MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 1814-1821
DOI: 10.12659/MSM.914234

Received: 2018.11.22
Accepted: 2019.01.03
Published: 2019.03.10

Treatment of Obstetric Hemorrhage with Fibrinogen Concentrate

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
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Source of support: Departmental sources

Background: Postpartum hemorrhage (PPH) is related to several factors but is frequently associated with coagulopathy with maternal mortality. Fibrinogen is a very important agent for bleeding. When its concentration is decreased, severe surgical blood loss may occur. Here, we investigate the association of postpartum bleeding characteristics with evolution of PPH in patients who were taking fibrinogen concentrate (FC).

Material/Methods: PPH patients' demographic parameters, outcome variables, and laboratory findings before and at ICU were recorded between January 2015 and July 2017. The duration of ICU stay and plasmapheresis, renal replacement therapy, maternal-fetal deaths, RBC, FFP, and PC replacement were calculated.

Results: Group I: Fibrinogen levels were ≤150 mg/dl (n: 31), Group II: Fibrinogen levels were >151 mg/dl (n: 18). In the peroperative period, there was no difference between the 2 groups in terms of RBC, FFP, or PC transfussion. In intraoperative and ICU admission period, patients in Group I had higher INR, APTT, and PT values than in the other group. FC replacement according to fibrinogen level was given, ranging from to 1 to 6 gr in Group I and 1–2 gr in Group II intraoperatively and at ICU 2–8 gr FC was given in both groups. In the intraoperative and ICU admission period, blood transfusion requirements of patients after fibrinogen replacement were evaluated and there was no statistically significant difference between groups. There were no differrences between groups in duration of intensive care unit stay, hospital stay, and mechanical ventilation.

Conclusions: Adequate FC therapy prevents unnecessary RBC, FFP, and PC replacement and prevents complications and volume overload.

MeSH Keywords: Fibrinogen • Obstetrics • Postpartum Hemorrhage

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914234

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Background

Postpartum hemorrhage (PPH) is related to several factors and is frequently associated with coagulopathy of dramatic initiation. PPH is a major cause of maternal mortality and morbidity. It causes increased risk of mechanical ventilation, and hysterectomy, and prologns intensive care unit and hospital stays [1–3]. Coagulation, especially thrombocytopenia, is affected by pregnancy. The procoagulant factors increase and fibrinolysis is reduced [4]. With circulating volume expansion, effective replacement fresh frozen plasma (FFP), red blood cells (RBC), and platelet concentrate (PC) (including coagulation factors) is very important for managing PPH [5,6]. Fibrinogen is a very important agent for bleeding, and when its concentration decreases, severe surgical blood loss may happen [7–9].

Fibrinogen is an essential endogenous component of hemostasis, and its plasma concentration increases during pregnancy [10]. Blood loss results in coagulopathy and reduced fibrinogen levels. Massive transfusion is frequently used to treat hemorrhage, but can itself result in dilutional coagulopathy. Indeed, fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and replacement with RBC [11]. Observational studies of patients with PPH indicate that a low fibrinogen concentration in the initial stage of PPH is associated with excessive subsequent bleeding and blood transfusion [12].

At term, hemostasis is tipped towards a prothrombotic state, along with levels of all procoagulant factors, especially marked for fibrinogen, von Willebrand factor, and factor VIII, but notfactor XI [12,13]. The fibrinogen level is 4–6 g/l, compared with the non-pregnant normal range of 2–4 g/l [14,15]. These changes result in shorter prothrombin and activated partial thromboplastin times (PT/aPTT), sometimes below the normal laboratory range, and a large increase in thromboelastographic parameters [16]. The platelet count may fall during pregnancy (gestational thrombocytopenia), although this is rarely to a level that significantly contributes to the risk of bleeding [17].

FC is produced from human plasma but has viral inactivation and does not require cross-match or thawing before use [21]. However, use of RBC, FFP, and PC is associated with several transfusion-related complications [22]. Recent studies recommended that with fibrinogen concentrate (FC) replacement, treatment can efficiently obtain hemostasis for PPH [18–20].

The identification of prepartum fibrinogen levels might be useful for prediction of PPH. In the present study, we present our experience in managing PPH and discuss clinically important outcomes in PPH in an obstetric hospital, which is the largest in our region, and show the efficacy of FC for treating coagulopathy in PPH in combination with conventional methods according to plasma fibrinogen levels.

