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Obstetrics

Viscoelastometry guided fresh frozen plasma infusion for postpartum haemorrhage: OBS2, an observational study

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Abstract

Background. Postpartum haemorrhage (PPH) can be exacerbated by haemostatic failure. Based on data from trauma studies, empirical infusions of fresh frozen plasma (FFP) are often given during severe PPH if coagulation tests are unavailable. This study observed a cohort of women with moderate/severe PPH in whom FFP infusion was guided by the use of viscoelastometric point-of-care testing (VE-POCT) and clinical assessment.

Methods. Women were enrolled into this observational study when blood loss was measured or suspected to be about 1000 mL. If Fibtem A5 determined by Rotem® thromboelastometry remained >15 mm, or bleeding stopped, FFP was withheld. If Fibtem A5 was ≤15 mm and bleeding ongoing, women were randomized into an interventional study as previously reported. Clinical and laboratory outcomes were recorded.

Results. The study recruited 605 women and 98% had FFP withheld. The median (25^{th}–75^{th} centile) total blood loss was 1500 (1300–2000) mL with 300 (50–545) mL occurring after enrolment. Total blood loss was >2500 mL in 40/605 (6.6%) women. RBCs were transfused in 141/605 (23.3%) patients and 11 (1.8%) received ≥4 units. At least one invasive procedure was performed in 283/605 (46.8%) women. Level 3 care was required for 10/605 (1.7%) women. No women developed clinically significant haemostatic impairment.

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Conclusions. Restrictive use of FFP guided by clinical assessment of bleeding and VE-POCT is feasible and did not result in clinically significant haemostatic impairment. Studies should compare the clinical and cost effectiveness of empirical FFP infusions, according to current guidelines, with targeted use of FFP based on VE-POCT.
Clinical trial registration: ISRCTN46295339 (http://www.isrctn.com/ISRCTN46295339) (accessed July 24, 2017), EudraCT 2012-005511-11 (https://www.clinicaltrialsregister.eu/ctr-search?query=2011-005511-11) (accessed July 24, 2017).

Key words: fresh frozen plasma; postpartum haemorrhage; viscoelastometric test

Editor's key points

- Guidelines recommend empiric plasma transfusion for postpartum haemorrhage (PPH) with haemostatic impairment.
- The effect of point-of-care thromboelastometry-guided plasma transfusion in women with moderate to severe postpartum haemorrhage was analysed.
- Restricted use of plasma based on thromboelastometry results was feasible and did not result in significant haemostatic impairment.

Postpartum haemorrhage (PPH) is precipitated predominantly by obstetric causes but can be exacerbated by haemostatic impairment. Some bleeds resolve before clinically significant coagulopathy develops, whilst others are associated with severe haemostatic impairment. The likelihood of coagulopathy depends on the cause and size of the bleed.[1–3] The Royal College of Obstetrics and Gynaecology (RCOG) defines established haemostatic impairment as ongoing bleeding associated with a prothrombin time (PT), or activated partial thromboplastin time (aPTT) >1.5 times normal and recommend infusing fresh frozen plasma (FFP) to maintain PT/aPTT below this ratio.[4] Guidelines recommend maintaining a fibrinogen >2 g L^{-1} and, if bleeding has stopped, no blood product replacement is required.[2 4]

Haemostatic impairment can evolve rapidly, and routine laboratory coagulation tests are often not available soon enough to be clinically useful. Clinicians, therefore, might not know whether a coagulopathy is developing.[5] This has led to guidelines recommending empirical fixed-ratios of red blood cells (RBC) and FFP to manage PPH.[2 4 6–8] This strategy is based on data derived from trauma studies with limited evidence in PPH.[9–11] The haemostatic system at term is hypercoagulable compared with the healthy non-pregnant population,[1 3] so trauma-induced-coagulopathy differs markedly from the coagulopathy associated with PPH.[12 13] It might be inappropriate, therefore, to extrapolate treatment strategies from trauma to PPH. Fixed-ratio transfusion can result in unnecessary transfusion of FFP, which can be associated with complications such as transfusion associated circulatory overload and allergic reactions.[12 14–16]

During PPH, fibrinogen decreases earlier than other coagulation factors[17] suggesting that if fibrinogen is maintained then other coagulation factors will be adequate. A viscoelastometric point-of-care test (VE-POCT), Fibtem A5 performed on the Rotem® machine, is a surrogate measure of fibrinogen with results available within 10 min. Fibtem A5 correlates with laboratory fibrinogen during PPH[18] and is predictive of progression from moderate to severe PPH.[19]

The aim of the OBS2 study was to investigate a cohort of women experiencing moderate to severe PPH. Women with Fibtem A5 ≤ 15 mm (Clauss fibrinogen ~ 3g L^{-1})[18 19] and ongoing bleeding were eligible to be randomized to the interventional part of the study comparing the effectiveness of fibrinogen concentrate or placebo. The randomized women showed that, if plasma fibrinogen was >2 g L^{-1} or Fibtem A5 >12 mm, infusion of fibrinogen concentrate did not affect outcomes.[20] The protocol instructed that for women in whom Fibtem A5 was >15 mm, or in whom bleeding had stopped, FFP should be withheld. These women are reported here.

