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Randomised Controlled Trial

Early and systematic administration of fibrinogen concentrate in postpartum haemorrhage following vaginal delivery: the FIDEL randomised controlled trial

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Objective To assess the benefits and safety of early human fibrinogen concentrate in postpartum haemorrhage (PPH) management.

Design Multicentre, double-blind, randomised placebo-controlled trial. Setting: 30 French hospitals.

Population Patients with persistent PPH after vaginal delivery requiring a switch from oxytocin to prostaglandins.

Methods Within 30 minutes after introduction of prostaglandins, patients received either 3 g fibrinogen concentrate or placebo.

Main outcome measures Failure as composite primary efficacy endpoint: at least 4 g/dl of haemoglobin decrease and/or transfusion of at least two units of packed red blood cells within 48 hours following investigational medicinal product administration. Secondary endpoints: PPH evolution, need for haemostatic procedures and maternal morbidity–mortality within 6 ± 2 weeks after delivery.

Results 437 patients were included: 224 received FC and 213 placebo. At inclusion, blood loss (877 ± 346 ml) and plasma fibrinogen (4.1 ± 0.9 g/l) were similar in both groups (mean ± SD). Failure rates were 40.0% and 42.4% in the fibrinogen and placebo groups, respectively (odds ratio [OR] = 0.99) after adjustment for centre and baseline plasma fibrinogen; (95% CI 0.66–1.47; $P = 0.96$). No significant differences in secondary efficacy outcomes were observed. The mean plasma FG was unchanged in the Fibrinogen group and decreased by 0.56 g/l in the placebo group. No thromboembolic or other relevant adverse effects were reported in the Fibrinogen group versus two in the placebo group.

Conclusions As previous placebo-controlled studies findings, early and systematic administration of 3 g fibrinogen concentrate did not reduce blood loss, transfusion needs or postpartum anaemia, but did prevent plasma fibrinogen decrease without any subsequent thromboembolic events.

Keywords Blood coagulation, erythrocyte transfusion, fibrinogen, postpartum haemorrhage.

Tweetable abstract Early systematic blind 3 g fibrinogen infusion in PPH did not reduce anaemia or transfusion rate, reduced hypofibrinogenaemia and was safe.

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Trial Registration ClinicalTrials.gov Identifier: NCT02155725, registered on June 4th 2014. https://clinicaltrials.gov/ct2/show/study/NCT02155725?term=NCT02155725&draw=2&rank=1.

Introduction

Postpartum haemorrhage (PPH) affects up to 10% of all deliveries, with a trend towards the incidence increasing over time in developed countries.[1,2] It is the leading cause of maternal mortality worldwide and accounts for up to 75% of severe maternal morbidity.[3] Multidisciplinary PPH management requires early diagnosis, identification of the underlying aetiology, rapid resuscitation, and medical and surgical treatment.[4,5]

Acquired coagulopathy is a major aggravating factor of blood loss.[6,7] During PPH, plasma fibrinogen is the first coagulation factor to drop precipitously due to bleeding, hyperfibrinolysis (consumption) and haemodilution.[8] Additionally, fibrinogen is an early biomarker for worsening of PPH. The risk of progression to severe PPH increases almost three-fold for each 1 g/l decrease in fibrinogen concentration, and a positive predictive value of 100% for progression to severe PPH is observed with fibrinogen concentrations <2 g/l.[9–12]

Fibrinogen replacement therapy for severe bleeding has therefore gained popularity.[13–15] A multidisciplinary task force for advanced bleeding care in PPH patients recommends fibrinogen replacement if the plasma level drops below 2 g/l.[16] However, it remains debated whether systematic fibrinogen administration at an earlier stage may be helpful,[17,18] namely, before plasma level determination. We therefore designed the FIDEL study based on the hypothesis that early and systematic treatment with a significant amount of fibrinogen concentrate (3 g) could reduce the need for red blood cell transfusion (to <2 RBC units) and/or would limit postpartum haemoglobin decreases 48 hours after delivery to <4 g/dl in PPH patients requiring a switch from oxytocin to prostaglandins.

Methods

Study design and study population

FIDEL (FIbrinogen in DELivery) is a randomised, multicentre, double-blind, placebo-controlled study on the efficacy and safety of a therapeutic strategy comparing early and systematic administration of human fibrinogen versus placebo in patients with PPH when switched from intravenous oxytocin to prostaglandins following vaginal delivery. The full study protocol is available in Appendix S1. The initial protocol was published in 2016.[19] The study was sponsored and funded by the company LFB (Les Ulis, France), which holds the marketing authorisation for Clottafact® (fibrinogen concentrate). The double-blind versus placebo research, data collection and interpretation of results were conducted by a contract research organisation (Euraxi Pharma, Joué-les-Tours, France) under the closed oversight of the scientific committee and the independent monitoring committee.