Material and Methods

This study was performed in the Anesthesiology and Reanimation Clinic of a tertiary training hospital in Turkey. After delivery and post-partum assessment, patients who require intensive care for postpartum complications are admitted to the ICU. We retrospectively identified patients with PPH who delivered at our hospital or surrounding centers (mostly state hospitals) and were admitted to the ICU between January 2015 and July 2017.

Medical records were reviewed and the data recorded were demographic parameters and pregnancy outcome variables (i.e., age, parity, gestational age, mode of delivery, accompanying obstetric disorders, and gestational period), and laboratory findings before and at ICU admission (i.e., complete blood count, coagulation tests, liver enzyme levels, renal function tests, and fibrinogen). We recorded the duration of ICU stay and specific interventions performed there, including mechanical ventilation, hemofiltration, dialysis, plasmapheresis, and administration of fresh frozen plasma, unit of erythrocytes, platelets, infusion of vasoactive drugs and fibrinogen infusion, plasmapheresis, and renal replacement therapy. Other conservative treatment (e.g., antihypertensive drugs and vasoactive drugs) were administered according to the patient's clinical conditions. Maternal mortality and fetal mortality rates were calculated.

The exclusion criterias of study were under the age of 18, known thrombophilic disease, and PPH patients that were not administered fibrinogen concentrate.

The study had ethics approval number 2018.9.19.

The clinical trial registration number of this study is NCT: 03723200 (*http://clinicaltrials.gov/show/NCT03723200*).

Results

Demographic data, ICU conditions, and outcome of patients are shown in Figure 1 and Tables 1, 2.

Six patients had HELLP syndrome and all were in Group I. Clinical parameters and fibrinogen concentrations are described in Tables 3–8. Two groups are described: Group I consisted of patients whose fibrinogen levels were ≤150 mg/dl (n: 31) and Group II consisted of patients whose fibrinogen levels were >151 mg/dl (n: 18).

In the intraoperative period, fibrinogen levels of 49 patients were measured. Fibrinogen levels were found to be ≤150 in 63.3% of patients. According to the results obtained from the comparison of blood counts according to the fibrinogen levels

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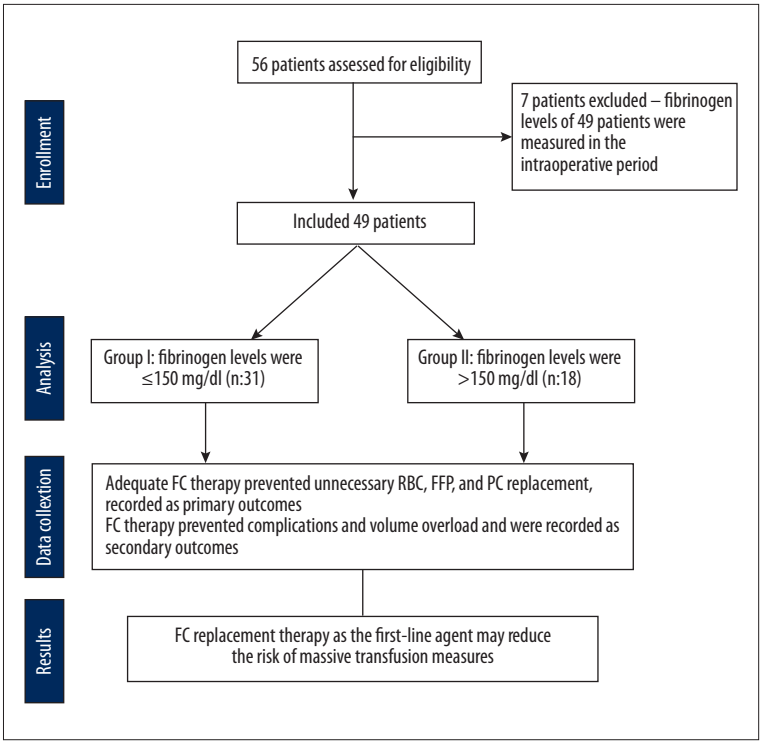

Figure 1. Flow diagram of the study.

of the patients, there was no statistically significant differences between Group I and Group II in white blood cell count (WBC), hemotocrit (Htc), platelet count (Plt), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), direct bilirubin, total bilirubin, or creatinine measurements (p>0.05). However, patients in Group I had higher hemoglobin (Hb), international normalized ratio (INR), activated partial thromboplastin time (APTT), and PT values than the other group and the differences between the 2 groups were statistically significant (p<0.05; p<0.01) (Table 3). Table 4 shows fibrinogen levels (mg/dl) in the intraoperative period, at admission, and at discharge from the ICU period.