Methods

This was an observational study conducted in teaching hospital obstetric units, and formed part of a multicentre trial to randomize women to fibrinogen or placebo. The protocol is published.[21] Trial registration: ISRCTN46295339 (http://www.isrctn.com/ISRCTN46295339) (accessed July 24, 2017), EudraCT 2012-005511-11 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-005511-11) (accessed July 24, 2017). The study was approved by Edinburgh, Multicentre Research Ethics Committee (13/SS/0008).

Women age ≥18 yr and ≥24 weeks gestation experiencing major PPH (measured or suspected blood loss of ~1000 mL) could be enrolled. Women were excluded if they declined blood transfusion, had placenta accreta diagnosed antenatally or there was clinical suspicion of amniotic fluid embolus.[21] Women received written information in their maternity notes. Verbal consent to participate was sought at enrolment and confirmed in writing once the woman had recovered. At study entry Fibtem assay was performed on delivery suite and samples sent to the laboratory for a full blood count (FBC), Clauss fibrinogen, PT and aPTT. Blood loss was estimated gravimetrically as described.[22] If the A5 was ≤15 mm, the baby delivered and bleeding ongoing, the woman was randomized to fibrinogen concentrate or placebo. If the A5 was >15 mm local standard treatment for PPH was given except that FFP should not have been infused (cryoprecipitate infusion was not excluded). Fibtem was repeated after each additional 500 mL blood loss or for clinical concern, and FFP continued to be withheld if A5 remained ≥15 mm or if bleeding stopped (Fig. 1).

Information was collected electronically. A full description of data points has been published.[21] Analysis of the observational group reported here was descriptive and no hypotheses were tested, therefore, a sample size calculation was not conducted. Established laboratory haemostatic failure was defined in accordance with RCOG guidelines as PT or aPTT >1.5 times the midpoint of the normal range (in this study ≥16.5 s and ≥48 s, respectively) or a fibrinogen <2 g L^{-1}.[4] Clinically significant haemostatic impairment was defined as established laboratory haemostatic failure associated with continuing bleeding. Level 3 care was advanced respiratory support or receiving 2 other organs support (usually renal or cardiac).

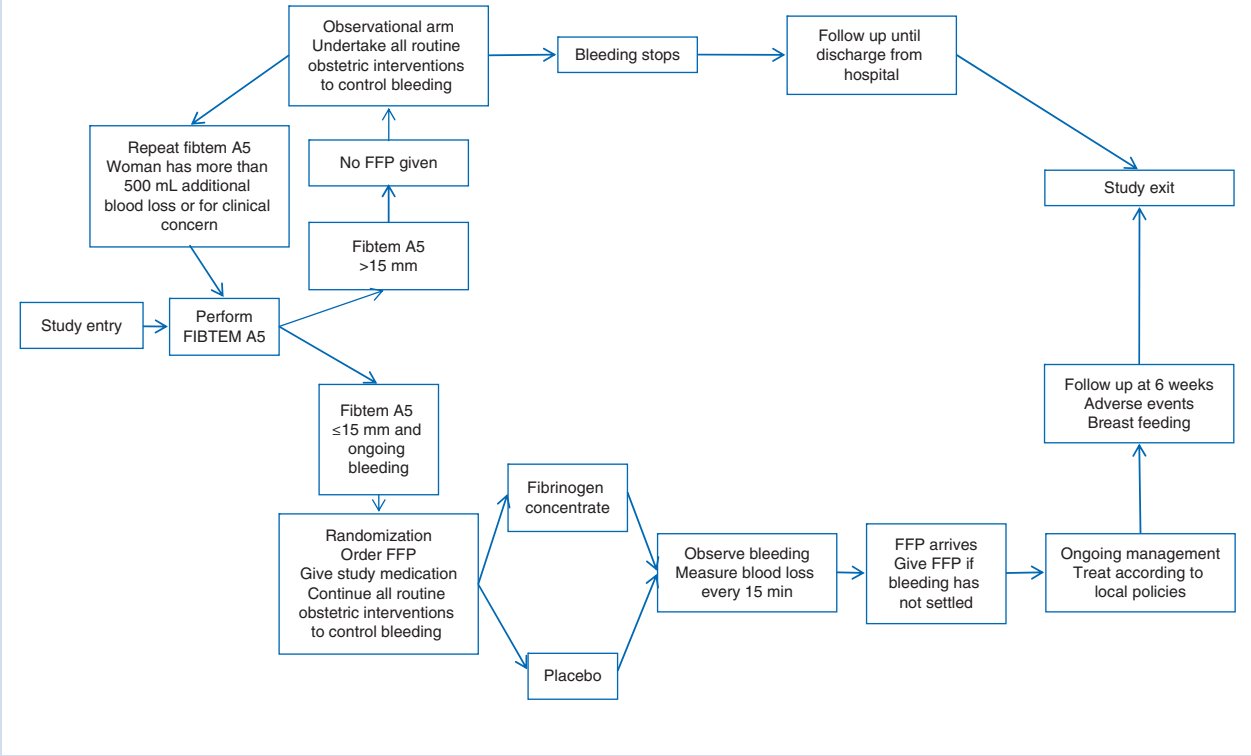

Fig 1 Study design.

