Original Article

Early cryoprecipitate transfusion versus standard care in severe postpartum haemorrhage: a pilot cluster-randomised trial

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Summary

There is a lack of evidence evaluating cryoprecipitate transfusion in severe postpartum haemorrhage. We performed a pilot cluster-randomised controlled trial to evaluate the feasibility of a trial on early cryoprecipitate delivery in severe postpartum haemorrhage. Pregnant women (>24 weeks gestation), actively bleeding within 24 h of delivery and who required at least one unit of red blood cells were eligible. Women declining transfusion in advance or with inherited clotting deficiencies were not eligible. Four UK hospitals were randomly allocated to deliver either the intervention (administration of two pools of cryoprecipitate within 90 min of first red blood cell unit requested plus standard care), or the control group treatment (standard care, where cryoprecipitate is administered later or not at all). The primary outcome was the proportion of women who received early cryoprecipitate (intervention) vs. standard care (control). Secondary outcomes included consent rates, acceptability of the intervention, safety outcomes and preliminary clinical outcome data to inform a definitive trial. Between March 2019 and January 2020, 199 participants were recruited; 19 refused consent, leaving 180 for analysis (110 in the intervention and 70 in the control group). Adherence to assigned treatment was 32% (95%CI 23–41%) in the intervention group vs. 81% (95%CI 70–90%) in the control group. The proportion of women receiving cryoprecipitate at any time-point was higher in the intervention (60%) vs. control (31%) groups; the former had fewer red blood cell transfusions at 24 h (mean difference −0.6 units, 95%CI −1.2 to 0); overall surgical procedures (odds ratio 0.6, 95%CI 0.3–1.1); and intensive care admissions (odds ratio 0.4, 95%CI 0.1–1.1). There was no increase in serious adverse or thrombotic events in the intervention group. Staff interviews showed that lack of awareness and uncertainty about study responsibilities contributed to lower adherence in the intervention group. We conclude that a full-scale trial may be feasible, provided that protocol revisions are put in place to establish clear lines of communication for ordering early cryoprecipitate in order to improve adherence. Preliminary clinical outcomes associated with cryoprecipitate administration are encouraging and merit further investigation.

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Introduction

Postpartum haemorrhage (PPH) that results in blood transfusion is associated with more long-term morbidity compared with other obstetric complications [1, 2], imposing a significant burden on women, their babies and healthcare resources [3]. Fibrinogen plays a key role in the achievement of haemostasis during bleeding. Several studies have consistently demonstrated that fibrinogen levels drop early during PPH [4–6] and that low fibrinogen levels (<2 $g.l^{-1}$) are associated with worse outcomes [4, 5, 7]. In the UK, current guidelines recommend administering cryoprecipitate when fibrinogen levels are <2 $g.l^{-1}$ [8, 9], or if the patient has received massive transfusion, that is ≥ 8 red blood cell (RBC) units [8]. However, no studies have examined the optimal timing of fibrinogen administration in correcting the coagulopathy of PPH [10].

There is emerging consensus that early fibrinogen replacement therapy in severe PPH may improve outcomes for women. A recent systematic review evaluating the effect of early fibrinogen replacement therapy on clinical outcomes in severe PPH highlighted the lack of evidence, with only two small randomised controlled trials totalling 299 women, and both comparing fibrinogen concentrate with placebo [11]. There were no trials on the early use of cryoprecipitate in PPH, even though this component has been used for many years and remains the standard fibrinogen replacement therapy in most countries.

It is crucial that the clinical impact of early administration of cryoprecipitate during PPH is reliably evaluated in good quality trials. Before performing a large trial, we evaluated the feasibility of delivering cryoprecipitate early in the treatment of PPH, in addition to assessing the feasibility of recruitment, data collection, obtaining consent, preliminary data on event rates and evaluating the acceptability of the study intervention to clinicians and participating women.

