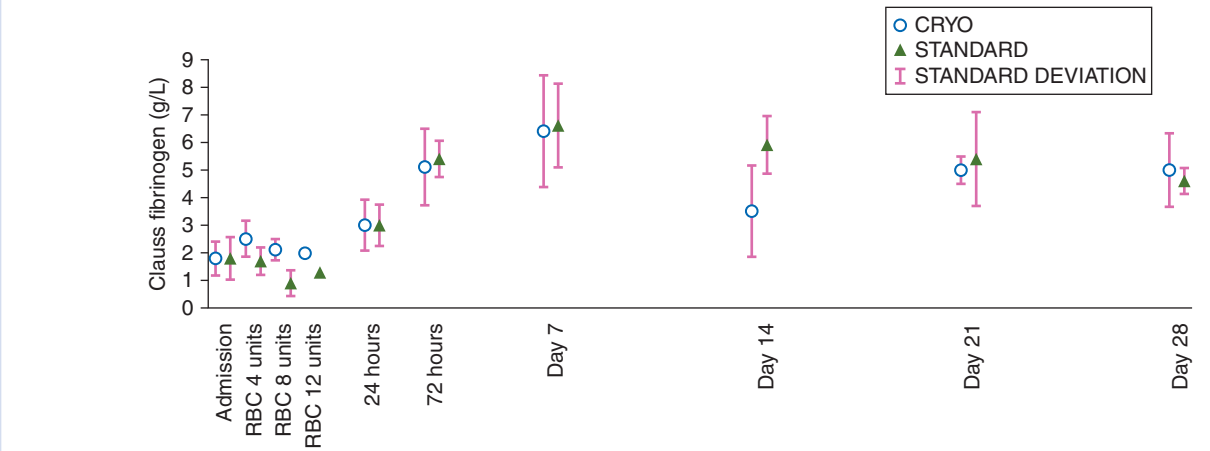

Fig 2 Comparison of Mean Fibrinogen Concentrations (Standard Deviation) between Study Arms for the Duration of the Trial. Changes of Clauss fibrinogen concentrations were compared using a two way ANOVA with repeated measures for patients in each arm of the trial. No evidence of a difference between changes in mean Clauss fibrinogen concentrations at 24 h and 72 h and the arm of the trial.

No significant difference was noted between mean Clauss Fg at 24 h and 72 h (P=0.64), although in both arms a significant increase in Fg was noted after 24 h and up to 72 h (P<0.0001). A trend to lower Fg was seen from day 7 to study end in the CRYO arm (Fig. 2), although the number of results was small. Mean Clauss Fg reached a peak in both arms at day 7; 6.4 g litre^{-1} compared with 6.6 g litre^{-1} in CRYO and STANDARD respectively. ROTEM FIBTEM CA5 and MCF values followed the same pattern as Clauss Fg at 24 h and 72 h. ROTEM EXTEM values rose significantly in both groups at 24 h and 72 h, with a greater increase seen in CRYO (Table 1 and Supplementary data).

Bleeding was assessed using a surrogate measure of transfusion (number of units administered). Transfusion requirements were not significantly different between arms at 6 h and 24 h

(Table 2). There was a significantly greater number of cryoprecipitate pools transfused in the CRYO arm by 6 h (P=0.03), but no difference at 24 h and 28 days. The time to receipt of the first units of RBC (P=0.14), FFP (P=0.33) and platelets (P=0.41) were not different between arms, in contrast to the median time to first cryoprecipitate (P=0.002). Six (30%) participants in the CRYO arm received cryoprecipitate between 30 and 60 min of admission, compared with 1 (5%) in the STANDARD arm. No significant differences were seen in units of RBC, FFP, platelets and cryoprecipitate at 28 days (Table 2).

Two subjects died in the CRYO arm and six died in the STANDARD arm (Table 3). All-cause mortality was 10.0 and 28.6% respectively, ITT analysis (P=0.14) and 13.0 and 27.8%, per-treatment analysis (P=0.22). Mean predicted mortality rates according to ITT analysis were: 21% (CRYO) and 42% (STANDARD). In the CRYO arm one subject died from severe head injury and one from sepsis. In the STANDARD arm: one subject died from uncontrolled haemorrhage, 4 from severe head injury and 1 from hypoxic ischaemic encephalopathy. The subject who died from exsanguination received TXA but no cryoprecipitate. On average, STANDARD arm patients remained in ICU for 7 days longer; but no difference was seen in total hospital stay (30 days *vs* 31 days, respectively (P=0.66)) (Table 3).