Descriptive summaries of maternal characteristics at study entry by cohort (observational or intervention) were performed and the means of continuous variables were compared using Student's *t*-test for continuous variables (Mann-Whitney *U*-test for non-normal distributions), and proportions of the binary variables were compared using the χ^2 test. Analyses were performed using SPSS version 23 (IBM SPSS Inc, Chicago, USA).

Results

The observational study cohort comprised 606 women with moderate to severe PPH recruited between 29th June 2013 and 26th November 2015, who were not eligible to be randomized to the interventional trial because either their Fibtem A5 remained >15 mm or bleeding stopped. One woman withdrew consent, therefore, 605 women are reported who were managed though the observational arm of the protocol and should have had FFP withheld (Fig. 2). The outcomes of the 57 women recruited to the interventional arm are reported elsewhere.[20]

Subject characteristics at enrolment, mode of delivery and cause of bleeding are shown in Table 1, enrolment characteristics of the women who were randomized are shown for comparison. Women in the observational group had smaller bleeds at study entry and, as a direct consequence of study design, had higher fibrinogen and Fibtem A5 than the interventional group although PT and aPTT were similar.

The outcomes of women in the observational group are shown in Table 2 and the interventional group is shown for comparison. The median (25th to 75thcentile) total blood loss was 1500 (1300–2000) mL with 300 (50–545) mL blood loss occurring after enrolment. Total blood loss was >2500 mL in 40/605 (6.6%) women. RBCs were transfused in 141/605 (23.3%) women and 11 (1.8%) received ≥4 units RBCs. At least one invasive procedure was performed in 283/605 (46.8%) patients, most commonly repair of perineal trauma (25.5%) or vaginal packing (13.2%). Level 3 care was required for 10/605 (1.7%) women.

Fibtem A5 was ≤15 mm in 97/605 (15.7%) women at some time during the observational study. The median (25th to 75th centile) blood loss after the A5 fell to ≤15 mm was 100 (0–335) mL indicating that bleeding was rapidly controlled by obstetric intervention in most cases. To investigate whether withholding FFP influenced outcomes, women who developed laboratory evidence of established haemostatic failure (*n*=8) (Table 3), were treated with FFP contrary to the protocol (*n*=12) (Table 4), admitted to ITU (*n*=10) (Table 4) or bled >2500 mL were reviewed in detail. Some women appear in more than one of these groups.

Women with laboratory tests associated with established haemostatic failure

The longest PT, aPTT and lowest fibrinogen are shown in Table 2. Where data were available, 3/537 (0.6%) had a PT ratio >1.5, 0/544 (0%) had an aPTT >1.5 and 6/544 (1.1%) had a fibrinogen <2 g L^{-1} at some time during the study. Eight women developed laboratory evidence of established haemostatic failure as defined by RCOG[4] (Table 3), these women had a median (25th to 75th centile) 50 (0–280) mL blood loss after study entry. In all patients bleeding stopped rapidly, despite abnormal coagulation results, after obstetric interventions and hence did not fulfil the criteria for clinical significant haemostatic impairment.