Methods

This was a pilot cluster-randomised trial with qualitative evaluation. The choice of design is discussed in our protocol publication [12], but, briefly, the cluster design was chosen to reduce the risk of contamination, and to streamline the administration of an intervention in a relatively rare emergency setting. The clusters from which participants were recruited were four London hospitals with large maternity units. Eligible participants were pregnant women at >24 weeks of gestation, actively bleeding within 24 h of delivery and for whom at least one unit of RBC was transfused to treat the bleeding. Participants were not eligible if they declined blood transfusion in advance, or if they had inherited Factor XIII or fibrinogen deficiencies.

Given the cluster design and the urgent nature of the intervention, advance consent for administering the intervention was waived with research ethics committee approval. Consequently, consent was sought for data collection post-intervention and before hospital discharge, or if this was not possible, consent was obtained post-discharge either in person or via mail. For women who died or could not be contacted after discharge, de-identified routine data were collected from medical notes following approval from the Confidentiality Advisory Group.

Two hospitals were randomly allocated by the trial statistician to the intervention group and two to the control group, using a 1:1 randomisation ratio. After randomisation, local haemorrhage protocols were amended for hospitals assigned to the intervention group and these were approved locally before the initiation of the trial. Due to the nature of the intervention and study design, treatment allocation was unblinded to participants, treating staff and the research team.

Participants in the intervention cluster were transfused two pools of cryoprecipitate (equivalent to 4 g of fibrinogen) within 90 min of the first RBC unit request plus standard care. Participants in the control group continued standard care in line with national guidelines [9]. Cryoprecipitate was defrosted within 20 min and administered intravenously.

The primary outcome was binary and presented as the proportion of women who received the allocated treatment in the intervention and control group. Secondary outcomes included: the proportion of women who consented to the trial, and for whom complete outcomes were obtained; proportion of cases where there was a study protocol violation; preliminary clinical outcome data to estimate

sample size for the large trial (see online Supporting Information, Appendix S1), including safety outcomes; identification of the optimal pathways for intervention delivery; and acceptability of the study intervention, through qualitative research.

All women were followed up to hospital discharge or 28 days after delivery, whichever was sooner. Women were also asked for consent to collect additional data, which included a fatigue questionnaire, a follow-up call 3 months after discharge and readiness to be contacted for qualitative interviews. Data were entered into a secure online database using a unique study ID for each participant. Additionally, qualitative interviews were conducted with staff and participants on acceptability of intervention and consent, which are published separately.

The study sample size was based on reported PPH incidences [13, 14], from which we estimated that 200 eligible women would be recruited over 12 months. We anticipated that approximately 100 participants per group (evenly distributed between clusters) would be recruited, although imbalance between the groups could be accommodated without undue effect on CIs. With this sample size, the precision of the 95%CI for the primary outcome was expected to be ±8% points if the estimated proportion was 80%.

Analyses were run on the intention-to-treat population. In the primary analysis, point estimates of proportions were provided for each hospital, or by group if no difference between hospitals was observed, along with corresponding 95%CI using the Wilson approach [15]. Additionally, the proportion of patients receiving the assigned treatment between groups was compared adjusted by hospital, using a fixed-effect logistic regression model where the hospital is nested within the levels of treatment. For secondary outcomes, point estimates and 95%CIs of differences in proportions and mean differences were obtained. Outcomes from this analysis should be interpreted as exploratory only; p values are not reported as the study was not powered to find any significant difference between groups, and CIs are shown for illustrative purposes only. The analysis was carried out using R version 3.6.2.

Criteria for progression to a full-scale trial were as follows: ≥80% adherence to allocated treatment for the study population, ≥80% data collection and ≥25% consent rate. Progression was considered not feasible if treatment adherence was <50%, data collection <50% and consent rate <10%. Rates that fell between these cut-off points meant that the future full-scale trial protocol would need to be adjusted. Additionally, all progression criteria were subject to insights gained through qualitative research.

A patient and public advisory group (Katie's Team, Barts Research Centre for Women's Health) [16] was involved throughout the development of the study and particularly contributed to the patient-facing materials, strategies to implement informed consent procedures and topics for exploration through qualitative interviews.

