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

Concise title: Rotem guided FFP infusion for PPH.

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Summary

Background

Postpartum haemorrhage (PPH) may 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 remained >15 mm, or bleeding stopped, FFP was withheld. If Fibtem A5 was ≤15 mm and bleeding ongoing women were randomised 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 (25th-75th 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%) cases 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.

Conclusions

A 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 a targeted use of FFP based on VE-POCT.

Key words: Postpartum haemorrhage; fresh frozen plasma; viscoelastometric test,

Introduction

Postpartum haemorrhage (PPH) is precipitated predominantly by obstetric causes but may 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 may evolve rapidly and routine laboratory coagulation tests are often not available soon enough to be clinically useful. Clinicians, therefore, may 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 with limited evidence in PPH.[9-11] The haemostatic system at term is hypercoagulant compared to the healthy non-pregnant population[1;3] and trauma-induced-coagulopathy differs markedly from the coagulopathy associated with PPH.[12;13] It may be inappropriate, therefore, to extrapolate treatment strategies from trauma to PPH. Fixed-ratio transfusion may result in unnecessary transfusion of FFP and be associated with complications such as transfusion associated circulatory overload and allergic reactions.[12;14-16]

During PPH, fibrinogen falls 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 and results are available within 10 minutes. Fibtem A5 correlates with laboratory fibrinogen during PPH[18] and is predictive of progression from moderate to severe PPH.[19]

The aim of the study was to investigate a cohort of women experiencing moderate to severe PPH. Women with Fibtem A5 ≤15 mm (Clauss fibrinogen about 3g/L)[18;19] and ongoing bleeding were eligible to be randomised to the interventional part of the study comparing the effectiveness of fibrinogen concentrate or placebo. The randomised women showed that, if plasma fibrinogen was >2 g/L or Fibtem A5 >12 mm, infusion of fibrinogen concentrate did not affect outcomes.[20] The

protocol instructed that for women in whom the 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 randomise women to fibrinogen or placebo. The protocol is published.[21] Trial registration: ISRCTN46295339 (http://www.isrctn.com/ISRCTN46295339), EudraCT 2012-005511-11 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-005511-11). The study was approved by Edinburgh, Multicentre Research Ethics Committee (13/SS/0008).

Women age ≥18 year and ≥24 weeks gestation experiencing major PPH (measured or suspected to be about 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 a Fibtem 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 randomised 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). A Fibtem was repeated after each additional 500 mL blood loss or for clinical concern and FFP continued to be withheld if the A5 remained ≥15 mm or if the bleeding stopped (Figure 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 sec and ≥48 sec, 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).

Descriptive summaries of maternal characteristics at study entry by cohort (observational or intervention) were performed and the means of the continuous variables were compared using

Student's *t*-test for continuous variables (Mann-Whitney 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 randomised 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 (Figure 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, the enrolment characteristics of the women who were randomised 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 75th centile) 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%) cases, 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 may have 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⁻ 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 cases bleeding stopped rapidly, despite the abnormal coagulation results, following obstetric interventions and hence did not fulfil the criteria for clinical significant haemostatic impairment.

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, 4 of whom received FFP and one cryoprecipitate (Table 4). In the 7 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 received FFP the median (25th to 75th 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 was known for 32 and was 3.4 (2.4-4.6, 2.3-6) g/L. None of the woman, on whom data were available (n=32), had laboratory evidence of established haemostatic failure at any time and lowest Fibtem A5s in the other 3 women were 20, 22 and 34 mm. In total 24/35 (68.6%) received RBCs and 23/35 (65.7%) women had between 1 and 4 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 randomised. One woman bled an additional 1500 mL after the Fibtem A5 was 11 mm. She bled a total of 3000 mL in 25 minutes due to uterine atony which was controlled with an intra-uterine balloon. The Fibtem A5 result of 11 mm was available about 10 minutes before the bleeding stopped and hence she was not randomised, she received 4 units of RBC and no FFP.