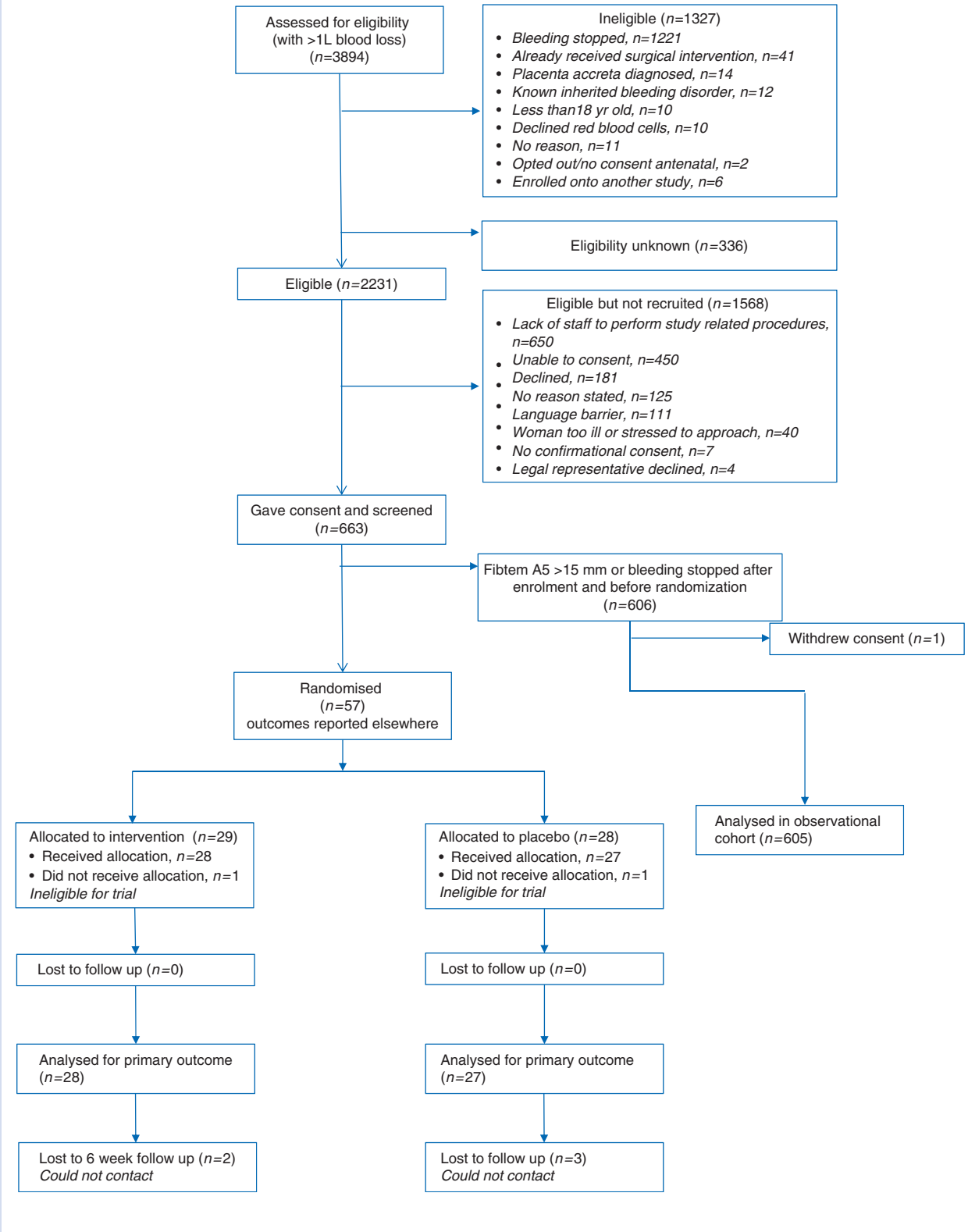

Fig 2 Consort diagram.

Table 1 Baseline maternal characteristics at study entry by cohort. *Women may have had more than one cause of bleeding, †for multiple pregnancies, the most invasive mode is taken, NA is not available because many women had multiple causes of bleeding

Variable	Observational cohort (*n*=605)	Interventional cohort (*n*=55)	*P* value
Patient characteristics			
Age at recruitment (yr) *Mean (range)*	31.9 (18–46)	32.1 (20–48)	0.8
BMI at booking *Mean* (SD)	27.4 (6.3)	25.9 (5.0)	0.04
Missing	*3*	*1*	
Previous caesarean section *N (%)*	123 (20)	18 (33)	0.03
Pre-eclampsia during this pregnancy *N (%)*	30 (5.0)	8 (14)	0.003
Past history of postpartum haemorrhage *N (%)*	59 (9.8)	11 (20)	0.02
Delivery			
Onset of labour *N (%)*			
Spontaneous	214 (35)	18 (33)	
Induced	224 (37)	11 (20)	0.004
No labour	167 (28)	26 (47)	
Multiple gestation *N (%)*			
Singleton	564 (93)	49 (89)	0.3
Twins	41 (6.8)	6 (11)	
Reported causes of postpartum haemorrhage*N *(%)*			
Uterine atony	373 (62)	39 (71)	NA
Surgical bleeding	207 (34)	19 (34)	
Trauma	174 (29)	10 (18)	
Retained placenta	70 (12)	6 (11)	
Placental abruption	23 (3.8)	5 (9.1)	
Placenta praevia	38 (6.3)	3 (5.5)	
Undiagnosed placenta accreta	2 (0.3)	1 (1.8)	
Mode of delivery†N *(%)*			
Spontaneous vaginal	167 (28)	13 (21)	
Instrumental vaginal	140 (23)	7 (13)	0.2
Elective caesarean section	132 (22)	16 (29)	
Non-elective caesarean section	166 (27)	19 (34)	
Estimated blood loss at study entry (mL) *Median (25th to 75th centiles)*	1200 (1000 to 1500)	1450 (1200 to 1800)	0.002
Haemostatic tests at study entry *Median (25th to 75th centiles)* Haemoglobin (g L^{-1})	107 (97 to 116)	95 (86 to 108)	<0.001
Missing	*8*	*0*	
Fibtem A5 (mm)	19 (17 to 22)	12 (9 to 14)	<0.001
Missing	*0*	*0*	
Clauss Fibrinogen (g L^{-1})	4.0 (3.4 to 4.6)	2.7 (2.4 to 3.3)	<0.001
Missing	*101*	*4*	
Prothrombin time (s)	10.8 (10.3 to 11.4)	10.9 (10.2 to 12.0)	0.2
Missing	*73*	*1*	
Activated partial thromboplastin time (s)	25.0 (23.2 to 27.2)	26.0 (22.8 to 30.0)	0.2
Missing	*86*	*7*	

Women who received FFP or were admitted to level 3 care

Twelve women (2.0%) received between 1-4 units of FFP despite this being contrary to the protocol. Individual details of coagulation tests, blood products received and outcomes are described in (Table 4). Ten/605 women (1.7%) were admitted to level 3 care, four of whom received FFP and one cryoprecipitate (Table 4). In the seven women on whom data were available, none had laboratory evidence of established haemostatic impairment or a low Fibtem.