Safety data are summarized in Table 4. There was no increase in thrombotic events in the CRYO group. All thrombotic events occurred in the STANDARD arm: 19% of participants experienced a thrombotic event, and all events were thromboembolic; 75% venous and 25% arterial. Serious adverse event data showed that no acute or non-acute transfusion reactions were attributed to cryoprecipitate. Eighteen serious adverse events were reported (Table 4).

Table 2 Transfusion timing and transfusion therapy (ITT population). Values are median (IQR). Cryoprecipitate results are expressed as numbers of pools (each pool contains 5 single units). Platelets are expressed as single pooled units. Time from admission was compared using a log rank test. Differences in transfusion requirements between arms were assessed separately using a quasi-Poisson model, and included only those participants still alive at each time point

	CRYO (n=20)	STANDARD (n=21)	P value
TIME FROM ADMISSION TO FIRST TRANSFUSION			
RBC (min)	6 (4–15)	11 (6–17)	0.14
FFP (min)	22 (11–42)	32 (15–53)	0.33
Platelets (min)	83 (64–150)	111 (67–160)	0.41
Cryoprecipitate (min)	60 (57–76)	108 (67–147)	0.002
UNITS AT 6 h			
RBC	7 (4–10)	7 (4–8)	0.49
FFP	7 (4–8)	5 (3–8)	0.31
Platelets	1 (0–1)	1 (0–1)	0.89
Cryoprecipitate	2 (2–4)	2 (0–2)	0.03
UNITS AT 24 h			
RBC	8 (5–11)	7 (6–9)	0.83
FFP	7 (4–8)	6 (3–8)	0.36
Platelets	1 (0–2)	1 (1–2)	0.56
Cryoprecipitate	2 (2–4)	2 (0–2)	0.23
UNITS AT 28 DAYS			
RBC	9 (7–15)	8 (7–11)	0.10
FFP	8 (4–12)	5 (3–8)	0.06
Platelets	1 (0–2)	1 (1–2)	0.82
Cryoprecipitate	2 (2–4)	2 (0–2)	0.06

Table 4 Safety outcomes. Absolute values provided

	INTENTION TO TREAT		PER TREATMENT	
	CRYO	STANDARD	CRYO	STANDARD
SUBJECTS				
N	20	21	23	18
Total number of serious adverse events	**7**	**11**	**9**	**9**
Sepsis	3	0	3	0
Multiple organ failure	1	0	1	0
ARDS	0	1	0	1
Other	3	6	4	5
Thrombotic events	0	4	1	3
Thromboembolic events:				
Arterial event total	**0**	**1**	**1**	**0**
Myocardial Infarction	0	0	0	0
Stroke	0	0	0	0
Other (arterial thrombus)	0	1	1	0
Venous thrombosis event total	**0**	**3**	**0**	**3**
Pulmonary embolism	0	2	0	2
Deep venous thrombosis	0	1	0	1

Table 3 Clinical outcomes. Values are median (IQR) or n (%)

	INTENTION TO TREAT			PER TREATMENT		
	CRYO	STANDARD	P value	CRYO	STANDARD	P value
SUBJECTS						
N	20	21		23	18	
28 day mortality	2 (10.0)	6 (28.6)	0.14	3 (13.0)	5 (27.8)	0.22
ICU Days	11 (5–17)	18 (16–20)	0.56	13 (9–17)	18 (13–23)	0.81
In patient Days	31 (29–33)	30 (22–38)	0.66	32 (17–47)	29 (21–37)	0.08

Discussion

This is the first randomised controlled trial evaluating transfusion of cryoprecipitate in trauma. A feasibility trial was conducted because of the multiple logistic and planning hurdles across transfusion and emergency departments. A 90 min target was chosen for this study as a very different target to standard practice, as cryoprecipitate is often given late in MHP protocols; in the PROMMTT study median time to transfusion was 2.7 h.[16] Cryoprecipitate was administered significantly earlier in the intervention arm.

One in three eligible patients was enrolled in the trial. Similar figures have been reported previously.[17] These rates of enrollment reflect the urgent and unpredictable nature of trauma and the high numbers of eligible admissions out of formal recruitment hours. Of the two centres, one actively recruited between 8 am and 8 pm and the other between 8 am and 10 pm. Twenty nine percent of eligible participants were missed as the research team was not notified or was unable to attend the trauma call. Looking towards future studies, trial resource could be planned to cover an extension of recruitment hours, targeting those times with higher frequency admissions.