The FIDEL study was conducted in 30 public or private tertiary care hospitals in France. Subjects meeting the following main inclusion criteria (age ≥18 years, with PPH, i.e. vaginal bleeding ≥500 ml) following vaginal delivery requiring continuous intravenous prostaglandin administration (sulprostone, at an initial rate of 500 mcg/h, according to guidelines[16]), with at least one haemoglobin (Hb) value available for the third trimester of pregnancy) were included and randomised. The other inclusion and non-inclusion criteria were described previously.[19] Given the emergency context, consent was obtained after brief delivery of information to the patient, or a relative or reliable person, depending on the patient's level of consciousness. In all cases, the patient was fully informed as soon as possible about the study and asked to sign a post-inclusion consent form to continue participating.

Funding

The study was sponsored and funded by LFB (Les Ulis, France) (Appendix S2), which holds the marketing authorisation for Clottafact® (fibrinogen concentrate). The study was conceived and performed according to a double-blind versus placebo design. Conception conduct of the study, quality assessment, data management, blinded data validation, statistical management quality and writing of the paper were conducted under the oversight of the scientific committee. The awarded grant included external peer review for data collection, applicable regulation and scientific quality.

PPH protocol

The patients were managed medically and surgically according to the most recent French guidelines.[4,20,21] Antifibrinolytic prophylaxis was given according to the investigators' choice in both groups. Administration of tranexamic acid (TXA) or fibrinogen within 48 hours prior to inclusion was a non-inclusion criteria but was allowed after inclusion.[19] After intravenous infusion of the investigational medicinal product (IMP 3 g [8.82 mcmol] fibrinogen concentrate or placebo), the decision on whether to transfuse blood was taken based on European guidelines.[22] Administration of fibrinogen concentrate (Clottafact®, LFB, Les Ulis, France) 60 minutes or more after the start of the IMP; other rescue procedures were allowed as safety measures following strict rules to control bias.[19] The start time of the IMP infusion corresponded to H0. Blood samples were taken at H0, H2, H6 and D2. The fibrinogen dose was set according to a preliminary kinetics study.

Objectives and endpoints

The primary objective was to assess the benefits of early administration of fibrinogen for PPH management and reduction of bleeding after initiation of a sulprostone

intravenous infusion. The primary efficacy criterion was a composite failure endpoint defined as loss of at least 4 g/dl of Hb and/or need for transfusion of at least two units of packed red blood cells (RBCs) within the 48 hours following the IMP infusion. The Hb reference level was the most recent Hb value recorded in the third trimester of pregnancy (to negate the influence of initial haemorrhage).

The secondary objectives were to assess the evolution of haemorrhage and its management by further haemostatic interventions, as well as the safety of fibrinogen administration via collection of adverse events.[19]

Study data were collected prospectively, from the day of delivery until the end of follow-up at 6 ± 2 weeks.[19]

Randomisation and blinding

Patients were randomised in a 1:1 ratio to either the Fibrinogen or placebo groups in a double-blind manner. Randomisation was stratified per centre with a block size of 4; IMP containers were sequentially numbered according to the computer-generated randomisation sequence. Reconstitution of fibrinogen and formulation of the placebo (two vials = 3 g of fibrinogen or placebo per patient) were carried out by trained research personnel not involved in the patients' care. Blinding of care providers and patients was maintained throughout using a masking system and tinted tubing. Each vial of fibrinogen concentrate (1.5 g) and placebo was reconstituted in 100 ml of sterile water and administered at a flow rate ≤20 ml/min within 30 minutes following the start of the sulprostone infusion.

Sample size determination

Failure rates of 42% and 27% were expected in the placebo and the fibrinogen groups, respectively, i.e. corresponding to a 15% absolute difference.[19] Assuming a 5% drop-out rate due difficulties collecting data in emergency conditions, 434 patients needed to be enrolled to achieve a power of 90% at the 2-sided significance level of 0.05. As there was uncertainty about expected rates impacting the variance of the failure rate difference, a blinded interim analysis to reassess sample size to maintain a power of 90% led to a sample size increase from 434 to 470 patients. Given the lower than expected drop-out rate of 1.55%, the trial was stopped on 30 June 2018 with 448 patients enrolled and a trial power of 89.6%.