Women with a total measured blood loss more than 2500 mL

Forty/605 (6.6%) women bled >2500 mL. Five women also received FFP and are reported in detail in Table 4. In the 35 women who did not receive FFP, median (25^{th} to 75^{th} centile, range) blood loss was 3000 (2700–3000, 2530–5500) mL and the lowest Fibtem A5 was 19 (16–22, 10–34) mm. The lowest laboratory fibrinogen (known for 32) was 3.4 (2.4–4.6, 2.3–6) g L^{-1}. None of the women for whom data were available (*n*=32) had laboratory evidence of established haemostatic failure at any time, and lowest Fibtem A5s in the other three women were 20, 22 and 34 mm. In total 24/35 (68.6%) received RBCs and 23/35 (65.7%) had between one and four invasive procedures to control bleeding. Five/35 (14.2%) women had a Fibtem A5 ≤15 mm but bleeding stopped soon afterwards and so they were not randomized. One woman bled an additional 1500 mL after the Fibtem A5 was 11 mm. She bled a total of 3000 mL in 25 min because of uterine atony which was controlled with an intrauterine balloon. The Fibtem A5 result of 11 mm was available about 10 min before the bleeding stopped and hence she was not randomized; she received four units of RBC and no FFP.

Table 2 Study outcomes by cohort. *Total blood loss was reported to be less than blood loss at study entry and so cases were excluded from this analysis, †women may have had more than one invasive procedure, ‡number of h for each woman is given as a result of low number of patients

Outcome	Observational cohort (*n*=605)	Interventional cohort (*n*=55)
Blood loss		
Blood loss after study entry (mL)	300	896
Median (25th to 75th centile)	(50–545)	(500 to 1400)
range	0 to 3800	0 to 3600
Missing	12*	
Total blood loss (mL)	1500	2480
Median (25th to 75th centile)	(1300 to 2000)	(1982.5 to 3260)
range	650 to 5500	1028 to 5300
Total blood loss >2500 mL *N* (%)	40 (6.6)	26 (47.3)
Transfusion		
Red blood cells		
Median (25th to 75th centile) units	0 (0 to 0)	2 (0 to 4)
Number transfused *N* (%)	141 (23)	35 (64)
Number transfused 4 or more units *N* (%)	11 (1.8)	16 (29)
Fresh frozen plasma		
Median (25th to 75th centile) units	0 (0 to 0)	0 (0 to 1)
Number transfused *N* (%)	12 (2.0)	14 (26)
Cryoprecipitate		
Median (25th to 75th centile) units	0 (0 to 0)	0 (0 to 0)
Number transfused *N* (%)	2 (0.3)	2 (3.6)
Platelets		
Median (25th to 75th centile) units	0 (0 to 0)	0 (0 to 0)
Number transfused *N* (%)	1 (0.2)	7 (12.7)
Cell salvage		
Median (25th to 75th centile) (mL)	0 (0 to 0)	0 (0 to 0)
Number transfused *N* (%)	27 (4.5)	3 (5.5)
Obstetric interventions to control bleeding		
Number of uterotonic doses used		
Median (25th to 75th centile)	2 (2 to 4)	3 (5 to 6)
range	1 to 9	2 to 8
Number of invasive procedures		
Median (25th to 75th centile)	0 (0 to 1)	1 (0 to 2)
range	0 to 5	0 to 4
Women requiring no invasive procedure *N* (%)	322 (53)	22 (40)
Women requiring one invasive procedure *N* (%)	173 (29)	10 (18)
Women requiring two invasive procedures *N* (%)	80 (13)	11 (20)
Women requiring three invasive procedures *N* (%)	21 (3.5)	11 (20)
Women requiring four invasive procedures *N* (%)	7 (1.2)	1 (1.8)
Women requiring five invasive procedures *N* (%)	2 (0.3)	0 (0)
Type of invasive procedure†		
Hysterectomy *N* (%)	1 (0.2)	(0)
Intra-uterine balloon catheter *N* (%)	45 (7.4)	15 (27)
Uterine compression sutures *N* (%)	9 (1.5)	2 (3.6)
Manual removal of placenta *N* (%)	57 (9.4)	4 (7.2)
Perineal repair *N* (%)	154 (26)	11 (20)
Vaginal pack *N* (%)	80 (13)	15 (27)
Examination under anaesthetic *N* (%)	62 (10)	18 (33)
Laparotomy *N* (%)	2 (0.3)	4 (7.3)
Bimanual compression *N* (%)	7 (1.2)	0 (0)
Other not stated *N* (%)	14 (2.3)	0 (0)
Interventional radiology *N* (%)	0 (0)	0 (0)
Uterine artery ligation *N* (%)	0 (0)	0 (0)
Use of tranexamic acid		
Number treated *N* (%)	182 (30.1)	55 (100%)
Hospital stay and Level 2 and 3 care		
Level 3 care *N* (%)	10 (1.7)	4 (7.3)
Length of stay of women admitted to level 3 care (h)		
Median (25th to 75th centile)	21 (9.2 to 25.2)	2, 4, 18, 168‡

Continued

Table 2 Continued

Outcome	Observational cohort (*n*=605)	Interventional cohort (*n*=55)
Level 2 care N (%)	518 (86)	51 (94)
Length of stay of women admitted to level 2 care (h)		
Median (25^{th} to 75^{th} centile)	10 (6 to18)	17 (10 to 26)
Length of hospital stay (days)		
Median (25^{th} to 75^{th} centile)	2 (2 to 4)	3 (2 to 4)

Discussion

A cohort of women with moderate to severe PPH had their blood product management stratified according to the criteria of ongoing bleeding and thromboelastometry. Of the 663 women recruited into the OBS2 study, including both the randomized and observational groups, 605 (91%) maintained Fibtem A5 >15 mm or, if the Fibtem decreased below 15 mm, bleeding was rapidly controlled by obstetric intervention. Despite restrictive use of FFP, none of the 605 women in this study developed clinically significant haemostatic impairment, defined as laboratory evidence of established haemostatic failure associated with continuing bleeding.