Results

A total of 481 women were screened (287 in the intervention group and 194 in the control group), of whom 202 were recruited from 4 March 2019 to 10 January 2020. Three women were found to be ineligible, bringing the total number of participants included in the trial to 199 (Fig. 1). Of the 199 eligible participants, 123 were included in the intervention group and 76 in the control group; however, this imbalance was likely due to differing case-loads and management of PPH rather than any recruitment bias, as illustrated by the screening conversion rates, which were similar in the two groups (43% in the intervention vs. 39% in the control group). Overall, 19 participants refused consent for data collection, leaving a total of 180 participants available for analysis (110 in the intervention and 70 in the control group).

Patient characteristics and medical history are provided in Table 1. Mean age of participants was 32 y, with 94% of the index pregnancies being singleton. Baseline characteristics between the two groups were well balanced. There were more normal vaginal deliveries in the intervention group (33% vs. 24%). The top three causes of PPH were uterine atony, trauma and retained tissue.

The overall primary outcome, expressed as the proportion of women receiving the allocated intervention for both groups, was 51.1% (95%CI 43.6–58.6%), with adherence being 31.8% (95%CI 23.3–41.4%) in the intervention group and 81.4% (95%CI 70.3–89.7%) in the control group. No variability was observed between hospitals with respect to adherence (intra-cluster correlation coefficient = 0), and hence only unadjusted results are presented (Table 2).

Overall, the consent rate was 65%, and the rate of refusal to participate was low (9.5%). Anonymised routine data in the absence of consent was collected in 25% of cases (see online Supporting Information, Table S1). Reasons for refusing consent were unwillingness to share data (n = 4); negative birth experience (n = 2); women too agitated to be approached (n = 2); language barriers (n = 2); and non-specific/unknown reasons (n = 9).

Data collection rates were high, with 100% of expected case report forms completed up to discharge, and 99% of expected follow-up forms completed. Three participants

