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Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial†

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Editor's key points

- Low fibrinogen is associated with excessive bleeding in postpartum haemorrhage.
- The effect of early empirical administration of fibrinogen concentrate on blood transfusion in postpartum haemorrhage was studied.
- In a multicentre, randomized trial of 249 subjects, pre-emptive administration of fibrinogen concentrate did not reduce red blood cell transfusion.

Background. In early postpartum haemorrhage (PPH), a low concentration of fibrinogen is associated with excessive subsequent bleeding and blood transfusion. We hypothesized that pre-emptive treatment with fibrinogen concentrate reduces the need for red blood cell (RBC) transfusion in patients with PPH.

Methods. In this investigator-initiated, multicentre, double-blinded, parallel randomized controlled trial, we assigned subjects with severe PPH to a single dose of fibrinogen concentrate or placebo (saline). A dose of 2 g or equivalent was given to all subjects independent of body weight and the fibrinogen concentration at inclusion. The primary outcome was RBC transfusion up to 6 weeks postpartum. Secondary outcomes were total blood loss, total amount of blood transfused, occurrence of rebleeding, haemoglobin <58 g litre^{-1}, RBC transfusion within 4 h, 24 h, and 7 days, and as a composite outcome of 'severe PPH', defined as a decrease in haemoglobin of >40 g litre^{-1}, transfusion of at least 4 units of RBCs, haemostatic intervention (angiographic embolization, surgical arterial ligation, or hysterectomy), or maternal death.

Results. Of the 249 randomized subjects, 123 of 124 in the fibrinogen group and 121 of 125 in the placebo group were included in the intention-to-treat analysis. At inclusion the subjects had severe PPH, with a mean blood loss of 1459 (SD 476) ml and a mean fibrinogen concentration of 4.5 (SD 1.2) g litre^{-1}. The intervention group received a mean dose of 26 mg kg^{-1} fibrinogen concentrate, thereby significantly increasing fibrinogen concentration compared with placebo by 0.40 g litre^{-1} (95% confidence interval, 0.15–0.65; $P=0.002$). Postpartum blood transfusion occurred in 25 (20%) of the fibrinogen group and 26 (22%) of the placebo group (relative risk, 0.95; 95% confidence interval, 0.58–1.54; $P=0.88$). We found no difference in any predefined secondary outcomes, per-protocol analyses, or adjusted analyses. No thromboembolic events were detected.

Conclusions. We found no evidence for the use of 2 g fibrinogen concentrate as pre-emptive treatment for severe PPH in patients with normofibrinogenaemia.

Clinical trial registration. ClinicalTrials.gov: http://clinicaltrials.gov/show/NCT01359878. Published protocol: http://www.trialsjournal.com/content/pdf/1745-6215-13-110.pdf.

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Postpartum haemorrhage (PPH) remains a leading cause of maternal morbidity and mortality.[1] Fibrinogen is an essential endogenous component of haemostasis,[2] and its plasma concentration increases during pregnancy.[3] Observational studies of patients with PPH indicate that a low fibrinogen concentration in the early phase of PPH is associated with excessive subsequent bleeding and blood transfusion.[4–7] Fibrinogen concentrate is widely used to correct acquired hypofibrinogenaemia, but evidence is lacking regarding the efficacy of this treatment.[8 9]

We aimed to assess the efficacy of a pre-emptive treatment with fibrinogen concentrate in patients with PPH,[10] and hypothesized that treatment with fibrinogen concentrate reduces the need for red blood cell (RBC) transfusion up to 6 weeks postpartum.

Methods

Ethical approval

The Danish National Committee on health research ethics approved this trial (protocol number 1002168/H-3-2010-004). Written informed consent was obtained from all subjects entering the trial.

Randomization and masking

This trial was investigator-initiated, without any financial or academic involvement from the manufacturers of fibrinogen concentrate. We designed a multicentre, double-blinded, centre-stratified trial with 1:1 parallel groups and used computer-generated allocation and blocks-of-four randomization (done by third party before study commencement). This was concealed by envelopes. When including a subject, an envelope was collected and the content decided/randomized the subject to either intervention or placebo. The stratification by centres implies that within each centre the number of envelopes with intervention or placebo was balanced, and an excess of envelopes was available at all times. We randomly assigned patients with primary PPH regardless of mode of delivery to early pre-emptive treatment with a single i.v. dose of fibrinogen concentrate (RiaSTAP©; CSL Behring, Marburg, Germany) or placebo (isotonic saline) administered by the anaesthetist on arrival in the operating theatre. Subjects received written project information during pregnancy. They were invited to participate and informed consent was sought by the attending anaesthetist at the pre-anaesthetic evaluation before Caesarean section, when labour epidural was performed, or following vaginal delivery with bleeding. In order to secure blinding, we used an anaesthetist doctor or nurse not involved in the treatment of the patient to carry out the randomization and dispensation. Subjects, care providers, outcome assessors, and the statistician were blinded to allocation. Opaque syringes (yellow coloured) were used to disguise the content of the study infusion. We assessed physician and subject blinding. No interim analysis was performed.