In the intraoperative period, 38 patients who were were given FC according to the fibrinogen levels were 1–6 g in Group I (n=31) (mean=3.13±1.20). In Group II, 7 patients who received FC had fibrinogen levels of 1–2 g (mean 1.86±38) (Table 5). Patients with fibrinogen levels above 200 mg/dl were not given FC (FC contains 1 g of fibrinogen in each vial).

We evaluated units of erythrocyte transfusion, fresh frozen plasma transfusion, and platelet transfusion requirements of the patients after FC infusion, and found no statistically significant difference between the groups in the intraoperative period (p>0.05) (Table 5) (1 unit of FFP is 200 ml, 1 unit of RBC is 250 ml, and 1 unit of PC is 200 ml).

Group I had lower hemoglobin, INR, APTT, and PT values, but with adequate FC replacement, there was no statistically significant difference between the 2 groups in terms of blood and blood products transfusion (p>0.05).

When the laboratory values were compared between the 2 groups according to the fibrinogen levels of 49 patients at admission of the ICU, we found that INR, APTT, PT, and total and direct bilirubin values were higher and the differences between the 2 groups were statistically significant (p<0.05; p<0.01) (Table 6).

At ICU admission, the amount of FC replacement was 2–8 g in Group I (n=20) (3.35±1.46). In Group II, 2–8 g FC was administered (3.72±1.57) to 25 patients (Table 7) (FC contains 1 g of Fibrinogen in each vial).

Blood transfusion requirements of patients were evaluated after FC replacement, showing no statistically significant difference between the 2 groups in terms of RBC, FFP, and PC suring ICU stay (p>0.05) (Table 7).

There were statistically significant differences between the 2 groups in values of PT, D bil, T Bil, and creatinine (p<0.05) at discharge from the ICU (Table 8).

No adverse effects were observed during treatment.

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Table 1. Demographic data of patients.

		n	%
Diagnosis	Previa	12	21.4
	Uterine atony	22	39.3
	Dekolman	7	12.5
	HELLP syndrome	6	10.7
	Preeclampsia/Eclampsia	4	7.1
	Other	5	8.9
Comorbidity	None	47	83.9
	Comorbidity	7	12.5
	Bleeding	2	3.6
Glascow Coma Scale	=15	44	78.6
	<15	12	21.4
Antiplatelet therapy	Yes	6	10.7
	No	50	89.3
Mortality	No	49	87.5
	Yes	7	12.5
Cardiopulmonary resuscitation	Yes	10	17.9
	No	46	82.1
Fetal outcome	Survivor	44	78.6
	Perinatal mortality	12	21.4
Mode of delivery	Vaginal birth	8	14.3
	Cesarean delivery	48	85.7
Antihypertensive therapy	Yes	8	14.3
	No	48	85.7
Vasoactive drug infusion	Yes	19	33.9
	No	37	66.1
Plasmapheresis	Yes	3	5.4
	No	53	94.6
Hemofiltration or dialysis	Yes	6	10.7
	No	50	89.3
Disseminated intravascular coagulation	Yes	5	8.9
	No	51	91.1
Elevated liver enzymes	Yes	11	19.6
	No	45	80.4

Table 2. Intensive care unit conditions and outcome of patients.

	n	Min–Max	Mean ±SD
Age (years)	56	18–49	31.64±6.82
Duration of intensive care unit stay (days)	56	1–42	5.98±7.39
Duration of hospital stay (days)	56	1–60	12.88±11.94
Mechanical ventilation (days)	33	1–40	5.00±8.31

Values are mean ± standard deviation (SD).

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Table 3. Intraoperative laboratory values of groups.