Statistical analysis

Analyses were conducted with SAS® software (version 9.4., SAS Institute Inc, Cary, NC, USA). The primary analysis was performed with the intention-to-treat (ITT) set, i.e. all randomised patients who received at least one dose of IMP. The primary endpoint was analysed using a logistic regression model with adjustments for treatment, baseline fibrinogen levels (categorised as ≤2, 1–3, 3, >1–4 g/l) and centre (23 centres that enrolled <20 patients by site were pooled as one centre; number of patients included by pooled sites: 1–14; total number of patients in the pool: 140). The treatment effect was estimated as an odds ratio (OR) along with its 95% confidence interval (95% CI) and tested with the Wald test at the 0.05 significance level. An OR <1 indicated a lower failure risk in the Fibrinogen group compared with the control group. Missing data were not replaced in the primary analysis. Sensitivity analyses for handling missing data were performed. Another supportive analysis was performed on the per-protocol (PP) set.

Changes in plasma fibrinogen levels from IMP administration to 2 hours (H2), 6 hours (H6) and 2 days (D2) were analysed in a Mixed Model for Repeated Measurements (MMRM). For continuous secondary efficacy endpoints, treatment groups were compared with a *t*-test or a Wilcoxon test, and binary endpoints were compared with a Pearson Chi-square test or a Fisher exact test. All *P*-values provided for secondary efficacy endpoints are for exploratory purposes only. No adjustments were made for multiple comparisons.

Results

Patients and PPH characteristics

From April 2014 to August 2018, 448 patients experiencing a PPH were eligible for the study. After initial screening, 443 patients were randomised; 437 received the IMP and were retained in the ITT population—224 in the fibrinogen group and 213 in the placebo group (Figure 1).

Baseline characteristics did not differ between the two groups (Tables 1 and S2). The predominant cause of haemorrhage was uterine atony (82%). The mean Hb value (± SD) at H0 was 10.9 ± 1.5 g/dl. The average time interval between third trimester blood sampling for Hb and the delivery was 17.8 days (median 11.5 days). Total mean estimated blood loss (± SD) was 877 ± 346 ml at the start of prostaglandin administration. Tranexamic acid was administered after inclusion to 48% of patients (median dose: 1 g; range: 0.5–2 g).

Primary outcome

The failure rates were similar in the fibrinogen and placebo groups, i.e. 40.0% versus 42.4%, respectively. Logistic regression analysis showed no significant between-group difference: OR = 0.99, 95% CI 0.66–1.47; $P = 0.96$). The planned sensitivity analyses yielded similar results.

Secondary outcomes and exploratory analyses

Bleeding was controlled in all cases, with mean total blood losses in the fibrinogen and placebo groups of 1555 and 1723 ml, respectively ($P = 0.21$). There were no maternal deaths (Table 2). The two components of the composite