The FIB-PPH (FIBrinogen concentrate as initial treatment for PostPartum Haemorrhage) trial was conducted between May 30, 2011 and July 11, 2013 in four university-affiliated public tertiary care hospitals in the Capital Region of Copenhagen, Denmark (Rigshospitalet, Hvidovre Hospital, Herlev Hospital, and Hillerød Hospital). Each centre had 3500–7000 deliveries yr^{-1}, which represents 99% of all deliveries in this region (1% are home deliveries). The trial protocol, including planned statistical analyses, has been published elsewhere.[10]

Subjects

All subjects entering the trial were randomized once the following PPH inclusion criteria were met: (i) age $\geq$18 yr; and (ii) PPH defined as bleeding from uterus and/or birth canal within 24 h postpartum. Additional inclusion criteria were Caesarean section with an estimated perioperative blood loss $>$1 litre or vaginal delivery with either estimated blood loss $>$0.5 litre and intended manual removal of placenta or estimated blood loss $>$1 litre and intended manual exploration of the uterus because of continuous bleeding after delivery of the placenta (Fig. 1). All hospitals in the Capital Region of Denmark follow our national guidelines for treatment of PPH, including treatment with oxytocin. Blood loss up to 0.5 litre was assessed by visual inspection of the absorbent delivery pad, and thereafter determined by weighing of drapes and pads as described in the national guidelines.[11] Exclusion criteria were as follows: (i) known inherited coagulation deficiencies; (ii) antenatal anti-thrombotic treatment; (iii) pre-pregnancy weight $<$45 kg; or (iv) refusal to receive blood transfusion.

Intervention and placebo

The fibrinogen group received a fixed dose of 2 g of fibrinogen concentrate dispensed in 100 ml sterile water. The placebo group received 100 ml of isotonic saline. This was applied in a pragmatic early pre-emptive treatment regimen, giving a fixed dose to all subjects irrespective of body weight and not guided by measurement of fibrinogen concentration or other haemostatic measures. The solution was dispensed using syringe-pump infusion over 20 min according to the manufacturer's recommendation.[12] Additional interventions, including the use of tranexamic acid and i.v. fluids, were at the discretion of the attending physician supported by regional guidelines.[13] The anaesthetists following study drug administration and subjects at the 6 week follow-up were asked to evaluate the blinding.

Haemostatic monitoring and adverse events

Blood samples were taken before intervention (baseline) and 15 min, 4 h, and 24 h after infusion of the study drug. Specially trained nurses obtained the samples and assessed fluid, transfusion status, and adverse events at 4 and 24 h after intervention. The haemostatic monitoring has been described previously.[10] Data on blood transfusions were retrieved from charts and validated in the Blood Bank Database. We approached all subjects 6 weeks postpartum by telephone and asked about contact with general physicians or hospitals. Charts were assessed for readmissions and thromboembolic events.

Outcomes

The primary outcome was RBC transfusion during a 6 week follow-up period postpartum. Danish national guidelines