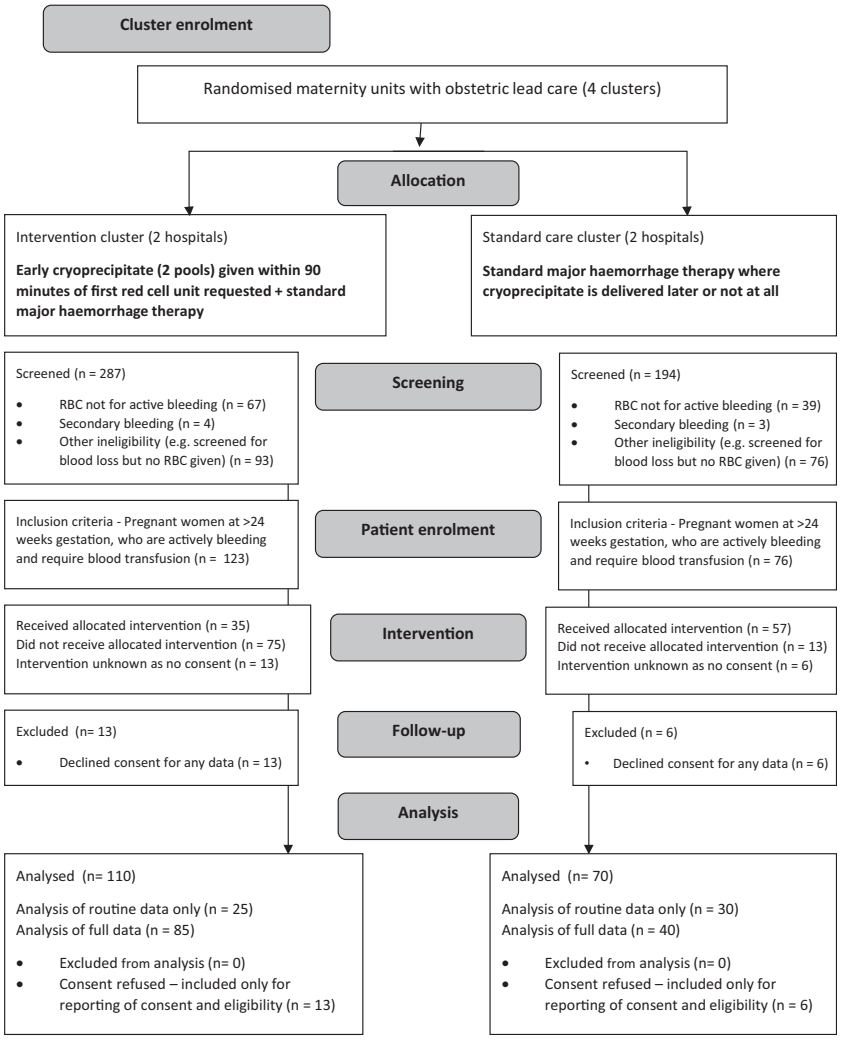

Figure 1 Study flow diagram.

were lost to follow-up at 3 months after discharge. Primary outcome data were completed in 100% of participants. Overall fatigue questionnaire collection rate was 66.4% (see online Supporting Information, Table S2).

Mean haemoglobin, platelet counts and fibrinogen levels, checked at the time of PPH, were not different between groups, while the mean estimated blood loss was lower in the intervention group compared with the control group (mean difference −362 ml, 95%CI −701 to −23). Mean (SD) intravenous fluid given for the management of PPH was 2.4 (1.2) l with no difference between groups (Table 3).

Overall, more women received cryoprecipitate at any time-point in the intervention group (60%) than in the control group (31%). In the intervention group, 31 participants received cryoprecipitate after 90 min and 44 did not receive any (Table 2). Overall blood transfusion (excluding intervention cryoprecipitate) was lower in the intervention group at both 24 h (4.1 vs. 5.1 units, mean difference −1, 95%CI −2.3–0.4) and at discharge (4.2 vs. 5.2 units, mean difference −1, 95%CI: −2.4–0.4). Further, the intervention group had fewer overall surgical procedures (46% vs. 59%, OR 0.6, 95%CI 0.3–1.1) and fewer ICU admissions compared with the control group (5% vs. 13%, OR 0.4, 95%CI 0.1–1.1) (Table 3).

In the intervention group, four transfusion-related reactions were reported, most of which were febrile/non-allergic reactions (n = 3). There were 22 serious adverse events across both groups (11% in the intervention and 14% in the control group), two of which were life-threatening (one case of disseminated intravascular coagulopathy and acute renal failure; one case of amniotic fluid embolism);

Table 1 Baseline characteristics for intervention (early cryoprecipitate) and control (standard care) in women with postpartum haemorrhage (PPH). Values are mean (SD) or number (proportion).

Variables	Intervention n = 110	Control n = 70	Total n = 180
Age, y	31.9 (5.9)	32.1 (6.3)	32 (6.1)
BMI; $kg.m^{-2}$	26.7 (7.2)	27.7 (6.7)	27.1 (7)
Ethnic group			
White	39 (36%)	27 (39%)	66 (37%)
Asian/Asian British	49 (45%)	20 (29%)	69 (38%)
Black/African/Caribbean/Black British	18 (16%)	18 (26%)	36 (20%)
Mixed/multiple ethnicity	0	1 (1%)	1 (1%)
Others	2 (2%)	4 (6%)	6 (3%)
Not answered	2 (2%)	0	2 (1%)
Past medical history			
Pre-existing thrombocytopenia ($< 80 \times 10^9.l^{-1}$)	2 (2%)	1 (1%)	3 (2%)
Inherited bleeding disorder	0	1 (1%)	1 (1%)
Previous PPH, n = (59, 40)[a]	6 (14%)	7 (19%)	13 (16%)
Previous caesarean/s, n = (59, 40)[a]	24 (41%)	15 (38%)	39 (39%)
Current pregnancy			
Singleton	103 (94%)	67 (96%)	170 (94%)
Multiple pregnancy	7 (6%)	3 (4%)	10 (6%)
Gravidity			
Primigravida	51 (46%)	30 (43%)	81 (45%)
Previous pregnancies 1 or 2	42 (38%)	24 (34%)	66 (38%)
Previous pregnancies > 2	17 (16%)	16 (23%)	33 (18%)
Complications during this pregnancy			
Pre-existing chronic hypertension	3 (3%)	3 (4%)	6 (3%)
Current pregnancy-induced hypertension/pre-eclampsia	10 (9%)	2 (3%)	12 (7%)
Mode of Delivery			
Normal vaginal	36 (33%)	17 (24%)	53 (29%)
Instrumental vaginal	23 (21%)	16 (23%)	39 (22%)
Caesarean (emergency)	35 (32%)	26 (37%)	61 (34%)
Caesarean (elective)	16 (15%)	11 (16%)	27 (15%)
Cause of PPH[b]			
Tone	45 (41%)	34 (49%)	79 (44%)
Trauma	52 (47%)	28 (40%)	80 (44%)
Tissue	26 (24%)	17 (24%)	43 (24%)
Thrombin	2 (2%)	4 (6%)	6 (3%)
Other	11 (10%)	9 (13%)	20 (11%)
Unknown	2 (2%)	5 (7%)	7 (4%)