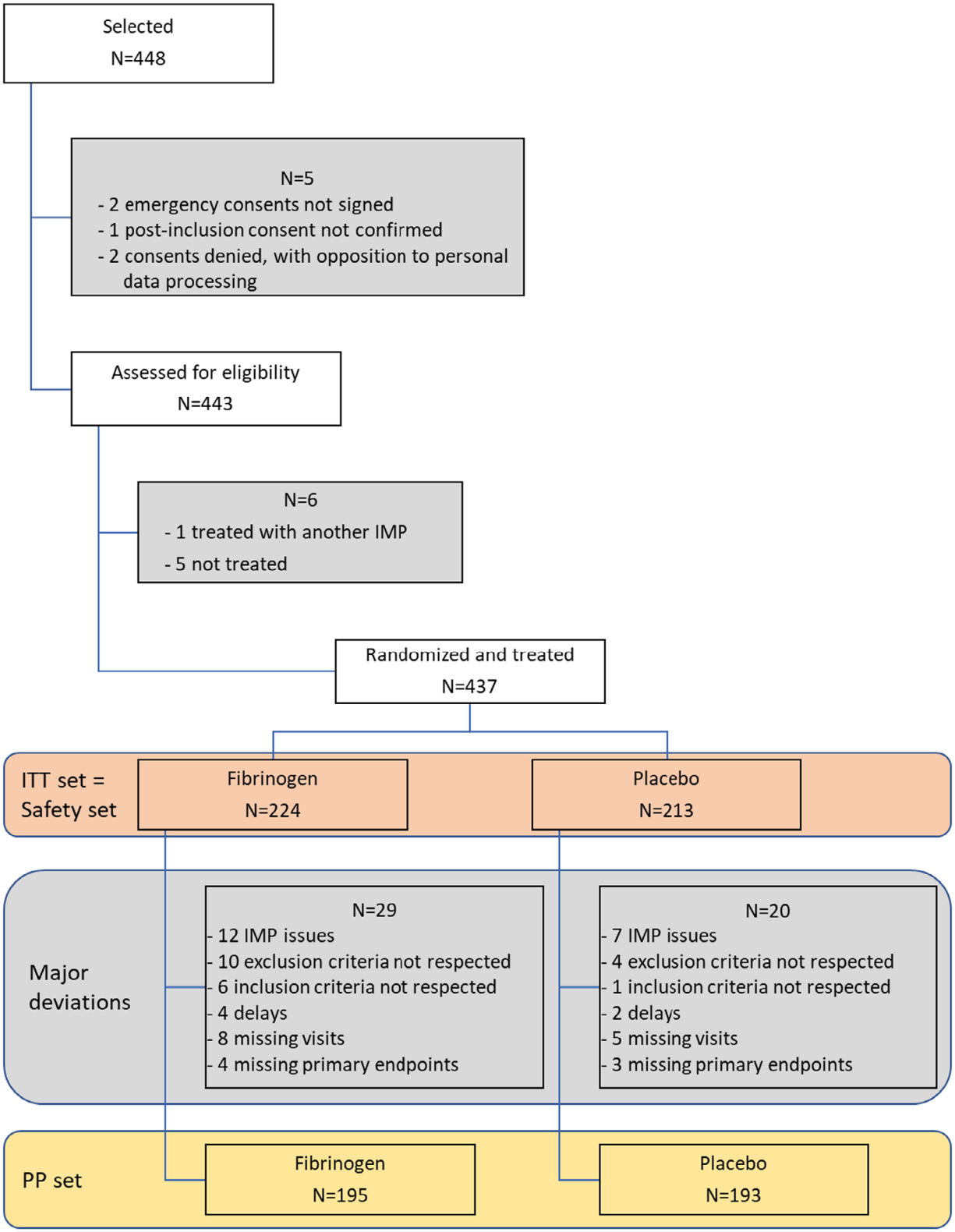

Figure 1. Patient flow through the trial. Primary and secondary outcomes were analysed on the ITT set with no missing data for the primary criterion, i.e. 430 patients (220 in the fibrinogen group and 210 in the placebo group).

Table 1. Baseline characteristics of the population

Characteristics	Fibrinogen *n* = 224	Placebo *n* = 213
Age, mean ± SD, y	30.5 ± 5.6	30.3 ± 5.4
Weight before pregnancy, mean ± SD, kg	65.2 ± 13.9	65.5 ± 14.8
Weight (last known), mean ± SD, kg	77.6 ± 13.6	77.8 ± 13.7
Height, mean ± SD, cm	165.8 ± 5.8	165.8 ± 6.5
Parity, *n* (%)		
Primiparous	113 (50.4%)	96 (45.1%)
Multiparous	111 (49.6%)	117 (54.9%)
Multiple pregnancy, *n* (%)	25 (11.2%)	24 (11.3%)
Term, mean ± SD, weeks	39.2 ± 1.9	38.9 ± 2.3
Prepartum Hb level, mean ± SD, g/dl	11.8 ± 1.0	11.9 ± 0.9
Induction of labour, *n* (%)	88 (39.3%)	65 (30.5%)
Instrumental vaginal delivery, *n* (%)	54 (24.1%)	43 (20.2%)
Cause of PPH, *n* (%)		
Atony	179 (79.9%)	182 (85.4%)
Placenta retention	67 (29.9%)	52 (24.4%)
Lower genital tract wound	19 (8.5%)	19 (8.9%)
Other	8 (3.6%)	1 (0.5%)
Time from…, mean ± SD, min		
Delivery to start of bleeding	41.2 ± 57.4	38.5 ± 58.4
Delivery to start of sulprostone administration	73.8 ± 70.5	74.7 ± 116.5
Delivery to start of study drug infusion	92.0 ± 70.8	85.2 ± 65.9
Prior tranexamic acid		
n (%)	107 (47.8%)	102 (47.9%)
Mean ± SD, g	1.1 ± 0.3	1.1 ± 0.3
Estimated blood loss at the start of prostaglandin infusion, mean (SD), ml	896 ± 373	857 ± 315
Plasma fibrinogen level at inclusion, mean ± SD, *n* (%)	4.2 ± 0.9	4.0 ± 1.0
≤2 g/l	2 (1.0%)	3 (1.5%)
1–3 g/l	19 (9.1%)	21 (10.8%)
3 g/l	62 (29.7%)	75 (38.5%)
>1–4 g/l	126 (60.3%)	96 (49.2%)