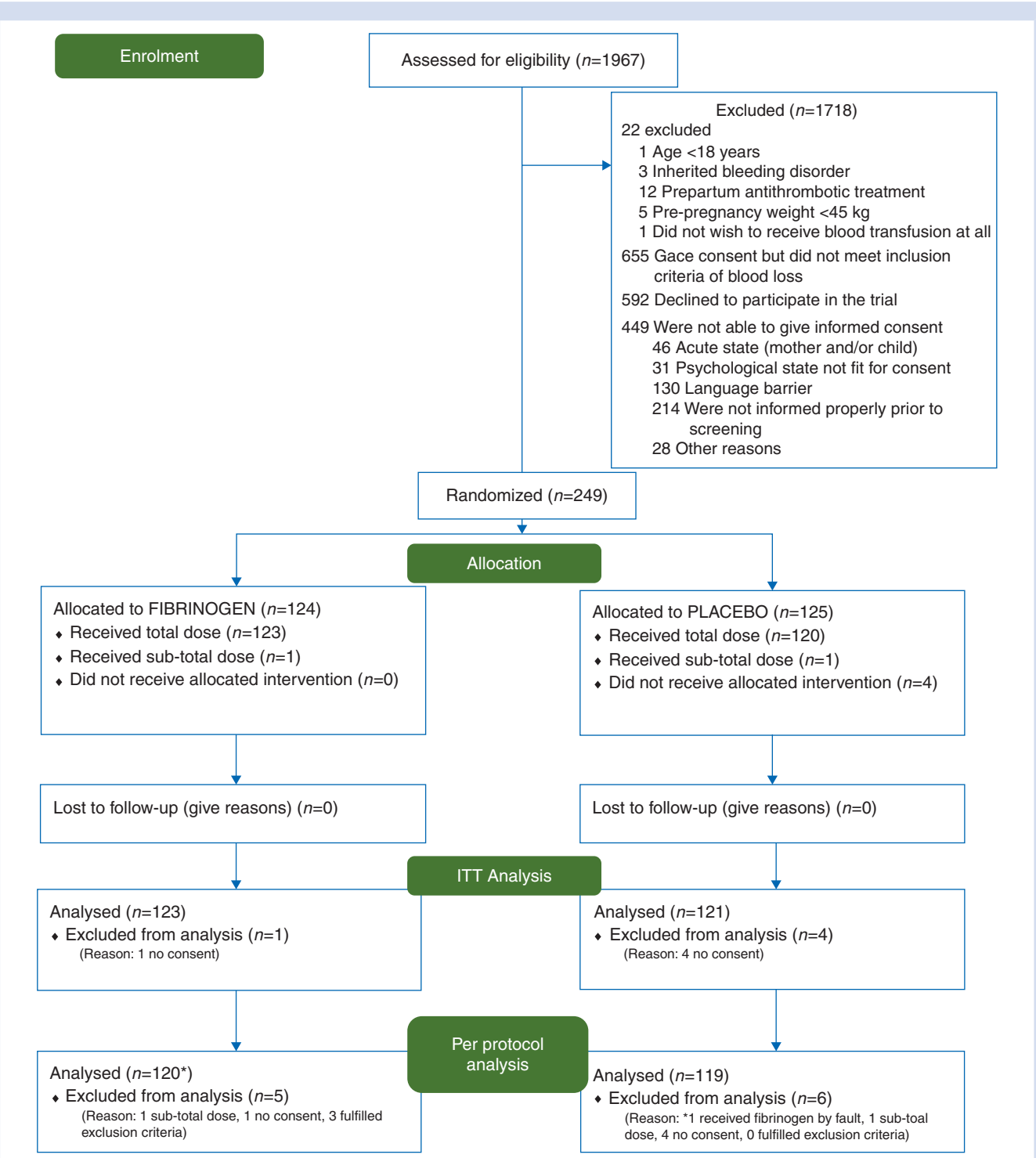

Fig 1 Consort flow diagram. ITT, intention to treat. *The subject who received fibrinogen despite allocation to placebo was included in the per-protocol analysis as part of the fibrinogen group (analysed as treated).

recommend transfusion with RBC if bleeding becomes uncontrollable (e.g. haemodynamic instability) or with significant anaemic symptoms provided haemoglobin (Hb) <72 g litre $^{-1}$ (Box 1).[14] Secondary outcomes were total blood loss, total amount of blood transfused, reoccurrence of bleeding, Hb <58 g litre^{-1}, RBC transfusion within 4 h, 24 h, and 7 days, and a composite outcome of 'severe PPH', defined by Charbit and colleagues[4] as a decrease in Hb of >40 g litre^{-1}, transfusion of ≥ 4 units of RBCs, haemostatic intervention (angiographic embolization, surgical arterial ligation, or hysterectomy), or maternal death.

Box 1 Summary of transfusion protocol.[11 13 14] RBC, red blood cell

Fluids

Initial infusion of 1–2 litres of crystalloids

If a plasma expander is needed, give human albumin 5%; avoid synthetic colloids

Blood transfusion

- Life-threatening haemorrhage (haemodynamic instability):
  Start balanced transfusion of RBC, fresh frozen plasma and platelets, aiming at a ratio of 1:1:1*
  Change strategy when haemodynamic stability is obtained
- Controllable bleeding (haemodynamic stability):
  Give RBC transfusion if haemoglobin is <72 g litre^{-1} (4.5 mM litre^{-1})
  Give fresh frozen plasma and platelets guided by thromboelastography (Kaolin TEG®: R time >11 min or angle <52 degrees and Maximum Amplitude <50 mm)

Tranexamic acid

Tranexamic acid 1 g i.v. should be considered early

*With Danish transfusion units, this corresponds to 5:5:2 of RBC: fresh frozen plasma:platelets

Statistical analyses

We calculated that 245 subjects were needed to show a reduction in relative risk of 33% with a power of 80%, a two-sided type I error of 0.05, and up to 15% dropouts. We estimated that fibrinogen would reduce the proportion of subjects receiving postpartum transfusion from 57 to 38%. The estimate of the proportion of subjects in need of RBC transfusion was based on approximately 1% (range 0.31–2.7%)[10] of parturients receiving RBC transfusion and 1.75% developing severe PPH (defined by a blood loss >1 litre).[15] Analyses of outcomes were performed before breakage of the randomization code. The intention-to-treat (ITT) population was used for analyses, including all randomized subjects with consent to participate regardless of exclusion criteria or having received the wrong dose. In the per-protocol analysis, we omitted those who met exclusion criteria or who did not receive the full dose. Estimates of treatment effect were compared for the pre-stated subgroups.[10] Unadjusted χ^2 tests for binary outcome measures and Student's *t*-test or Wilcoxon rank-sum test were used for continuous measures. Results are presented as the relative risk with a 95% confidence interval (CI), mean (SD), and *P*-value. Logistic regression was used to assess association with baseline variables, and we present adjusted analysis with odds ratio (OR), 95% CI, and *P*-value. Explanatory *post hoc* analyses using logistic regression were performed, including factors with baseline imbalance, statistical interaction, or suspected additional confounding effect. The stratification variable (centre) and baseline variables that were significant in the univariate analysis were included in the adjusted analyses. All analyses were performed with the use of R statistical software, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value of <0.05 was considered statistically significant. Changes in fibrinogen and Hb during the first 24 h after study drug infusion were compared between groups using longitudinal analysis (mixed-effect model).