Number of participants with missing data (intervention, control): pre-existing thrombocytopenia (0, 1); inherited bleeding disorder (0, 1); previous PPH (16, 3); pre-existing chronic hypertension (1, 1); and current pregnancy-induced hypertension/pre-eclampsia (0, 1).
[a]Reported out of n = 99 participants who had a previous pregnancy.
[b]n = 49 participants had more than one single cause of PPH documented, hence the total of causes exceeds 100%. A total of eight patients had missing data regarding the cause of PPH.

none were considered related to the intervention. There was no increase in thrombotic events (see online Supporting Information, Tables S3 and S4).

During the recruitment period, several measures were taken to improve primary outcome adherence in the intervention group, including increased communication/

Table 2 Primary outcome (adherence to allocation) for intervention (early cryoprecipitate (cryo)) and control (standard care) in women with postpartum haemorrhage. Values are number (proportion).

Variable	Intervention n = 110	Control n = 70	Total n = 180
Women receiving the allocated treatment[a]	35[b] 32% (CI 23–41%)	57[c] 81% (CI 70–90%)	92 51% (CI 44–59%) OR 0.1 (CI 0.05–0.2)
Detail on timing of cryo			
Total number of women receiving cryo at any time-point	66 (60%)	22 (31%)	88 (49%)
Received cryo within 90 min	35 (32%)	13 (19%)	48 (27%)
Received cryo between 91 and 120 min	10 (9%)	4 (6%)	14 (8%)
Received cryo > 120 min	21 (19%)	5 (7%)	26 (14%)
Did not receive any cryo	44 (40%)	48 (69%)	92 (51%)
Reason for protocol deviation regarding administration of cryo			
Administrative failure	34 (45%)	N/A	34 (39%)
Logistical failure	19 (25%)	N/A	19 (22%)
Cryo medically indicated	N/A	7 (54%)	7 (8%)
Physician decision	4 (5%)	4 (31%)	8 (9%)
Other/unknown	18 (24%)	2 (15%)	20 (23%)
Source of RBC			
Issued by laboratory	67 (61%)	69 (99%)	136 (76%)
Remote blood fridge	42 (39%)	1 (1%)	43 (24%)
Adherence to allocation by source of RBC			
Issued by laboratory	18/67 (27%)	57/69 (83%)	75/136 (55%)
Remote blood fridge	17/42 (40%)	0/1	17/43 (40%)

RBC, red blood cells
Number of participants with missing data (intervention, control): Source of RBC (1, 0).
[a]95%CI is shown for illustrative purposes only. Adjusted estimates are not presented as we did not find any difference after adjusting by hospital.
[b]This includes three participants who received only 1 unit of cryoprecipitate within 90 min.
[c]Four participants in the control group received only 1 unit of cryoprecipitate early; for this analysis, they are also classed as non-adherent.

training sessions with site teams; dedicated collaborators' meetings; and updating study materials such as staff posters and reminder badges. This temporarily improved the adherence in one of the intervention sites, but this was not sustained over the duration of the study. Our qualitative interviews highlighted lack of study awareness as one of the major barriers to adherence, as well as lack of clear roles and lines of communication for ordering early cryoprecipitate.