Population: ITT set.

primary endpoint were analysed separately. Transfusion rates (proportion of patients who had more than two RBC units) were similar in the fibrinogen and placebo groups (23.4% versus 25.0%; OR = 1.01; $P = 0.98$). Similarly, the proportion of patients with Hb drops >4 g/dl on D2 compared with the reference value were identical in the fibrinogen and placebo groups, i.e. 19.1% and 19.5%, respectively (OR = 1.02; $P = 0.95$).

All patient characteristics, PPH management actions, transfusion outcome, and haemostatic rescue procedures are shown in Appendix S1 and Tables S1 and S4. There were no between-group differences in secondary outcomes (Table 2) or recorded adverse events (Table S5) in either the ITT or PP populations.

Total blood loss >1000 ml and Hb loss >2 g/dl (>1.2 mmol/l) and plasma fibrinogen level ≤4 g/l were identified as significant baseline predictive factors of failure as per the composite primary endpoint (multivariate analysis). Conversely, the centre, a baseline heart rate >100 beats per minute (bpm), and baseline TXA administration were not. Some post-randomisation markers of PPH severity (fresh frozen plasma transfusion, the need for a rescue procedure and a heart rate >100 bpm) were also significantly associated with an excess risk of failure (Table S3). However, adjustment of the effect of IMP supplementation on those variables demonstrated no between-group differences either (not shown). The number of subjects with initial fibrinogen concentrations ≤2 g/l was too small ($n = 5$) to assess a treatment effect in this subgroup of patients.

At baseline, the plasma fibrinogen concentration was 4.1 ± 0.9 g/l, with no between-group difference. Around 11% of patients had fibrinogen levels ≤3 g/l, including 1% whose levels were ≤2 g/l (Table 1). Following administration of 3 g fibrinogen concentrate, mean plasma fibrinogen concentrations were 4.2 ± 0.8 g/l at H2, and 5.1 ± 0.9 g/l on D2. By contrast, the fibrinogen concentration decreased in the placebo group at H2 (3.5 ± 0.8 g/l) and remained lower than in the fibrinogen group on D2 (4.6 ± 0.8 g/l) (Figure 2). The mean change between baseline and H2 was +0.03 ± 0.69 g/l in the fibrinogen group and −0.56 ± 0.56 g/l in the placebo group. The MMRM showed a treatment–time interaction ($P = 0.023$), indicating that the overall plasma fibrinogen level time-course was different between the two groups.

Longitudinal analysis of Hb concentration and haematocrit showed significant decreases during the first 48 hours compared with baseline but did not show any time-course differences between the two groups (not shown).

Concomitant treatments and invasive procedures

Tranexamic acid (median dose: 3 g; range: 1.5–6) was administered to 65% of patients as rescue therapy, after IMP administration, with no significant between-group differences (Table S1). At least one fibrinogen concentrate (1.5 g) was administered as rescue therapy to 4.0% of patients in the fibrinogen group and 8.0% in the placebo group ($P = 0.080$). Intrauterine balloon was used in 29% of patients with no between-group differences, but the need for invasive haemostatic procedures (mainly arterial embolisation) remained rare (3.6% and 4.8% in the fibrinogen and placebo groups, respectively; $P = 0.56$). All patients received crystalloids after baseline (median volume: 2000 ml), and 28% received hydroxyethyl starch (median