Role of the funding source

This trial was funded by independent funds and without any financial or academic involvement from the manufacturer of fibrinogen concentrate. The funding source had no involvement. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study population

A total of 249 subjects were randomized, and 244 were available for final analysis on transfusion requirements up to 6 weeks; 123 in the fibrinogen group and 121 in the placebo group (Fig. 1). All 244 subjects had severe PPH, with a mean blood loss of 1.5 litre, and 10% with a systolic arterial pressure <100 mm Hg at inclusion. The distribution of subjects by inclusion criteria was as follows: exploration of the uterine cavity after vaginal delivery [$n=123$ (50%)], Caesarean section and blood loss >1 litre [$n=40$ (16%)], and decision on manual removal of a retained placenta with initial blood loss ≥ 0.5 litre [$n=81$ (33%); Table 1]. Three subjects (all assigned to the fibrinogen group) had exclusion criteria discovered following intervention; one with Factor Leiden V mutation, and two with antithrombotic treatment during pregnancy. Baseline characteristics are presented in Table 1. Baseline fibrinogen concentration was 4.5 g litre^{-1}, with 25% of values being subnormal for pregnancy (<3.7 g litre^{-1}),[3] but very few were <2 g litre^{-1} (2.2%). The single fibrinogen concentrate dose of 2 g of fibrinogen concentrate corresponded to a dose of 26 mg kg^{-1} and significantly increased plasma fibrinogen concentration. We obtained a mean difference of 0.40 g litre^{-1} between the groups 15 min after intervention (Fig. 2).

Intervention, placebo, and additional treatment

The mean fibrinogen dose administered to the intervention group was 26 (SD 4.2) mg kg^{-1} body weight at term. Tranexamic acid (median dose, 1 g; range, 1–2) was part of the standard treatment within 24 h in 92 subjects (38%), and five subjects (2%) received hydroxyethyl starch postintervention, with no significant difference between groups (Table 1). A similar amount of crystalloids (isotonic saline or Ringers acetate) were given postintervention, with a median infused volume of 1325 ml [inter-quartile range (IQR) 900–2000]. Longitudinal analysis (mixed-effect model) showed changes in fibrinogen during the first 4 h following study drug infusion. The fibrinogen group had a significantly higher fibrinogen concentration of 0.40 g litre^{-1} (95% CI, 0.15–0.65) at 15 min after study drug infusion compared with the placebo group (Fig. 2). Additional longitudinal analysis of Hb concentrations showed a significant decrease during the first 24 h compared with baseline, but with no difference between the fibrinogen group and the placebo group (details of additional treatment and fibrinogen concentration can be found in Fig. 2 and Supplementary data).

Table 1 Baseline characteristics of trial population (ITT). Data are presented as *n* (%) or mean (SD). HELLP, haemolysis, elevated liver enzymes, low platelet count; IQR, inter-quartile range; ITT, intention to treat; IU, international units; SD, standard deviation. *$P<0.05$, **$P<0.01$. †Predefined baseline characteristic according to protocol.[10] ‡'Start of bleeding' is defined as the time when the midwife recognizes blood loss exceeding the expected. Maternal weight at term is based on hospital charts and self-reported weight; weight of child is missing from calculations in the case of twins. ¶Cumulative group count and percentage

Characteristic		Fibrinogen (*n*=123)	Placebo (*n*=121)	
Inclusion criteria†				
Manual exploration of the uterus because of continuous bleeding after delivery of the placenta and blood loss ≥1 litre		67 55%	56 46%	
Manual removal of placenta and blood loss ≥0.5 litre		37 30%	44 36%	
Caesarean section and blood loss ≥1 litre		19 15%	21 17%	
Centre†	No. 1	24 20%	24 20%	
	No. 2	22 18%	22 18%	
	No. 3	27 22%	25 21%	
	No. 4	50 41%	50 41%	
Cause of haemorrhage (it is possible to have more than one cause of haemorrhage)				
Tone†		**68** **55%**	**54** **45%**	¶
Trauma†		**54** **44%**	**55** **46%**	¶
	Paravaginal haematoma	1 1%	1 1%	
	Laceration of cervix	11 9%	13 11%	
	Laceration of vagina	21 17%	21 17%	
	Laceration of perineum	33 27%	32 26%	
	Uterine rupture	0 0%	0 0%	
	Bleeding from uterotomy	6 5%	8 7%	
	Episiotomy	6 5%	1 1%	
Tissue†		**76** **62%**	**80** **66%**	¶
	Retained placental tissue	74 60%	78 65%	
	Placenta accreta or percreta	3 2%	4 3%	
	Placenta praevia	1 1%	1 1%	
Thrombin†		**10** **8%**	**13** **11%**	¶
	Diffuse Intravascular coagulopathy	0 0%	0 0%	
	Placental abruption	2 2%	2 2%	
	Pre-eclampsia	8 7%	12 10%	
	HELLP	0 0%	0 0%	
	Gestational thrombocytopenia	1 1%	0 0%	

