Early high-dose cryoprecipitate to reduce mortality in adult patients with traumatic haemorrhage: the CRYOSTAT-2 RCT with cost-effectiveness analysis

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Scientific summary

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Scientific summary

Background

Worldwide, trauma accounts for 5.8 million deaths every year, equivalent to 1 death every 9 minutes, and is the leading cause of death in persons under the age of 44 years. Bleeding accounts for 40% of all injury-related deaths, many within hours of injury, and there is a high burden from major haemorrhage on both patients and the NHS.

Twenty-five per cent of all trauma patients have abnormal blood clotting, which causes higher rates of bleeding, major haemorrhage and a three- to fourfold increase in the risk of death. There are two main clotting abnormalities: low fibrinogen levels (hypofibrinogenaemia) and increased clot breakdown (fibrinolysis).

Cryoprecipitate is the current standard source of concentrated fibrinogen in the UK. Cryoprecipitate may improve outcomes for patients with traumatic haemorrhage by improving clot strength, reducing blood loss and, hence, increasing survival. This is supported by data from our pilot study (CRYOSTAT-1) that showed that the early replacement of fibrinogen with cryoprecipitate was able to rapidly restore fibrinogen levels and may reduce mortality rates from traumatic haemorrhage.

Objectives

We assessed the effects and cost-effectiveness of the early administration of high-dose cryoprecipitate to traumatic haemorrhage patients on death rates, transfusion requirements and adverse events.

Methods

The CRYOSTAT-2 trial was a randomised, parallel-group, unblinded, multicentre, international trial conducted in 25 major trauma centres in the UK and at one level 1 trauma centre in the USA. Adults who had traumatic haemorrhage following severe injury necessitating activation of the major haemorrhage protocol (MHP) and received a blood transfusion were eligible. (Standard MHPs in the UK include empiric cryoprecipitate in the second pack of blood components if a patient continues to bleed.)

Patients were randomly allocated to receive early high-dose cryoprecipitate (3 pools, equivalent to 15 single units of cryoprecipitate or 6 g of fibrinogen supplementation) in addition to the standard MHP or the standard MHP only. Fibrinogen levels were not required at randomisation.

The primary outcome was all-cause mortality at 28 days. The secondary outcomes were all-cause mortality at 6, 24 hours, 6 months and 12 months from admission; death from bleeding at 6 hours and 24 hours; transfusion requirements for red blood cells, platelets, fresh-frozen plasma and cryoprecipitate at 24 hours from admission; destination of participant at discharge; quality-of-life measurements (EuroQol-5 Dimensions, five-level version, and Glasgow Outcome Scale) at discharge/day 28 and 6 months after injury; and hospital resource use up to discharge or day 28 (including ventilator-days, hours spent in critical care and inpatient stays).

We assessed the cost-effectiveness of the early administration of high-dose cryoprecipitate in addition to the standard MHP compared with that of standard MHP only.

The original planned sample size was 1568 (later amended).

Results

Patients were allocated to early cryoprecipitate in addition to the MHP (*n* = 799) or to the MHP alone (*n* = 805). A total of 1604 patients were enrolled, of whom 1531 had outcome data available for analysis (intervention arm, *n* = 760; standard care arm, *n* = 771). Patients in both treatment arms were well matched on all baseline clinical characteristics, with a median age of 39 [interquartile range (IQR) 26–55] years; 79% were male. The median Injury Severity Score was 29 (IQR 18–43), consistent with major injury.

Overall, any cryoprecipitate was administered within the first 24 hours of arrival at hospital to 85% of patients in the intervention arm and 32% of patients in the standard care arm. By intention-to-treat analysis, 25.3% died in the intervention arm compared with 26.1% in the standard care arm [odds ratio (OR) 0.96; *p* = 0.74]. Mortality was also similar between the treatment arms at 6 and 24 hours. There were no differences between the treatment arms in secondary outcomes, including 24-hour transfusion requirements (other than cryoprecipitate) and safety outcomes (thrombotic).

Conclusions

Our findings do not support empiric fibrinogen supplementation for all trauma patients suspected of bleeding.

The study supports current MHP practices, whereby concentrated fibrinogen therapies such as cryoprecipitate are given often in the second 'MHP pack', or reactively in response to repeated monitoring for low fibrinogen concentrations.

Trial registration

This trial is registered as ISRCTN14998314.

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