Discussion

We report on the first multicentre randomised pilot trial evaluating cryoprecipitate transfusion for the management of severe PPH, gathering evidence for the feasibility of a full-scale trial. We showed that overall adherence for the primary outcome (timing of administration of cryoprecipitate) was >50% but <80%, meaning that revisions to the protocol will be needed to improve adherence. Data collection and consent rates were sufficient to move towards a full-scale trial. Compared with the control group, more women received cryoprecipitate (at any time-point) in the intervention group, and the latter group received less RBC transfusion and had fewer surgical procedures and ICU admissions, although clinical findings from this pilot trial should be considered with caution. There was no increase in serious adverse events with cryoprecipitate transfusion.

As this was a pilot cluster trial, we were able to assess how different transfusion infrastructures in hospitals impacted on the delivery of intervention as well as obtain useful information from a wide range of healthcare professionals and patients to improve the delivery of a large trial in the future. A limitation of the study is the relatively small number of clusters included in the trial. However, unlike individualised randomised controlled trials, sample sizes for feasibility cluster trials are not well defined and are dependent on the objectives chosen [17].

Table 3 Medical and surgical management for intervention (early cryoprecipitate (cryo)) and control (standard care) in women with postpartum haemorrhage (PPH). Values are mean (SD) or number (proportion).

	Intervention n = 110	Control n = 70	Total n = 180	Mean difference/ OR (95% CI)[a]
Estimated blood loss, ml	2326 (985)	2688 (1315)	2467 (1135)	−362 (−701 to −23)
Initial blood values (first values during PPH)				
Haemoglobin; $g.l^{-1}$	102 (17)	97 (17)	100 (17)	5 (−0.6–10)
Platelets; x $10^9.l^{-1}$	174 (60)	171.5 (60)	173 (60)	2.5 (−16–21)
Fibrinogen; $g.l^{-1}$, n = (37,41) [b]	2.8 (1.3)	3.1 (1.3)	3 (1.3)	−0.3 (−0.9–0.3)
Blood transfusion requirements from PPH up to 24 h				
RBC; units	2.5 (1.8)	3.1 (2.2)	2.7 (2)	−0.6 (−1.2–0.0)
FFP; units	0.8 (1.7)	1.1 (1.6)	0.9 (1.6)	−0.2 (−0.7–0.3)
Platelets; units	0.1 (0.5)	0.2 (0.6)	0.2 (0.6)	−0.1 (−0.3–0.1)
Cryo; units[c]	0.6 (1)	0.7 (1.3)	0.7 (1.1)	0 (−0.4–0.3)
Total; units[c]	4.1 (4)	5.1 (5.2)	4.5 (4.5)	−1 (−2.3–0.4)
Cell salvage (ml) up to 24 h, n = (5,2)	317 (458)	100 (141)	255 (393)	
Intravenous fluids (l) up to 24 h	2.3 (1.2)	2.5 (1.2)	2.4 (1.2)	−0.2 (−0.6–0.2)
Blood transfusion requirements from PPH to discharge				
RBC; units	2.5 (1.9)	3.2 (2.3)	2.8 (2.1)	−0.7 (−1.3 to −0.1)
FFP; units	0.8 (1.7)	1.1 (1.6)	0.9 (1.6)	−0.2 (−0.7–0.3)
Platelets; units	0.1 (0.5)	0.2 (0.6)	0.2 (0.6)	−0.1 (−0.3–0.1)
Cryo; units[c]	0.7 (1)	0.7 (1.3)	0.7 (1.1)	0 (−0.3–0.3)
Total; units[c]	4.2 (4.1)	5.2 (5.2)	4.6 (4.6)	−1 (−2.4–0.4)
Medical management (obstetric drugs)				
Tranexamic acid	85 (79%)	57 (86%)	142 (82%)	
Syntometrine	15 (14%)	18 (30%)	33 (20%)	
Syntocinon/oxytocin	97 (91%)	45 (75%)	142 (85%)	
Ergometrine	42 (40%)	27 (45%)	69 (42%)	
Carboprost	58 (54%)	36 (57%)	94 (55%)	
Misoprostol	38 (36%)	30 (48%)	68 (40%)	
Other[d]	1 (1%)	10 (17%)	11 (7%)	
Surgical Procedures	50 (46%)	41 (59%)	91 (51%)	0.6 (0.3–1.1)
Hysterectomy	2 (2%)	3 (4%)	5 (3%)	
Uterine balloon	24 (22%)	28 (40%)	52 (29%)	
Laparotomy and primary repair	8 (7%)	3 (4%)	11 (6%)	
Other intra-abdominal packing	7 (6%)	10 (14%)	17 (10%)	
Uterine artery embolisation	2 (2%)	0	2 (1%)	
Uterine tamponade	0	4 (6%)	4 (2%)	
Others[e]	21 (19%)	12 (17%)	33 (19%)	
Mortality	0	0	0	
Admission to ICU	6 (5%)	9 (13%)	15 (8%)	0.4 (0.1–1.1)
Days in ICU	3.7 (3.4)	2.1 (2.4)	2.7 (2.9)	1.6 (−1.7–4.8)
Admission to HDU	48 (44%)	29 (43%)	77 (44%)	1.0 (0.6–1.9)
Days in HDU	1.7 (1.5)	1.8 (1.1)	1.8 (1.4)	-0.1 (−0.8–0.6)
Number of days in hospital	3.8 (2.7)	4.1 (3.9)	3.9 (3.2)	-0.3 (−1.3–0.7)
Cardiac arrest	1 (1%)	0	1 (1%)	