Continued

Table 1 *Continued*

Characteristic		Fibrinogen (*n*=123)	Placebo (*n*=121)	
Time from delivery to start of bleeding‡ (min)†	Mean (SD)	35 (63)	28 (54)	
Obstetrical characteristics				
Parity	Multipara	58 47%	58 48%	
	Primipara	65 53%	63 52%	
No. of previous Caesarean sections	None	113 92%	107 88%	
	One	10 8%	14 12%	
Multiple gestation	Singleton	117 95%	118 98%	
	Twins	6 5%	3 3%	
Previous postpartum haemorrhage		14 11%	16 13%	
Antepartum bleeding		9 7%	14 11%	
Maternal weight at term (kg)†	Mean (SD)	79 (13)	82 (14)	*
BMI before pregnancy (kg m^{-2})	Mean (SD)	22.8 (3.3)	24.4 (4.5)	**
Weight of child (g)	Mean (SD)	3562 (574)	3625 (579)	
Gestational age at delivery (days)	Median [IQR]	282 [273;289]	284 [274;288]	
Type of anaesthesia†	General	27 22%	18 15%	
	Regional	96 78%	103 85%	
Status at inclusion				
Time from consent to randomization (h)	Median Range (min;max)	1 (0;70)	0 (0;67)	
Time from start of bleeding‡ to infusion of study drug (min)†	Median [IQR]	81 [59;130]	67 [46;115]	
Estimated blood loss at inclusion (ml)†	Mean (SD)	1493 (489)	1426 (463)	
Systolic arterial pressure (mm Hg)	Mean (SD)	122 (21)	124 (20)	
Systolic arterial pressure <100 mm Hg		14 11%	10 8%	
Diastolic arterial pressure (mm Hg)	Mean (SD)	73 (17)	72 (15)	
Heart rate (beats min^{-1})	Mean (SD)	98 (23)	99 (19)	
Haemoglobin at baseline (g $litre^{-1}$)†	Mean (SD)	105 (14)	103 (19)	
Incidence of initial hypofibrinogenaemia (baseline fibrinogen <2 g $litre^{-1}$ with Clauss method)†	Fibrinogen <2 g $litre^{-1}$	1 (1%)	4 (4%)	
	Fibrinogen >2 g $litre^{-1}$	119 99%	107 96%	
Initial fibrinogen concentration (g $litre^{-1}$)†	Mean (SD)	4.5 1.1	4.5 1.3	
Crystalloids given before inclusion (ml)†	Mean (SD)	1460 (796)	1298 (797)	

Continued

Table 1 *Continued*

Characteristic		Fibrinogen (*n*=123)	Placebo (*n*=121)	
Use of hydroxyethyl starch before inclusion†		1 1%	6 5%	
Transfusion of red blood cells before inclusion†		2 2%	0 0%	
Use of tranexamic acid before intervention†		40 33%	36 30%	
Tranexamic acid dose	Median [IQR]	1000 [1000;1000]	1000 [1000;1000]	
Oxytocin		117 95%	118 98%	
Oxytocin dose (IU)	Mean (SD)	15 (6)	15 (7)	
Misoprostol		91 74%	86 71%	
Misoprostol dose (mg)	Median [IQR]	0.4 [0.4;0.4]	0.4 [0.4;0.4]	
Methergine		32 26%	16 13%	*
Methergine dose (mg)	Median [IQR]	0.2 [0.2;0.2]	0.2 [0.2;0.2]	
Carboprost		27 22%	10 8%	**
Carboprost dose (mg)	Median [IQR]	0.2 [0.2;0.2]	0.2 [0.2;0.2]	

Outcome and adverse events

Red blood cell transfusion during the 6 week follow-up period postpartum was given to 25 (20.3%) of the fibrinogen group and 26 (21.5%) of the placebo group (relative risk, 0.95; 95% CI, 0.58–1.54; P=0.88; Table 2). Similar results were obtained in the per-protocol and the adjusted analysis (Supplementary data). No significant difference was found between transfusion incidences in the two groups at any time point recorded. No subjects received fresh frozen plasma or platelets. We found no difference in any secondary outcomes (Table 2) or registered adverse events (Table 3) between groups in either the ITT or the per-protocol analyses. We found no thromboembolic events. Trauma causing PPH, estimated blood loss, and Hb at baseline were significant risk factors for postpartum transfusion, but adjusted analyses did not change effect estimates of intervention (Supplementary data). Increased fibrinogen concentration following intervention was associated with a decreased risk of postpartum transfusion (OR, 0.65; 95% CI, 0.47–0.87; P=0.005), but this association was not significant (OR, 0.90; 95% CI, 0.60–1.34; P=0.61) when adjusted for estimated blood loss and Hb at baseline, dilution with crystalloids (at baseline and postintervention), hypovolaemia (systolic arterial pressure <100 mm Hg), centre, and cause of PPH (trauma or tissue). No change in effect estimates was found in the preplanned subgroups of subjects with vaginal or Caesarean deliveries. Too few subjects were available to assess a subgroup effect in patients with initial fibrinogen concentration <2 g litre^{-1}, and *post hoc* subgroup analysis in those with initial fibrinogen below the normal pregnancy concentration[3] (<3.7 g litre^{-1}) did not change effect estimates. No statistical interaction between initial fibrinogen concentration and effect of fibrinogen concentrate was identified.