Table 2. Primary and secondary outcomes

Outcome	Fibrinogen *n* = 220	Placebo *n* = 210	OR (95%CI)	*P*-value
Primary outcome				
Failure, *n* (%)	88 (40.0%)	89 (42.4%)	0.99 (0.66–1.47)	0.96*
Secondary outcomes				
RBC transfusion ≥2 Units from H0 to D2, *n* (%)	51 (23.4%)	52 (25.0%)	1.00 (0.63–1.60)	0.98*
RBC transfusion ≥4 Units from H0 to D2, *n* (%)	6 (2.7%)	5 (2.4%)		0.87**
Number of RBC units per transfused patient from H0 to D2, mean ± SD	2.7 ± 1.2	3.1 ± 2.5		0.99***
Hb loss ≥4 g/dl from reference level to D2, *n* (%)	42 (19.1%)	41 (19.5%)	1.02 (0.62;1.67)	0.95*
Hb loss ≥3 g/dl from reference level to D2, *n* (%)	102 (46.4%)	98 (46.9%)		0.91**
Hb loss ≥4 g/dl from H0 to D2, *n* (%)	16 (7.3%)	17 (8.3%)		0.69**
Hb level < 9 g/dl from reference level to D2, *n* (%)	112 (50.9%)	117 (56.0%)		0.29**
Total blood loss (from baseline to D2), mean ± SD, ml	1555 ± 849	1723 ± 1193		0.21***
Additional blood loss (from H0 to D2), mean ± SD, ml	304.7 ± 386.2	319.7 ± 417.1		0.33***
Intrauterine balloon, *n* (%)	63 (28.6%)	61 (29.0%)		0.93**
At least one rescue procedure, *n* (%)	65 (29.5%)	64 (30.5%)		0.83**
At least one invasive haemostatic procedure, *n* (%), including:	8 (3.6%)	10 (4.8%)		0.56**
Arterial embolisation	6 (2.7%)	10 (4.8%)		0.27**
Arterial ligation	0 (0%)	0 (0%)		—
Hysterectomy	0 (0%)	1 (0.5%)		0.49****
Intensive care or resuscitation, *n* (%)	62 (28.2%)	54 (25.7%)		0.56**
Length of stay in intensive care or resuscitation unit, mean ± SD, day	0.7 ± 0.6	0.7 ± 0.9		0.84***
SOFA score of patients admitted to intensive care or resuscitation unit, median [min; max]	0 [0;4]	0 [0;6]		0.32***
Death, *n* (%)	0 (0%)	0 (0%)		—

The primary efficacy outcome variable is a composite endpoint of failure, defined as a patient having lost at least 4 g/dl of Hb compared with the reference Hb level within the 48 hours following investigational medicinal product (IMP) administration;, and/or requiring transfusion of at least two units of packed RBCs within 48 hours following the administration of the IMP.
Reference Hb value: last value measured during the 3rd trimester of pregnancy.
Population: ITT set with no missing data for the primary criterion.
*Wald test for treatment effect (Placebo is the reference class), as per the logistic regression adjusted on centre and baseline fibrinogen.
**Chi-square test.
***Wilcoxon Mann–Whitney test.
****Fisher exact test.

volume: 500 ml) with no between-group differences. Blood products were also used; there were no between-group differences with 25% of patients having received RBCs (median: two units), 10% fresh frozen plasma (median: two units) and 1.6% platelets (median: three units).

Safety

Two patients in the placebo group experienced a thromboembolic event, whereas no such events were reported in the fibrinogen group (Table S5). The proportion of patients with severe morbidity requiring intensive care or resuscitation was similar in both groups (Table 2) and organ failure was rare (two patients in each group had a SOFA score ≥3).

Discussion

Main findings

FIDEL is a large, randomised, double-blind, placebo-controlled multicentre trial conducted to assess the value of early and systematic fibrinogen supplementation (3 g) in PPH patients requiring prostaglandin administration following vaginal delivery.[19] Despite the large study size, we failed to demonstrate an effect of the strategy on transfusion requirements or postpartum anaemia, total blood loss, or the need for balloon tamponade or invasive haemostatic procedures. Our study results are in agreement with those of two other recent randomised studies: FIB-PPH, conducted in Denmark and OBS2, conducted in the UK.[17] No

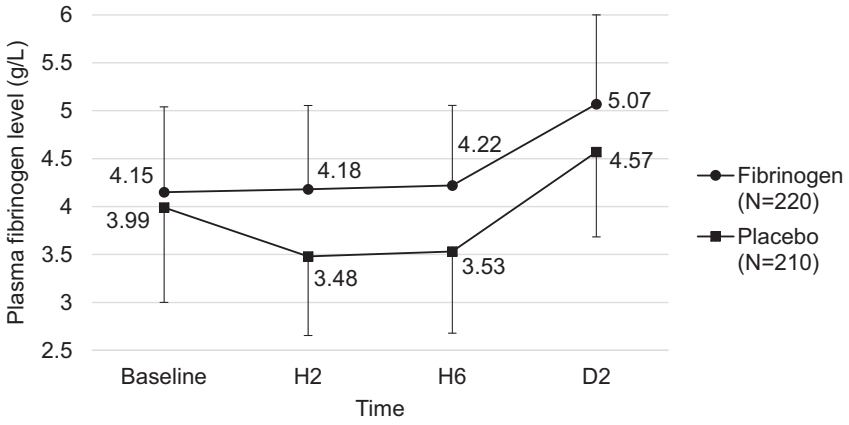

Figure 2. Mean fibrinogen concentrations in fibrinogen and placebo groups from baseline to D2 after study drug administration (ITT set with no missing data for the primary criterion). Values: mean. Error bars: SD (presented one-sided instead of two-sided for readability purposes only). The mixed model for repeated measures showed a treatment * time interaction, with an overall *P*-value = 0.023.