	Group I (n=31, 63.3%)	Group II (n=18, 36.7%)	p
WBC count (10^3 cells/μL)	19.95±7.30	18.30±8.63	0.367
Hemoglobin (g/dL)	7.92±2.50	9.51±2.59	**0.012***
Hemotocrit (%)	24.00±7.50	27.78±7.38	0.063
Plt (10^3 cells/μL)	108.608±610.46	138.014±120.04	0.803
APTT (s)	55.68±37.39	34.77±17.30	**0.007****
PT (s)	24.68±20.70	15.23±5.11	**0.002****
INR	1.86±1.10	1.48±1.22	**0.004****
AST (U/L)	99.23±267.11	190.72±472.11	0.836
ALT (U/L)	50.52±115.58	93.78±219.22	0.819
LDH (U/L)	387±227.03	723.33±1038.89	0.622
Serum bilirubin (mg/dL) (direct)	1.02±2.41	0.98±1.86	0.559
Serum bilirubin (mg/dL) (total)	1.38±2.68	1.39±2.32	0.871
Serum Creatinine (mg/dL)	0.93±0.47	0.71±0.301	0.166

* p<0.5; ** p<.01. Values are mean ± standard deviation (SD). PT-INR – prothrombin time-international normalized ratio; APTT – activated partial thromboplastin time; WBC – white blood cell; Plt – platelet count; AST – serum aspartate aminotransferase; ALT – serum alanine aminotransferase; LDH – serum lactate dehydrogenase.

Table 4. Value of fibrinogen levels (mg/dl) in intraoperative, admission, and ICU discharge.

	n	Intraoperative	n	Admission of ICU	n	Discharge of ICU
Grup I	31	81.5±33.7	31	167.3±83.6	30	318.0±142.7
Grup II	18	291.4±104.6	18	188.2±73.1	18	325.9±146.3

Values are mean ± standard deviation.

Table 5. Units of blood and blood products transfused and amount of FC intraoperatively.

	RBC (n=36)		FFP (n=37)		PC (n=10)		FC	
	n	Mean ±SD	n	Mean ±SD	n	Mean ±SD	n	Mean ±SD
Group I	24	5.08±3.67	25	4.00±2.50	8	6.50±3.55	31	3.13±1.20
Group II	12	4.08±2.84	12	3.17±2.22	2	7.00±4.24	7	1.86±0.38
p		0.398		0.061		1.000		–

Discussion

This study shows the effectiveness of FC in terms of plasma fibrinogen levels as the first-line treatment for coagulopathy from PPH. RBC, FFP, and PC requirement were reduced after using FC. Adequate FC therapy prevented unnecessary RBC, FFP, and PC replacement and prevented blood product-related complications and volume overload.

Low fibrinogen is associated with excessive bleeding in postpartum hemorrhage. A study showed that prescription of 1 to 4 g of fibrinogen can significantly reduce the need for blood transfusion [23]. Decrease in need for blood transfusion in those receiving fibrinogen compounds was also confirmed [24]. Akbari et al. suggested that patients receiving fibrinogen needed an average of 600–800 cm^3 less blood for resuscitation compared to FFP and control groups [25].

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Table 6. Laboratory values at ICU admission.

	Group I (n=20, %40.8)	Group II (n=29, %59.2)	p
WBC count (10^3 cells/μL)	19.02±9.84	18.41±6.84	0.799
Hemoglobin (g/dL)	8.03± 2.02	7.91±2.02	0.976
Hemotocrit (%)	23.81±6.23	24.00±5.93	0.815
Plt (10^3 cells/μL)	88.448±46.439	103.506±83.597	0.887
APTT (s)	52.34±34.78	40.08±27.52	**0.023***
PT (s)	21.52±8.21	15.18±3.26	**0.001****
INR	1.84±.76	1.21±.34	**<0.001*****
AST (U/L)	175.82±332.82	160.59±672.50	0.404
ALT (U/L)	239.00±580.75	77.55±318.62	0.127
LDH (U/L)	641.16±876.05	551.50±803.94	0.468
Serum bilirubin (mg/dL) (direct)	2.73±3.96	0.646±1.22	**0.004****
Serum bilirubin (mg/dL) (total)	3.74±5.40	1.14±2.02	**0.010***
Serum Creatinine (mg/dL)	1.09±.63	0.84±.39	0.230

* p<0.5; ** p<.01. Values are mean ±SD. PT-INR – prothrombin time-international normalized ratio; APTT – activated partial thromboplastin time; WBC – white blood cell; Plt – platelet count; AST – serum aspartate aminotransferase; ALT – serum alanine aminotransferase; LDH – serum lactate dehydrogenase.

Table 7. Units of blood and blood products transfusud and amount of FC in ICU.