Blinding

A total of 220 (94%) of the 235 anaesthetists who evaluated blinding following intervention had no idea of which treatment was provided, but nine (4%) had noticed a small amount of foam in the tubes, indicating fibrinogen concentrate. Besides the deliberate unblinding of one subject (placebo) who developed universal urticaria 2 days after the intervention, no subjects had discovered their allocation. Based on recovery or experience of adverse events, 98 (41%) patients felt they knew their allocation group. However, the same proportion believed they had received fibrinogen in both groups (Supplementary data). Sensitivity analysis of complete blinding did not affect estimates of treatment effect (Supplementary data).

Discussion

In this investigator-initiated, randomized, double-blinded, multicentre trial, we found no reduction in RBC transfusion during a 6 week follow-up period postpartum following administration of 2 g of fibrinogen concentrate.

The FIB-PPH trial is the largest randomized controlled trial investigating fibrinogen concentrate.[8] It is investigator initiated, the first trial in obstetric patients, and the only trial

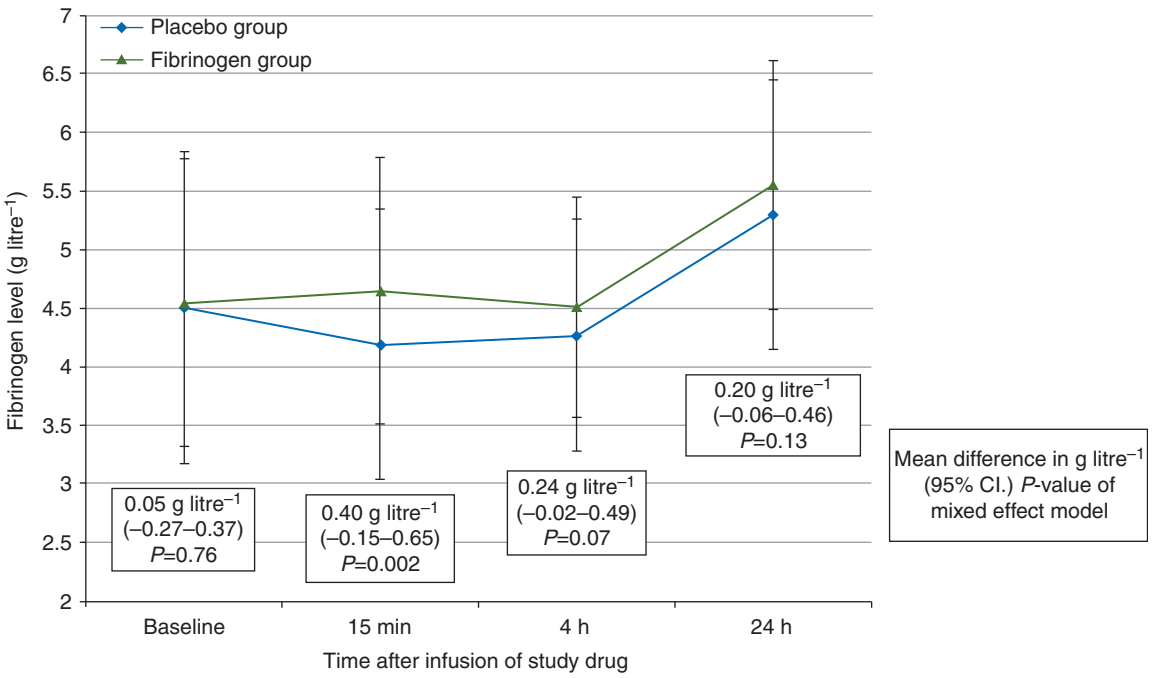

Fig 2 Mean fibrinogen concentrations in placebo and fibrinogen groups from baseline to 24 h after study drug administration, with whiskers indicating standard deviation. Mean difference of the fibrinogen concentration between the fibrinogen and placebo group is given below at each time point from baseline to 24 h after the study drug administration, with 95% confidence interval (CI) given in parenthesis and *P*-value.