thromboembolic or any other relevant undesirable events were recorded in the fibrinogen group, underlining the apparent safety of early administration of 3 g fibrinogen concentrate in this context.

Strengths and limitations

The main selection criterion was PPH following vaginal delivery requiring uterotonic prostaglandin administration as per French guidelines.[17,23] The hypothesis was that patients with persistent PPH would present a significant decrease in plasma fibrinogen levels. We therefore expected that these patients would benefit from early fibrinogen supplementation before their plasma fibrinogen level results became available. However, we could not to recruit enough patients with an ongoing coagulopathy (as shown by changes in plasma fibrinogen levels in Figure 2) in whom fibrinogen concentrate was expected to be beneficial. We encountered similar issues to those reported in the Danish and UK studies.[17,23] This is partly due to the difficulty of including and obtaining informed consent from subjects with massive and rapid ongoing bleeding. This condition limits the generalisability (external validity) of the study results to the population of the FIDEL study.

Moreover, the globally improved management of PPH, at least in developed countries, may explain why the FIDEL study failed to demonstrate any benefit from early systematic fibrinogen administration. Nowadays, management not only involves timely decision-making shared by obstetricians and anaesthesiologists, but also the early use of TXA and intrauterine balloon tamponade, routinely applied after prostaglandin administration.[5,7,24,25] Following a pragmatic approach to optimise their security (including the possibility of administering rescue fibrinogen in both groups), all patients were treated with standard procedures as per guidelines and as decided by the investigators. We may have in fact correctly selected and randomised patients at risk for severe PPH, but at a very early stage. Postpartum haemorrhage was rapidly controlled and, in most cases, with no significant hemodynamic disorders, no coagulopathy and subsequently normal fibrinogen levels. Very few invasive haemostatic procedures were required, and the quite common use of balloon tamponade in both groups (29%) may be regarded as an evolution of a practice that dramatically reduces embolisation and hysterectomy rates.[26] This change occurred during the course of the FIDEL study.

FIDEL protocol was designed to recruit severe PPH and administer the fibrinogen or placebo as early as possible, avoiding the delay of laboratory fibrinogen results. By contrast, older studies reported substantial delays from inclusion to measurement of plasma fibrinogen prior to fibrinogen administration during which important blood loss and haemodilution occurred and fibrinogen levels dropped significantly.[9,11] The proactive PPH management associated with the national guidelines and the research programme improved the PPH outcome. We therefore failed to demonstrate a benefit from the 'pre-emptive' administration of fibrinogen to patients at risk of severe PPH.

The single block method used to generate the randomisation sequence made it possible to determine which intervention (fibrinogen or placebo) the patient received. It would have been better to use different block sizes to generate the randomisation sequence.

Interpretation

Interestingly, in the OBS2 study, fibrinogen was administered after immediate estimation of fibrinogen levels using the Rotem® (Werfen, Barcelona, Spain) viscoelastomeric

point-of-care test.[17] The objective of the viscoelastic test was the recruitment of PPH associated with active coagulopathy. However, because coagulopathy is rare, life-threatening and unpredictable, the study recruited only seven patients with a fibrinogen plasma level <2 g/l. In women with plasma fibrinogen concentrations estimated <2.0g/l and supplemented with fibrinogen, a nearly two-fold decrease in total allogenic blood product transfusion rate was observed. However, the difference was not significant due to a lack of power. Our study and its negative results further contribute to the attractiveness of rapid plasma fibrinogen assays for initiating and guiding treatment when necessary, i.e. only in the most severe cases associated with coagulopathy and low fibrinogen levels.[15]