The CRASH-2 RCT[12] indicated the importance of delivery of haemostatic therapy early (i.e. within 3 h).[18] In our trial, median time to receipt of cryoprecipitate was 60 min, but no participant received it in <30 min; reflecting the complexity of requesting, preparing and transfusing a frozen blood component. Further reduction of these times in future trials will be challenging, although options might include pre-thawed cryoprecipitate.

Early delivery of cryoprecipitate raised blood Fg above admission concentrations. In the small number of subjects (n=3) where full data were available, average Fg concentrations were raised by 0.8 g litre^{-1} (range 0.15–1.47 g litre^{-1}), a figure in keeping with other studies, where 4 g of Fg has been reported to effect a 1 g litre^{-1} increase in blood concentrations.[19 20] This fibrinogen increment, when compared with the STANDARD arm, was maintained during active haemorrhage with a clear difference between study arms. Larger studies are required to confirm these preliminary findings.

To inform management of trauma haemorrhage, real time, rapid blood results are required. Standard laboratory tests have a long turnaround time, limiting their utility.[7] We found that FIBTEM (in particular CA5) mirrored Clauss Fg. FIBTEM has been used to guide Fg replacement in other studies.[21] Future trauma studies could use admission FIBTEM CA5 measures to dose adjust Fg supplementation.

This study showed no difference in blood transfusion requirements between study arms. In a recent systematic review of 35 RCTs evaluating interventions for trauma haemorrhage, including the CRASH-2 trial, no association was also found between reduction in blood transfusion and reduction in mortality.[22] This could in part reflect the difficulty in standardising reporting of a surrogate measure of bleeding (i.e. transfusion) but might also reflect survival bias.

A possible concern with administering fibrinogen is the potential increased risk of thromboembolic disease.[23–25] No thrombotic events were seen in the CRYO arm in this study. Non-thrombotic serious adverse events were balanced across arms. No unexpected serious adverse events and no transfusion adverse events related to cryoprecipitate were reported, although the study was not powered to detect differences in those outcomes.

This was a feasibility study designed to test a transfusion process. It had several limitations. Cryoprecipitate is a pooled blood component with a variable Fg concentration and volume, and it was not possible to determine Fg concentration in each administered pool. Central laboratory testing was not used for laboratory sampling, as ROTEM is a point of care test and needs to be performed on whole blood. Quality assurance schemes in the UK monitor reliability of Clauss Fg and coefficients of variation were consistently <5% in the participating hospitals. Some baseline imbalances, including ISS, were seen between arms, reflecting the small sample size. The average age of participants was higher than many other published trauma studies which could limit its applicability to younger trauma populations. Missing data for blood samples were frequent, due in part to the practical difficulties in taking blood from patients with such critical injuries and a limited budget. Primary endpoint data were missing for one subject. More focused data capture forms will be used for subsequent studies. This study was designed to test a process, and secondary endpoint results should be viewed with caution as this study was not powered to evaluate clinical outcomes.

Conclusions

Early administration of Fg supplementation, as cryoprecipitate, appears feasible. Lessons learned from the study will be invaluable in the design of larger trials, including defining clear blood sampling 'windows' to reduce missing data and targeting recruitment hours. The results of this study, raising possible associations between higher Fg blood concentrations, shorter ICU stay and, lower mortality, with no evidence of increased thromboembolic events, coupled with other reports,[4] continue to highlight the further need for larger studies to determine the clinical benefit of early Fg supplementation.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Authors' contributions

N.C. contributed to the study design, patient recruitment, study conduct, data collection, data analysis, and writing the paper. C.R. contributed to the study design, patient recruitment, data collection, study conduct and the critical review of the paper. S.B. contributed to the study design, patient recruitment, data collection and the critical review of the paper. L.P. and H.T. contributed to the statistical analysis of data and the critical review of the paper. A.D. contributed to the study design, study conduct and the critical review of the paper. C.L. contributed to the study design, study conduct and the critical review of the paper. L.G. and K.B. contributed to the study design and the critical review of the paper. H.D. contributed to the study design, study conduct and oversight and the critical review of the paper. G.N. contributed to the study design, patient recruitment, study conduct and oversight and the critical review of the paper. S.S. contributed to the study design, study conduct and oversight, data analysis and the critical review of the paper. All of the authors read and approved the final manuscript.

Declaration of interest

None declared.

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