Table 2 Primary and secondary outcomes, intention to treat. RBC, red blood cell. Data are presented as the median [IQR] or *n* (%). *One hundred and forty-eight values are missing (61%). †Mean difference with 95% confidence interval (CI; Student's *t*-test). ‡Wilcox rank sum test

Outcome	Fibrinogen (*n*=123)	Placebo (*n*=121)	Relative risk (95% CI)	*P*-value
Primary outcome				
Need for RBC transfusion (during the 6 week period postpartum)	25 (20.3%)	26 (21.5%)	0.95 (0.58–1.54)	0.88
Secondary outcomes				
Estimated blood loss after study drug (ml)	1700 [1500–2000]	1700 [1400–2000]	66 [−78; 210]†	0.37
Need for RBC transfusion (up to 4 h after study drug)	4 (3.3%)	10 (8.3%)	0.39 (0.13–1.22)	0.11
Need for RBC transfusion (up to 24 h after study drug)	14 (11.4%)	19 (15.7%)	0.72 (0.38–1.38)	0.35
Need for RBC transfusion (up to 7 days after study drug)	25 (20.3%)	26 (21.5%)	0.95 (0.58–1.54)	0.88
Total amount of blood transfused	0 [0,0]	0 [0,0]	‡	0.83
Range [min, max]	[0,7]	[0,4]		
Severe PPH*	20 (40.0%)	24 (52.2%)	0.77 (0.49–1.19)	0.31
Death	0 (0.0%)	0 (0.0%)	–	
Haemostatic intervention	0 (0.0%)	0 (0.0%)	–	
Transfusion of ≥4 units of RBCs	8 (6.5%)	3 (2.5%)	2.62 (0.71–9.65)	0.22
Decrease in haemoglobin >40 g litre^{-1}*	20 (40.0%)	24 (52.2%)	0.77 (0.49–1.19)	0.31
Rebleeding	2 (1.6%)	2 (1.7%)	0.98 (0.14–6.87)	1.00
Lowest haemoglobin <58 g litre^{-1}	1 (0.8%)	5 (4.1%)	0.20 (0.02–1.66)	0.12

where subjects were randomized in an emergency setting. Only two of six previous randomized controlled trials investigating fibrinogen concentrate blinded subjects and clinicians,[8] but in this trial we successfully blinded most clinicians and all the subjects. The pragmatic multicentre trial set-up and our few exclusion criteria strengthen the external validity, with the randomized design reducing selection and performance bias. However, our results are limited by the wide confidence intervals on the primary result caused by the lower than expected proportion of included subjects in need of RBC transfusion.[10] The primary reason for this is probably the inability to include subjects with massive and rapid bleeding because of

Table 3 Adverse events, intention to treat. Data are presented as *n* (%). *One hundred and forty-eight values are missing (61%)

	Fibrinogen (*n*=123)	Placebo (*n*=121)	Relative risk (95% CI)	*P*-value
Adverse events				
Up to 24 h				
Dizziness	27 (22.0%)	33 (27.3%)	0.80 (0.52–1.25)	0.37
Shivering	7 (5.7%)	6 (5.0%)	1.15 (0.40–3.32)	1.00
Fever (>38.0°C)	12 (9.8%)	8 (6.6%)	1.48 (0.63–3.48)	0.49
Abdominal pain	10 (8.1%)	3 (2.5%)	3.28 (0.93–1.62)	0.08
Headache	12 (9.8%)	10 (8.3%)	1.18 (0.53–2.63)	0.82
Nausea or vomiting	6 (4.9%)	6 (5.0%)	0.98 (0.33–2.97)	1.00
Fainting	5 (4.1%)	2 (1.7%)	2.46 (0.49–12.43)	0.45
Palpitations	3 (2.4%)	5 (4.1%)	0.59 (0.14–2.42)	0.50
Allergic reaction	0 (0.0%)	1 (0.8%)	–	
Urticaria	0 (0.0%)	1 (0.8%)	–	
Itching	2 (1.6%)	0 (0.0%)	–	
Shortness of breath	1 (0.8%)	3 (2.5%)	0.33 (0.04–3.11)	0.37
Facial oedema	1 (0.8%)	2 (1.7%)	0.49 (0.05–5.35)	0.62
Six week follow-up				
Thromboembolic complications	0 (0.0%)	0 (0.0%)	–	
Readmission with the need for re-evacuation of uterine cavity	1 (0.8%)	2 (1.7%)	0.49 (0.05–5.35)	0.62

the need for informed written consent obtained in the emergency setting. As a result of our early pre-emptive treatment regimen, inclusion was not restricted to patients with hypofibrinogenaemia, and fibrinogen dose was not adjusted to body weight or haemostatic measures. Included patients should be able to give informed consent. The median time from screening to inclusion was <1 h. This reflects that most subjects delivered vaginally, not by planned Caesarean section, and therefore consent was obtained when epidural anaesthesia was provided or when PPH was diagnosed. The use of antepartum written information and obtaining final consent was in accordance with the recommendations of Royal College of Obstetricians and Gynaecologists.[16] In 46 screened patients, it was impossible to obtain consent. Not being able to include cases with severe and rapid PPH is probably reflected in the low number of subjects with initial hypofibrinogenaemia and a lower incidence of RBC transfusion than expected. The incidence of venous thromboembolic events in our population is estimated to be 0.7–2 per 1000 pregnancies.[17] The sample of 244 subjects is insufficient to assess the risk of thrombosis associated with fibrinogen concentrate, but no symptomatic thromboembolic events were seen at the 6 week follow-up.