Discussion

This study reports on a cohort of women with moderate to severe PPH whose blood product management was stratified according to the criteria of ongoing bleeding and Fibtem A5. Of the 663 women recruited into the OBS2 study, including both the randomised and observational groups, 605 (91.2%) maintained a Fibtem A5 >15 mm or, if the Fibtem fell below 15 mm, the bleeding was rapidly controlled by obstetric intervention. Despite a restrictive use of FFP, none of the 605 women reported 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 a placental abruption than the interventional group. This might be explained because abruption is known to be associated with a reduced fibrinogen [1;23-25] and this precipitated randomisation. In contrast, the observational group had a higher proportion of bleeds due to 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 levels at study entry as dictated by the study design. Despite this, PT and aPTTs were similar between the observational and randomised groups. This supports previous observations that fibrinogen falls earlier than other coagulation factors during PPH[17] and that an adequate fibrinogen can be used as a surrogate for normal laboratory haemostasis during PPH.

The women who were not randomised had better outcomes than the women who were not. 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 any conclusions to be drawn on whether a 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 randomised arm of this study showed that if the Fibtem A5 was >12 mm or the 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 cases the 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 9 cases FFP was infused when the bleeding had stopped and tests of haemostasis were normal therefore giving FFP is unlikely to have influenced outcomes. FFP infusion in these cases may 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 may 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 minutes, therefore, early knowledge of the 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 a Fibtem ≤15 mm or laboratory tests consistent with established haemostatic failure, although 4 received FFP and 1 cryoprecipitate. It is unlikely that a more liberal use of FFP would have improved outcomes, however, it is not possible to exclude that giving FFP may have influenced outcomes unrelated to haemostasis, for example development of respiratory complications. Four women were admitted to level 3 care for respiratory distress or fluid overload, 3 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 in any case. 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 a Fibtem A5 ≤15 mm entered the randomised study. In the whole OBS2 study (the cohort reported here and the randomised women combined) 26.8% 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, 29.7% received a RBC transfusion, 9% received ≥4 units RBC and 10.7% had a bleed of >2500 mL[19]. This suggests that some women with larger bleeds were not recruited into the study compared to 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 may develop rapidly, appear to be under-represented in this study.

Despite these limitations, our data support the observation that, if the 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 and our study further highlights the need for larger more definitive studies.

The strengths of this study include the large number of women treated on a standardised haemostasis management protocol. There was good compliance with the protocol despite the involvement of large numbers of clinicians, with varying levels of experience, at multiple sites suggesting that it is feasible to integrate VE-POCT into the 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] may have prevented some women developing haemostatic impairment and entering the randomised arm of the study. Some critically unwell women were not recruited because clinicians could not follow trial procedures whilst managing these challenging cases. Whether a restrictive use of FFP, guided by VE-POCTs, is appropriate for these women is unknown and requires future study.

Conclusion

This study shows that, in the cohort of women recruited, a 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 a liberal, empirical use of FFP, as recommended by current guidelines,[2;4;8] with a restrictive use of FFP and early fibrinogen replacement based on point-of-care testing.

K Hood: study design and sample size calculation, oversight of study conduct and governance, oversight of data analysis, data interpretation and critical revision of manuscript

K Harding: recruitment of patients, data interpretation and critical review of manuscript

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Reference List

1. Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. British Journal of Haematology 2014;164:177-188.

2. Collins PW, Kadir R, Thachil J. Management of coagulopathy associated with postpartum haemorrhage: guidance from the SSC of ISTH. Journal of Thrombosis and Haemostasis 2016;14:205-210.

3. Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia 2015;70:78-86.

4. Mavrides E, Allard S, Chandraharan E et al. Prevention and management of postpartum haemorrhage. British Journal of Obstetrics and Gynaecology: An International Journal of Obstetrics and Gynaecology 2016

5. Solomon C, Collis RE, Collins PW. Haemostatic monitoring during postpartum haemorrhage and implications for management. British Journal of Anaesthesia 2012;109:851-863.

6. Shields LE, Smalarz K, Reffigee L et al. Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. American Journal of Obstetrics and Gynecology 2011;205:368.

7. Shields LE, Wiesner S, Fulton J, Pelletreau B. Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. American Journal of Obstetrics and Gynecology 2015;212:272-280.