A lower proportion of the observational group had placental abruption than the interventional group. This might be explained because abruption is known to be associated with reduced fibrinogen,[1 23–25] and this precipitated randomization. In contrast, the observational group had a higher proportion of bleeds as a result of genital tract trauma, which is known to be less often associated with reduced fibrinogen.[19 26] The observational group had higher laboratory fibrinogen and Fibtem values at study entry as dictated by the study design. Despite this, PT and aPTT values were similar between the observational and randomized groups. This supports previous observations that fibrinogen decreases earlier than other coagulation factors during PPH,[17] and that adequate fibrinogen can be used as a surrogate for normal laboratory haemostasis during PPH.

The women who were not randomized had better outcomes than the women who were. This is because the two groups were stratified by Fibtem A5 and Clauss fibrinogen levels which are known to be predictive of progression of PPH.[19 27–29] The difference in outcomes between the two groups does not allow conclusions to be drawn on whether restrictive use of FFP based on Fibtem A5, as described here, is an appropriate treatment strategy.

Guidelines recommend maintaining PT and aPTT <1.5 times normal and fibrinogen >2 g L^{-1}.[2 4 8] The randomized arm of this study showed that if Fibtem A5 was >12 mm or Clauss fibrinogen >2 g L^{-1}, infusion of fibrinogen concentrate did not affect outcomes, supporting the conclusion that a fibrinogen of 2 g L^{-1} (or Fibtem >12 mm) is adequate for haemostasis during PPH.[20] In the cohort of women reported here, FFP was withheld if the Fibtem A5 remained >15 mm, or a fibrinogen of about 3 g L^{-1}.[20] Only eight women subsequently developed laboratory evidence of established haemostatic failure. In all of these patients Fibtem A5 was ≤15 mm but bleeding stopped soon after enrolment through obstetric intervention, indicating that bleeding was not caused primarily by coagulopathy. Therefore, withholding FFP guided by Fibtem did not result in clinically significant haemostatic impairment because bleeding was controlled with obstetric intervention in all cases.

Twelve women received FFP and it is not possible to be certain whether FFP infusion influenced outcomes in these women. In nine patients FFP was infused when bleeding had stopped and tests of haemostasis were normal, therefore giving FFP is unlikely to have influenced outcomes. FFP infusion in these patients could have been influenced by human factors such as concern about the risk of further bleeding or the desire not to waste FFP that had been thawed. The study involved a large number of investigators and these factors could have varied between individuals.

None of the 40 women with a total blood loss >2500 mL developed laboratory evidence of established haemostatic failure, and it is unlikely that fibrinogen or FFP infusion would have reduced bleeding. Clinicians would not have known the results of laboratory coagulation tests for about 60 min, therefore, early knowledge of Fibtem A5 appears to have been useful in managing blood product replacement, even in women with massive PPH. If a strategy of empirical, fixed-ratio FFP had been used, some of these women would have been exposed to FFP because 73% received RBCs. These findings suggest that withholding FFP based on clinical assessment of bleeding and the Fibtem A5 is unlikely to result in clinically significant haemostatic impairment.

None of the 10 women admitted to level 3 care had Fibtem ≤15 mm or laboratory tests consistent with established haemostatic failure, although four received FFP and one cryoprecipitate. It is unlikely that a more liberal use of FFP would have improved outcomes, however it is not possible to determine whether giving FFP influenced outcomes unrelated to haemostasis, for example development of respiratory complications. Of the four women admitted to level 3 care for respiratory distress or fluid overload, three had received FFP and one had not. Some of the women had received large volumes of fluids, although this did not lead to evidence of haemostatic failure. No data were collected on catecholamine usage. Careful review of fluid balance is an important part of the management of PPH.[4 8]

The 605 women reported in this study are a selected cohort because women with ongoing bleeding and Fibtem A5 ≤15 mm entered the randomized study. In the whole OBS2 study (the cohort reported here and the randomized women combined), 27% received RBCs, 4.1% received ≥4 units RBC and 9.2% had total blood loss >2500 mL. In our previously published, unselected, consecutive cohort of 356 women recruited with similar inclusion criteria, 30% received RBC transfusion, 9% received ≥4 units RBC and 11% had a bleed of >2500 mL.[19] This suggests that some women with larger bleeds were not recruited into the study compared with an unselected cohort of women with PPH. It is likely, therefore, that a higher proportion of women with PPH would develop a coagulopathy than reported here because some cases of severe bleeding, where coagulopathy can develop rapidly, appear to be underrepresented in this study.