(continued)

Table 3 (*continued*)

	Intervention n = 110	Control n = 70	Total n = 180	Mean difference/ OR (95% CI)[a]
Any organ failure	0	1 (1%)	1 (1%)	
Septicaemia	0	3 (4%)	3 (2%)	
Disseminated intravascular coagulopathy	0	2 (3%)	2 (1%)	

Number of participants with missing data (intervention, control): haemoglobin (2, 2); platelets (2, 2); intravenous fluids (5, 18); tranexamic acid (3, 4); syntometrine (4, 10); syntocinon/oxytocin (3, 10); ergometrine (4, 10); carboprost (3, 7); misoprostol (3, 8); other obstetric drugs (8, 11); surgical procedures (2, 0); and admission to HDU (0, 3).
RBC, red blood cells; FFP, fresh frozen plasma.
[a]CI provided for illustrative purposes only, and these are provided only where there is a sufficient number of outcomes present.
[b]Tests for fibrinogen were not mandated for the study and given only where this was done as part of their clinical care.
[c]Excluding early cryoprecipitate units given as part of the intervention. Discrepancies in total number of transfusion units are due to rounding up or down to the nearest exact number.
[d]All other uterotonic drugs documented were carbetocin.
[e]Other surgical procedures reported were as follows: vaginal packs, vaginal repair, manual removal of placenta, evacuation of clots/ haematoma, Robinson and Redivac drains.

