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ARTICLE

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

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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.

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 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

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