8. Klein AA, Arnold P, Bingham RM et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 2016;71:829-842.

9. Pacheco LD, Saade GR, Costantine MM, Clark SL, Hankins GDV. The role of massive transfusion protocols in obstetrics. American Journal of Perinatology 2013;30:1-4.

10. Pasquier P, Gayat E, Rackelboom T et al. An observational study of the fresh frozen plasma: Red blood cell ratio in postpartum hemorrhage. Anesthesia and Analgesia 2013;116:155-161.

11. Saule I, Hawkins N. Transfusion practice in major obstetric haemorrhage: Lessons from trauma. International Journal of Obstetric Anesthesia 2012;21:79-83.

12. Frith D, Brohi K. The pathophysiology of trauma-induced coagulopathy. Current Opinion in Critical Care 2012;18:631-636.

13. Davenport R, Brohi K. Causes of trauma-induced coagulopathy. Current opinions in Anesthesiology 2016;29:212-219.

14. Mallaiah S, Chevannes C, McNamara H, Barclay P. A reply. Anaesthesia 2015;70:760-761.

15. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia 2015;70:166-175.

16. Teofili L, Bianchi M, Zanfini BA et al. Acute lung injury complicating blood transfusion in post-partum hemorrhage: Incidence and risk factors. Mediterranean Journal of Hematology and Infectious Diseases 2014;6:e2014.069.

17. De Lloyd L, Bovington R, Kaye A et al. Standard haemostatic tests following major obstetric haemorrhage. International Journal of Obstetric Anesthesia 2011;20:135-141.

18. Huissoud C, Carrabin N, Audibert F et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG: An International Journal of Obstetrics and Gynaecology 2009;116:1097-1102.

19. Collins PW, Lilley G, Bruynseels D et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood 2014;124:1727-1736.

20. Collins PW, Cannings-John R, Bruynseels D et al. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: a double blind randomised controlled trial: OBS2. British Journal of Anaesthesia 2017; In press.

21. Aawar N, Alikhan R, Bruynseels D et al. Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: Study protocol for a randomised controlled trial. Trials 2015;16:

22. Lilley G, Burkitt St Laurent D, Precious E et al. Measurement of blood loss during postpartum haemorrhage. International Journal of Obstetric Anesthesia 2015;24:8-14.

23. Levi M. Pathogenesis and management of peripartum coagulopathic calamities (disseminated intravascular coagulation and amniotic fluid embolism). Thrombosis Research 2013;131:S32-S34.

24. McNamara H, Mallaiah S, Barclay P, Chevannes C, Bhalla A. Coagulopathy and placental abruption: Changing management with ROTEM-guided fibrinogen concentrate therapy. International Journal of Obstetric Anesthesia 2015;24:174-190.

25. Thachil J, Toh CH. Disseminated intravascular coagulation in obstetric disorders and its acute haematological management. Blood Reviews 2009;23:167-176.

26. Jones R, Hamlyn V, Collis RE et al. Platelets in postpartum haemorrhage. International Journal of Obstetric Anesthesia 2015;24:S10.

27. Charbit B, Mandelbrot L, Samain E et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. Journal of Thrombosis and Haemostasis 2007;5:266-273.

28. Cortet M, Deneux-Tharaux C, Dupont C et al. Association between fibrinogen level and severity of postpartum haemorrhage: Secondary analysis of a prospective trial. British Journal of Anaesthesia 2012;108:984-989.