Table 3 Women who developed laboratory evidence of established haemostatic failure. Laboratory haemostatic failure defined as lowest reported fibrinogen<2 g L^{-1} or PT/aPTT>1.5 times normal. RP is retained products of conception. ND is no data recorded

Patient	Blood loss at study entry (mL)	Total blood loss (mL)	Blood loss after study entry (mL)	Mode of delivery	Cause of bleed	Lowest Fibtem A5 (mm)	Lowest Fibrinogen (g L^{-1})	Longest PT (sec)	Longest aPTT (sec)	Red blood cell (units)	FFP (units)	Crystalloid infusion (mL)	Colloid infusion (mL)	Invasive procedures to control bleed	Vignette
1	1800	2100	300	Vaginal	Atony	19	2.4	16.7	ND	0	0	4000	1000	None	Bleeding stopped soon after recruitment despite prolonged PT.
2	2000	2000	0	Vaginal	Atony Trauma RP	11	1.9	11.8	26.8	0	0	2000	500	Intra-uterine balloon Manual removal of placenta Vaginal pack Perineal repair	Obstetric interventions were being performed at the time coagulation tests were taken. Bleeding stopped at this time despite low fibrinogen.
3	1800	1800	0	Instrumental vaginal	Atony Trauma	24	4.3	16.6	32.5	2	0	4700	1000	Vaginal pack Perineal repair	Bleeding stopped 5 min after blood tests despite prolonged PT.
4	1700	1700	0	Non-Elective C section	Abruption Atony	9	1.7	10.8	26.4	0	0	2000	ND	None	Bleeding had stopped as coagulation tests were performed.
5	1500	1600	100	Instrumental vaginal	Atony	3	0.9	19.1	43	2	0	5000	500	None	Bleeding settling as coagulation tests were taken.
6	400	1500	1100	Vaginal	Abruption Atony	8	1.8	9.9	25.7	3	0	1000	ND	None	Bleeding started 8 h before delivery. Abnormal coagulation tests associated with an abruption. Fibrinogen of 1.8 g/L was taken at the time of delivery when bleeding stopped.
7	1040	1300	260	Non-elective C section	Surgical	12	1.8	11.2	24.7	0	0	4000	ND	None	Bleeding stopped 15 min after blood tests despite low fibrinogen.
8	1300	1300	0	Instrumental vaginal	Atony	14	1.2	10.9	22.5	0	0	2000	ND	None	Bleeding stopped 13 min after blood tests despite low fibrinogen.

Table 4 Women who received FFP or were admitted to level 3 care. 1. 6000 mL given in first 24 h. 2. Defined as lowest reported fibrinogen <2 g L^{-1} or PT/aPTT>1.5 time normal. RP is retained placenta. ND is no data, no laboratory coagulation tests were performed or volume of crystalloid or colloid not recorded. RP is retained products of conception. EUA is examination under anaesthetic. NA is not applicable

Patient	Blood loss study entry (mL)	Total blood loss (mL)	Blood loss after study entry (mL)	Mode of delivery	Cause of bleed	Lowest Fibtem A5 (mm)	Laboratory haemostatic failure[2]	Red blood cell (units)	FFP (units)	Crystalloid infusion (mL)	Colloid infusion (mL)	Invasive procedures to control bleed (N)	Reason for level 3 admission	Vignette
Admitted to level 3 care and infused either FFP or cryoprecipitate														
1	2500	5500	0	Non-Elective caesarean section	Atony	16	No	1	0 (1 pool cryo)	4000	500	Intra-uterine balloon EUA	Postpartum haemorrhage	Cryoprecipitate transfused at the time of return to theatre and intra-uterine balloon insertion 3 h after C section. Fibtem and coagulation test not performed at this time.
2	1200	5000	3800	Non-Elective caesarean section	Abruption Atony Praevia	20	ND	1	2	1000	500	EUA	Desaturating	Antenatal haemorrhage 1200 mL over 17 hrs and proceed to C section. Transfused FFP when total blood loss 2400 mL and Fibtem 21 mm 1 h after start of C section. Further 2600 mL blood loss over next 4 h, resolved after EUA, no further tests of haemostasis were done.
3	3000	3000	0	Vaginal	RP	22	No	3	2	3000	500	Manual removal of placenta	Respiratory distress	Transfused FFP 90 min after bleeding had stopped and when coagulation was normal.
4	1600	2400	800	Non-Elective caesarean section	Surgical	19	No	1	1	6000[1]	ND	None	Laparotomy for bowel obstruction	Transfused FFP 50 min after bleeding had stopped when coagulation was normal. Laparotomy performed the following day.
5	2000	2000	0	Elective caesarean Section	Atony Praevia Surgical	21	No	0	2	4000	1000	None	Sepsis, fluid overload	Transfused FFP 60 min after bleeding had stopped when coagulation was normal.
Infused FFP and not admitted to level 3 care														
6	3000	3800	800	Non-Elective caesarean section	Atony Surgical	18	No	3	3	5000	1000	None	NA	Transfused FFP 45 min after bleeding had stopped when coagulation was normal.