	RBC (n=36)		FFP (n=37)		PC (n=10)		FC	
	n	Mean ±SD	n	Mean ±SD	n	Mean ±SD	n	Mean ±SD
Group I	17	6.82±5.11	17	8.71±12.70	11	13.18±21.65	20	3,35±1,46
Group II	26	5.35±4.99	22	14.55±42.42	13	10.08±12.94	25	3,72±1,57
p	0.354		0.528		0.733		–	

Values are mean ± standard deviation (SD) or number. FC – fibrinogen concentrate (g); FFP – fresh frozen plasma (1 Unit: 200 ml); RBC – red blood cells (1 Unit: 250 ml); PC – platelet concentrate (1 Unit: 200 ml).

The present study showed that, in Group I, hemoglobin, INR, APTT, and PT values were lower at ICU admission and there was no significant difference between the 2 groups in terms of blood transfusion because of adequate FC replacement. Thus, complications such as excessive volume and allergic reactions due to transfussion were prevented. In addition, concentrated red blood cells lead to increased rates of infection [26]. In the peroperative period, there were no statistically significant differences between groups in terms of blood and blood product transfusion, and this was associated with good mangement of PPH with low fibrinogen levels.

In the intraoperative and ICU admission periods, patients in Group I (≤150 mg/dl fibrinogen) had higher INR, APTT, and PT values than the other group. Because of the fibrinogen levels of patients in Group I, bleeding parameters were expected to be higher. INR, APTT, and PT levels increased bleeding but there were no differences between amount of RBC, FFP, PC transfussion because of adequate FC replacement. Lower fibrinogen level is a direct independent risk factor before delivery, and targeted fibrinogen therapy might be warranted during severe PPH [9]. Guasch et al. showed FC was the only product that can increase mean plasma fibrinogen levels from 3.3 g/L to 4.4 g/L. In our study, FC replacement according to the fibrinogen level was given and ranged from 1 to 6 g in Group I and 1–2 g in Group II intraoperatively, and at ICU admission 2–8 g FC was given to both groups. Patients with fibrinogen levels above 200 mg/dl were not given FC.

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Table 8. Laboratory values at discharge from ICU.

	Group I (n=3, 6.3%)	Group II (n=46, 93.8%)	p
WBC	37.63±6.55	11.57±4.01	0.613
Hb	7.77±1.65	8.51±1.50	0.776
Htc	24.30±6.01	25.47±4.29	0.480
Plt	47.39±40.905	160.86±112.66	0.454
APTT	84.63±9.41	36.52±30.92	0.975
PT	26.77±3.46	13.72±2.81	**0.036***
INR	2.38±0.35	1.09±0.20	0.072
AST	910.67±1474.15	31.58±40.66	0.958
ALT	1027.67±1328.86	26.13±59.98	0.453
LDH	1867.33±1960.05	328.09±144.39	0.341
BilD	4.90±5.34	1.04±2.55	**0.010***
BilT	5.63±6.01	1.41±3.08	**0.025***
Creatinine	2.12±0.64	1.57±4.54	**0.017***

* p<0.5; ** p<.01. Values are mean ±SD. PT-INR – prothrombin time-international normalized ratio; APTT – activated partial thromboplastin time.

Early administration of FC can be useful in the absence of viscoelastic measurements such as thrombelastography. During the intraoperative and ICU admission periods, blood transfusion requirements of patients after fibrinogen replacement were evaluated, and there was no statistically significant difference between the groups in RBC, FFP, or PC. Thus, we avoided complications such as excessesive volume overload and allergic reaction.

In our study, ALT, LDH, and bilirubin levels at ICU admission were higher than at ICU discharge because of patients with HELLP syndrome (10.7%), and that includes elevated liver enzymes.

HELLP syndrome is a life-threatening obstetric complication and is considered a multisytemic disorder, and also treated in the ICU. Maternal and perinatal complications are frequently observed in patients with this syndrome. Mortality among women with HELLP syndrome was linked with low platelet count, low fibrinogen level, high INR value, and high serum levels of AST, ALT, and LDH, and complications in this patient group are associated with maternal death [27]. A study reported that 30% of patients with HELLP syndrome required mechanical ventilation in the ICU [28]. In the present study, there were no differences between duration of intensive care unit stay, hospital stay, and mechanical ventilation. Longer duration of ICU stay might reflect the severity of the patient's clinical situation.

Conclusions

Massive transfusion takes time and raises volume overload for PPH, which can cause acute lung injury and pulmonary edema. This study demonstrated that FC therapy as the first-line agent can reduce the risk of massive transfusion complications. Nevertheless, further study is needed to assess the role of FC in PPH.

Conflict of interest

None.

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