29. Gayat E, Resche-Rigon M, Morel O et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Medicine 2011;37:1816-1825.

Table 1.Baseline maternal characteristics at study entry by cohort

Variable	Observational cohort (n=605)	Interventional cohort (n=55)	p-value
Demographics			
Age at recruitment (years) *Mean (range)*	31.87 (18-46)	32.1 (20-48)	0.8
Body mass index at booking *Mean (sd)*	27.43 (6.29)	25.91 (5.00)	0.04
Missing	*3*	*1*	
Previous caesarean section *N (%)*	123 (20.3)	18 (32.7)	0.03
Pre-eclampsia during this pregnancy *N (%)*	30 (5.0)	8 (14.5)	0.003
Past history of postpartum haemorrhage *N (%)*	59 (9.8)	11 (20.0)	0.02
Delivery			
Onset of labour *N (%)*			
Spontaneous	214 (35.4)	18 (32.7)	
Induced	224 (37.0)	11 (20.0)	0.004
No labour	167 (27.6)	26 (47.3)	
Multiple gestation *N (%)*			
Singleton	564 (93.2)	49 (89.1)	0.3
Twins	41 (6.8)	6 (10.9)	
Reported causes of postpartum haemorrhage*N (%)*			
Uterine atony	373 (61.7)	39 (70.9)	NA
Surgical bleeding	207 (34.2)	19 (34.5)	
Trauma	174 (28.8)	10 (18.2)	
Retained placenta	70 (11.6)	6 (10.9)	
Placental abruption	23 (3.8)	5 (9.1)	
Placenta praevia	38 (6.3)	3 (5.5)	
Undiagnosed placenta accrete	2 (0.3)	1 (1.8)	
Mode of delivery[†] *N (%)*			
Spontaneous vaginal	167 (27.6)	13 (23.6)	
Instrumental vaginal	140 (23.1)	7 (12.7)	0.2
Elective caesarean section	132 (21.8)	16 (29.1)	
Non-elective caesarean section	166 (27.4)	19 (34.5)	

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)	107 (97 to 116)	95 (86 to 108)	<0.001
Missing	*8*	*0*	
Fibtem A5 (mm)	19 (17 to 22.5)	12 (9 to 14)	<0.001
Missing	*0*	*0*	
Clauss Fibrinogen (g/L)	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 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

Table 2. Study outcomes by cohort

Outcome	Observational cohort (n=605)	Interventional cohort (n=55)
Blood loss		
Blood loss after study entry	300	896
Median (25th to 75th centile)	(50-545)	(500 to 1400)
range	0 to 3800	0 to 3600
Missing	12*	
Total blood loss	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 (23.3)	35 (63.6)
Number transfused 4 or more units *N (%)*	11 (1.8)	16 (29.1)
Fresh frozen plasma		
Median (25th to 75th centile) units	0 (0 to 0	0 (0 to 1)
Number transfused *N (%)*	12 (2.0)	14 (25.5)
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)	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 (53.2)	22 (40.0)
Women requiring one invasive procedure N (%)	173 (28.6)	10 (18.2)
Women requiring two invasive procedures N (%)	80 (13.2)	11 (20.0)
Women requiring three invasive procedures N (%)	21 (3.5)	11 (20.0)
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†	1 (0.2)	(0)
Hysterectomy N (%)	45 (7.4)	15 (27.3)
Intra-uterine balloon catheter N (%)	9 (1.5)	2 (3.6)
Uterine compression sutures N (%)	57 (9.4)	4 (7.2)
Manual removal of placenta N (%)	154 (25.5)	11 (20)
Perineal repair N (%)	80 (13.2)	15 (27.3)
Vaginal pack N (%)	62 (10.2)	18 (32.7)
Examination under anaesthetic N (%)	2 (0.3)	4 (7.3)
Laparotomy N (%)	7 (1.2)	0 (0)

Outcome	Observational cohort (n=605)	Interventional cohort (n=55)
Bimanual compression *N (%)*	14 (2.3)	0 (0)
Other not stated *N (%)*	0 (0)	0 (0)
Interventional radiology *N (%)*	0 (0)	0 (0)
Uterine artery ligation *N (%)*		
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 (hrs)		
Median (25th to 75th centile)	21 (9.25 to 25.25)	2, 4, 18, 168[‡].
Level 2 care *N (%)*	518 (85.6)	51 (94)
Length of stay of women admitted to level 2 care (hrs)		
Median (25th to 75th centile)	10 (6 to18)	17 (10 to 26)
Length of hospital stay (days)		
Median (25th to 75th centile)	2 (2 to 4)	3 (2 to 4)

*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 hours for each woman is given due to low number of cases.