7	2000	3500	1500	Instrumental vaginal	Atony RP	18	No	5	4	5000	ND	EUA	NA	Transfused FFP more than 24 h after bleeding had stopped. Coagulation normal at time of bleeding.
8	1250	3300	2050	Non-Elective caesarean section	Surgical	12	ND	6	2	ND	ND	Laparotomy	NA	Recruited when bleeding started 8 h after C section. Returned to theatre for laparotomy and transfused FFP as bleeding stopped when Fibtem A5 was 12 mm.
9	1500	2500	1000	Vaginal	Atony	29	No	4	4	1000	ND	Intra-uterine balloon	NA	Transfused FFP 75 min after start of bleed when most recent Fibtem was 29 mm, fibrinogen 4.8 g/L and coagulation tests were normal.
10	2000	2300	300	Instrumental vaginal	Atony	19	No	2	4	2500	ND	EUA	NA	FFP given as the bleed stopped when coagulation tests were normal.
11	1400	2300	900	Vaginal	Atony Trauma	19	No	2	2	2300	ND	Perineal repair	NA	FFP given 30 min before bleeding had stopped when coagulation was normal.
12	1000	2000	1000	Non-Elective caesarean section	Accreta Surgical Atony	14	No	4	4	ND	ND	Hysterectomy	NA	Hysterectomy at time of delivery for undiagnosed accreta. Fibtem 14 mm and coagulation tests normal when recruited at 1000 mL. Transfused FFP 105 min after start of surgery, Fibtem and coagulation tests not performed at time of FFP infusion.
13	1100	1300	200	Elective caesarean Section	Surgical	19	ND	0	2	6000	ND	None	NA	FFP transfused as bleeding stopped when Fibtem 19 mm.
Admitted to level 3 care and did not receive haemostatic blood products														
14	1500	2900	1400	Elective caesarean Section	Praevia Atony Surgical	22	No	2	0	2000	ND	None	Tachycardia	Level 3 admission not as a result of postpartum haemorrhage
15	1300	1800	500	Vaginal	Atony RP	19	No	2	0	6000	2000	EUA	Sepsis	Level 3 admission not as a result of postpartum haemorrhage
16	1500	1500	0	Vaginal	Atony RP	28	No	1	0	4000	1000	Manual removal of placenta	Respiratory distress	Level 3 admission not due to postpartum haemorrhage

Continued

Table 4 Continued

Patient	Blood loss study entry (mL)	Total blood loss (mL)	Blood loss after study entry (mL)	Mode of delivery	Cause of bleed	Lowest Fibtem A5 (mm)	Laboratory haemostatic failure[2]	Red blood cell (units)	FFP (units)	Crystalloid infusion (mL)	Colloid infusion (mL)	Invasive procedures to control bleed (N)	Reason for level 3 admission	Vignette
17	1400	1400	0	Instrumental vaginal	Atony Trauma	17	ND	0	0	3000	ND	Perineal repair	Spinal block	Level 3 admission not due to postpartum haemorrhage
18	1000	1320	320	Elective caesarean Section	Surgical	28	ND	2	0	1000	ND	None	No reason reported	Reason for level 3 admission not reported

Despite these limitations, our data support the observation that, if Fibtem A5 is maintained or bleeding has stopped, FFP is not required to maintain clinically adequate haemostasis, as previously reported.[14 15] Restrictive use of FFP, guided by Fibtem, is not standard practice and many guidelines recommend empirical, fixed-ratio FFP if laboratory results are not available.[2 4 8] The challenge facing clinicians treating PPH is that they do not have timely tests of coagulation and, to treat the minority of women with haemostatic compromise, women with normal haemostasis must also be treated.[6 7 9–11] At present NICE does not support the use of VE-POCTs during PPH, but recommends studies investigating the clinical and cost effectiveness of this technology. This is an appropriate assessment of available data. Similarly, recent studies have not supported the use of prophylactic fibrinogen supplementation without the results of tests of haemostasis being known or antifibrinolytic therapy for prevention of PPH.[30 31 32] Our study further highlights the need for larger more definitive studies of haemostatic interventions in PPH.

A strength of this study is the large number of women treated on a standardized haemostasis management protocol. There was good compliance with the protocol despite involvement of many clinicians, with varying levels of experience, at multiple sites suggesting that it is feasible to integrate VE-POCT into management of PPH. The main weaknesses are that the study is observational and there is no control arm of women who received fixed-ratio RBC:FFP transfusion for comparison. It remains possible that a more liberal use of FFP, as recommended by many clinicians,[6 7 9 10] would have prevented some women developing haemostatic impairment and entering the randomized arm of the study. Some critically unwell women were not recruited because clinicians could not follow trial procedures whilst managing these challenging patients. Whether restrictive use of FFP, guided by VE-POCTs, is appropriate for these women is unknown and requires future study.

Conclusions

In a cohort of women with PPH, restrictive use of FFP based on clinical observation of bleeding and Fibtem A5 is feasible and did not result in clinically significant haemostatic impairment. Studies that recruit women with all severities of PPH are needed to compare the clinical and cost effectiveness of liberal, empirical use of FFP, as recommended by current guidelines,[2 4 8] with restrictive use of FFP and early fibrinogen replacement based on point-of-care testing.

Authors' contributions

Study design/planning: P.W.C., R.C.-J., J.S., J.E.H., R.E.C., K.H.
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Declaration of interest

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