A Cochrane review showed that fibrinogen concentrate in bleeding patients was associated with a 53% reduction in RBC transfusion,[8] but it included only 208 patients, mainly undergoing cardiac surgery. The fibrinogen concentration was <2 g litre^{-1} at inclusion, except for one study investigating preoperative prophylactic treatment of patients with a mean preoperative fibrinogen of 2.9 g litre^{-1}.[18] Few of our subjects received colloids, and given that fibrinogen concentrate can alleviate the haemostatic impairment of synthetic colloids (e.g. hydroxyethyl starch),[19] this could explain the lack of efficacy in our trial compared with trials in the Cochrane review. Tranexamic acid reduces fibrinolysis and protects endogenous fibrinogen. Tranexamic acid was given to 31% of subjects before intervention and few had a fibrinogen <2 g litre^{-1} at inclusion, and thus they might have had a lesser degree of initial coagulopathy compared with patients after cardiopulmonary bypass.[20] A total of 38% of subjects received tranexamic acid within 24 h, and even if our adjusted analysis did not detect a direct influence on blood transfusion it might be that co-administration of tranexamic acid would have given another result.[9] As other co-interventions can dilute fibrinogen and thus affect the validity of our findings, we have provided detailed description of co-interventions and aimed to reduce their impact on our findings. The change in fibrinogen before and after study drug administration is not only a result of the study treatment, but mainly because of ongoing dilution by fluids (mainly crystalloids) and consumption (e.g. fibrinogen concentration decreased by 0.3 g litre^{-1} in the placebo group). Fibrinogen concentration was 0.4 g litre^{-1} higher in the fibrinogen group following administration of study drug compared with placebo. The fibrinogen increment of 0.1 g litre^{-1} obtained in the fibrinogen group shows that 2 g of fibrinogen concentrate was enough to avoid a decrease, and even to restore and increase fibrinogen concentration. In the study by Charbit and colleagues,[4] 10% of patients with PPH after manual exploration of the uterine cavity requiring i.v. prostaglandin administration had an initial fibrinogen concentration <2 g litre^{-1}. Unfortunately, no data were presented on blood loss or resuscitation with crystalloids or colloids. In our study, fewer subjects had an initial fibrinogen concentration <2 g litre^{-1}, fewer received fresh frozen plasma and were in need of haemostatic intervention, but an equal proportion

presented with hypovolaemia and a higher rate of RBC transfusion within 24 h. Charbit and colleagues[4] reported a longer delay from inclusion to baseline blood sampling in those patients who developed the most severe course of bleeding;[4] this delay might be associated with increased dilution, loss of blood, and loss of fibrinogen such that the initial concentration of fibrinogen may be a surrogate marker of blood loss.[21] This corresponds to our finding that the risk of postpartum transfusion was lower in those with increased fibrinogen concentration following intervention, but this effect disappeared after adequate adjustments for dilution, blood loss, tranexamic acid use, and the cause of PPH.

Fibrinogen concentrate is increasingly used in acquired hypofibrinogenaemia associated with bleeding and as pre-emptive treatment in PPH.[22] Some even recommend 2–4 g of fibrinogen concentrate in the case of 1.5 litre bleeding.[23] However, this represents off-label use in most countries.[24] Several observational studies have reported on the use of fibrinogen concentrate in obstetrical haemorrhage;[25–30] in patients with low fibrinogen (1–1.5 g litre^{-1}) and co-administration of multiple transfusions, including fresh frozen plasma. These studies are based on retrospective chart evaluation, without appropriate control groups, and are associated with a high risk of selection bias, especially the risk of confounding by indication. In addition, most trials investigating fibrinogen concentrate have been sponsored by the manufacturer of fibrinogen concentrate.[8] Based on our findings, further pre-emptive use of fibrinogen concentrate in PPH[22] is not justified. Future studies on PPH should investigate the impact of goal-directed fibrinogen substitution in patients with hypofibrinogenaemia and apply a method of consent that allows for inclusion of patients with rapid and massive bleeding.

In conclusion, we found no evidence for the use of pre-emptive treatment with fibrinogen concentrate for severe postpartum haemorrhage in patients with normofibrinogenaemia.

Supplementary material

Supplementary data are available at *British Journal of Anaesthesia* online.

Authors' contributions

A.J.W., H.M.E., A.A., J. Stensballe, J.L.-R., and A.M.M. developed the concept and trial design, and served as steering and writing committee. A.J.W. and H.M.E. served as trial managers, collected and validated data, and secured funding. A.J.W. designed data collection tools and wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper; she is guarantor. Analyses were recalculated by independent statistician and data manager Tobias Wirenfeldt Klausen, Clinical research Unit, Department of hematology, Herlev Hospital, University of Copenhagen, Denmark. C.A., K.E., G.H., E.L.S., H.F.S., A.U.M., L.F., J. Svare, A.T., L.M.P., J.L., M.G.M., and B.B. made substantial contributions to the implementation of the trial at each centre, the enrolment of patients, the solving of logistics, and the overall concept of the trial. All authors were involved in drafting of the manuscript and revising it critically. All have approved the final version. All authors had full access to data, including statistical reports and tables, and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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None declared.

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Appendix

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