Thus, three major randomised and well-conducted controlled studies, FIB-PPH, OBS2 and FIDEL, all found that early systematic fibrinogen replacement is not beneficial in the course of severe PPH management. Nonetheless, several other and older observational studies or reports from the UK, Japan and Turkey still maintain that fibrinogen supplementation is effective and beneficial.[14,27–31] This is not surprising, as most patients in those studies presented very severe and advanced PPH, and much greater blood loss and much lower plasma fibrinogen concentrations (usually <1 g/l) than those reported in the randomised studies. Although the patients received numerous transfusions (including fresh frozen plasma, FFP) and were not compared with adequate control groups, the studies documented safety and established the usefulness of massive doses of fibrinogen (up to 8 g) to avoid FFP transfusion and fluid overload, and for rapid correction of very low fibrinogen levels. Although the randomised controlled trial is the gold standard methodology for demonstrating the efficacy of a therapeutic strategy, it is not always adapted to field constraints, especially in life-threatening emergencies. In light of this, observational or uncontrolled studies provide potentially biased, but better targeted data, which are truly informative and complementary to those of randomised controlled trials.

Altogether, these studies underline the limitations of blind, systematic and early or pre-emptive administration of fibrinogen in PPH. To improve the selection of the patient experiencing a coaguloapthy and target any treatment of this coagulopathy,[32,33] a perspective should be the development of newly available 'plug-and-play' viscoelastometry bedside devices allowing a quick and convenient assay in the emergency room. This approach would help clinicians identify coagulopathies in 'real-time' and determine when emergency fibrinogen supplementation is required, especially in severe cases of PPH or in specific situations such as placental abruption or amniotic fluid embolism.[32,33]

Conclusion

In patients with PPH requiring prostaglandins after vaginal delivery, a strategy consisting in administering 3 g fibrinogen concentrate prior to determination of plasma fibrinogen levels as a systematic adjuvant to standard care, did not reduce blood loss, transfusion needs or postpartum anaemia, but did prevent plasma fibrinogen decreases without generating any subsequent thromboembolic events. As judged by the findings of the present study and in line with those of previous placebo-controlled studies, the use of fibrinogen concentrate in a routine blind and systematic setting for PPH cannot be recommended.

Disclosure of interests

ASD-B, FJM, AM, CH and JMG received fees from LFB as members of the FIDEL trial Scientific Committee. FJM also received fees from LFB for symposium lectures. FBr and FV received fees from LFB as FIDEL investigators. ALG, FV and FBa received fees from LFB for dispensing medical training. FBr and AL were invited by LFB to a congress. TB received fees from LFB for a work of expert. OC reports grants from LFB as an Euraxi Pharma employee. The other authors of the present manuscript do not declare any disclosures of interest.

Contribution to authorship (Appendix S2)

All authors contributed substantially to the work, provided important intellectual content, had full access to data and had the final responsibility for the decision to submit for publication. ASD-B (coordinating investigator) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All members of the scientific committee (ASD-B, FJM, AM, CH and JMG) participated actively in the trial design, the monitoring of inclusions, data validation, data analysis and interpretation; they also demonstrated a strong commitment to informing and motivating the study investigators throughout the trial. OC contributed to data presentation and interpretation of statistical analyses, and was involved in the writing of the manuscript and answers to the referees. All investigators (FB, JC, AL, TR, FB, FV, AL and FIDEL Working group investigators) contributed actively to the inclusions, their monitoring, data validation and analysis.

Details of ethics approval

The FIDEL study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments and Good Clinical Practices (CPMP/ICH/135/95). It was approved by an independent French Ethics Committee (Comité de Protection des Personnes Nord

Ouest IV, approval given on 10 December 2013) as required by French law.

The research was also submitted to the French Regulatory Agency (Agence Nationale de Sécurité du Médicament et des produits de santé). Authorisation was given on 25 November 2013.

Given the emergency context, consent to participate was obtained after brief delivery of information to the patient, or a relative or reliable person, depending on the patient's level of consciousness. In all cases, as soon as possible, the patient was fully informed about the study and asked to sign a post-inclusion consent form to continue participating.

The FIDEL study was registered in the European and US trial databases under Eudract No. 2013-002484-26 and NCT02155725, respectively.

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Consent to participate

Given the emergency context, consent to participate was obtained after brief delivery of information to the patient, or a relative or reliable person, depending on the patient's level of consciousness. In all cases, as soon as possible, the patient was fully informed about the study and asked to sign a post-inclusion consent form to continue participating.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Extended characteristics of the population (ITT set).

Table S2. Summary of PPH management.

Table S3. Multivariate analysis of factors associated with failure (ITT set with no missing data for the primary criterion).

Table S4. Characteristics of rescue procedures (ITT set).

Table S5. Summary of adverse events.

Appendix S1. FIDEL trial protocol.

Appendix S2. Contributions to the study and manuscript. ■

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Appendix A

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