As this was a cluster-randomised study, we sought to ensure there was a difference in cryoprecipitate timing between the intervention and control groups, and hence the primary outcome of the trial was to determine the adherence to the allocated treatment in both groups. We found that in the control group, adherence to the primary outcome was better than in the intervention group, indicating that it is feasible to include a control group in a future full-scale randomised controlled trial. The choice of 90 min to administer cryoprecipitate in the intervention group was pragmatic, taking into consideration the time required to thaw the products, distances from the laboratory to labour ward and observational data showing that delivery of cryoprecipitate for the management of bleeding is on average 180 min [18]. However, 'early' fibrinogen replacement therapy in PPH is not well defined. Two randomised controlled trials that aimed to evaluate the effect of early fibrinogen concentrate vs. placebo on overall transfusion in women with less severe PPH (estimated blood loss between 1 l and 1.5 l) than in our study (approximately 2.5 l) showed no reduction in transfusion requirements with fibrinogen concentrate [19, 20]. Recently, a large observational study in the USA and Canada [21] showed that cryoprecipitate administered within the first 4 h of hospital arrival to injured children who required massive transfusion reduced 24-h mortality. Therefore, it is plausible that in more severe bleeds, transfusion of cryoprecipitate in general, rather than its timing, is what matters. For the large trial, the timing of cryoprecipitate administration could be extended, considering that over two-thirds of patients in the control group did not receive any cryoprecipitate. Furthermore, in contrast to the above two randomised controlled trials [19, 20], we used cryoprecipitate to replace fibrinogen rather than fibrinogen concentrate. Compared with fibrinogen concentrate, cryoprecipitate additionally contains Factor XIII, fibronectin, von Willebrand factor antigen and Factor VIII [22, 23]. A recent in-vitro study observed significant differences in fibrin clot structure formed by cryoprecipitate vs. fibrinogen concentrate, suggesting that the additional coagulation factors in cryoprecipitate allow for stronger fibrin clot formation [24]. Currently, a UK multicentre randomised controlled trial is ongoing, assessing the efficacy and safety of early cryoprecipitate transfusion vs. standard care in trauma major bleeding patients [25], and its results will hold important lessons for transfusion across all indications, including PPH.

In the intervention group, we saw a higher number of participants who received the first unit of RBC from the remote fridge (39%) compared with only one case (1%) in the control group, leading to cases where early cryoprecipitate was not ordered in time in the intervention group. Further, our qualitative research showed that delays to administering the intervention were due to misperception around whose responsibility it is to request blood products, highlighting the need for a dedicated leadership role during the management of PPH to improve communication. This has already successfully been implemented in the trauma setting. Moreover, there is a need to improve the speed of making cryoprecipitate available for bleeding patients. To this end, efforts are being made to extend the shelf-life of thawed cryoprecipitate [22, 26]. This would allow for pre-thawed cryoprecipitate to be made available earlier for transfusion.

More women received cryoprecipitate in the intervention group compared with the control group, which

may have contributed towards the lower overall transfusion rate (particularly of RBCs), fewer surgical procedures and lower ICU admissions seen, given an absence of differences in baseline characteristics. Even though this trial was not powered to quantify clinical effect sizes, the results suggest a potential benefit that is worth investigating further and provide guidance for the outcome measures to be used in the future work to evaluate cryoprecipitate transfusion in severe PPH. Reduction in all these outcomes (RBC transfusion, surgery and ICU admission) would have substantial financial implications for healthcare providers, and these will be considered for a future full-scale trial; the final decision on the future primary outcome will be subject to stakeholder consultation.

In this study, we found that women in both groups were administered over 2 l of intravenous fluid to treat PPH, similar to previous reports [10]. In the trauma setting, the resuscitation of bleeding patients with intravenous fluid has now been superseded, and early and continuous haemostatic resuscitation with RBC and plasma in a 1:1 ratio is currently the gold standard [9] with improved outcomes. While these protocols cannot be generalised to women experiencing PPH, they nonetheless raise important questions around the role of intravenous fluid and optimal transfusion management for women with severe PPH, and future studies need to address these issues to improve standards of care.

This trial shows that revisions to the protocol are needed to improve adherence of administering early cryoprecipitate, with a focus on unambiguous allocation of responsibility in communicating study requirements within the clinical team and utilising emerging new technologies to make cryoprecipitate available at shorter notice. Cryoprecipitate administration in severe PPH at any time-point was accompanied by reductions in RBC transfusions, surgery and ICU admission, suggestive of benefits which merit further evaluation in large trials. Future large randomised controlled trials are needed to evaluate the impact of cryoprecipitate transfusion in severe PPH and evaluate the role of intravenous fluid in the management of PPH.

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Appendix 1

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1 Clinical outcome data collected.

Table S1 Consent rates.

Table S2 Multidimensional Fatigue (MFI) Inventory.

Table S3 Safety outcomes.

Table S4 Serious adverse events.