Crit Care Shock (2022) 25:301-308

The impact of fresh frozen plasma versus fibrinogen concentrates on maternal outcomes in a severe postpartum hemorrhage requiring massive transfusion

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Abstract

***Objective*: Massive transfusions after major postpartum hemorrhage can lead to severe maternal morbidity and mortality. The aim of this study was to compare the impact of early fibrinogen concentrates versus a high ratio of fresh frozen plasma over red blood cells (FFP/RBC) on maternal outcomes.**

***Design*: This was a retrospective study.**

***Setting*: The study was conducted in the Hedi Chaker University Hospital, University of Sfax, Tunisia from January 2019 to January 2022.**

***Patients and participants*: In this study, we included all patients requiring a massive transfusion after severe postpartum hemorrhage. We also excluded patients with incomplete data or who did not adhere to the protocol of the study. Finally, 42 patients were included.**

***Interventions*: Patients were divided into 2 groups:**

Group 1: Patients who received 2 g of fibrinogen concentrates followed by a ratio of FFP/RBC of 1.

Group 2: Patients who received a ratio of FFP/RBC of 2 without fibrinogen concentrates administration.

Then, we compared maternal outcomes and transfusion-related adverse events in both groups.

***Measurements and results*: Demographic and preoperative parameters were comparable. The blood loss was 4731 and 4576 ml in Group 1 and Group 2, respectively (p=0.604). The need for platelets transfusion was lower in Group 2 (p=0.001) as well as the incidence of transfusion-related acute lung injury (TRALI) (p=0.039) and renal failure (p=0.044). A high ratio of FFP/RBC reduced the length of stay in intensive care units from 5.58±2.1 to 3.07±1.6 days (p=0.002). The need for catecholamine infusion more than 24 hours after massive transfusion was seen in 17 patients in Group 1 versus 8 patients in Group 2 (p=0.038). Mortality rates were comparable in both groups.**

***Conclusions*: A 2:1 ratio of FFP/RBC without fibrinogen concentrates transfusion seems to be beneficial in massive transfusion in postpartum hemorrhage. However, further high-quality, adequately powered studies are needed to assess the impact of this ratio and the role of fibrinogen concentrates on maternal outcomes.**

Key words: Fibrinogen concentrates, postpartum hemorrhage, coagulopathy, massive transfusion, maternal outcomes.

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Introduction

Major postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality. (1) When it occurs, a massive transfusion protocol (MTP) can be needed to treat and prevent induced coagulopathy. (2) The massive transfusion protocol in peripartum patients is still controversial. To date, hypofibrinogenemia in early bleeding is a predictor of the severity of PPH, and maintaining fibrinogen levels above 2 g/l is a recommended therapeutic target. (3,4) Some studies suggest using fibrinogen

concentrates as first-line therapy to reduce bleeding (1,4,5) and MTP-related morbidity. (6) Other studies suggest using cryoprecipitate to reduce transfusion or infusion volume requirements, which can improve clinical outcomes, such as reducing the need for a ventilator, or the duration of an intensive care unit (ICU) stay. (7) Others had used a higher ratio of fresh frozen plasma over red blood cells (FFP/RBC) and it was associated with a lower requirement for advanced interventional hemostatic procedures. (8)

The purpose of this study was to describe our experience in the management of massive transfusions after PPH and to compare the impact of early fibrinogen concentrates versus a high FFP/RBC ratio on maternal outcomes.

Materials and methods

Study design and settings

After obtaining approval from the medical committee of the Hedi Chaker University Hospital, in Sfax, Tunisia, a retrospective monocentric study was conducted. We analyzed the database of patients who needed a massive transfusion for the treatment of severe postpartum hemorrhage from January 2019 to December 2021.

Participants

In this study, we included all patients aged more than 18 years, with a pregnancy of more than 24 weeks gestation, who had either before delivery or within 12 hours after, a major postpartum hemorrhage defined by a blood loss >2000 ml and needed a massive transfusion defined by the need for more than 4 RBC within the first hour or more than 10 RBC within the first 24 hours following delivery, whatever the cause of bleeding.

We excluded patients with inherited hemostasis troubles (hemophilia or thrombophilia), clinical suspicion of amniotic fluid embolism, and secondary postpartum hemorrhage (abnormal bleeding starting after the first 24 hours following delivery). We also excluded patients who had already received genital tract sutures, uterine tamponade balloons, radiology intervention, or hysterectomy before the massive transfusion (placenta accreta diagnosed antenatally). We also excluded patients with incomplete data or who did not adhere to the protocol of the study.

Variables and data measurement

In this study, we collected data from the transfusion register of the Anesthesiology Department and by consulting computerized medical records of the Obstetrics and Gynecology Department and the Obstetrical Intensive Care Unit. We collected data about:

- Demographic parameters: age, weight, term of pregnancy, parity, mode of delivery, and comorbidities.
- Etiology of bleeding: uterine atony, abnormal placentation, or genital tract lesion.
- Blood loss was estimated by the adapted Gross formula based on the variation of hemoglobin concentration and the transfusion requirements. Blood loss (Gross formula) = total blood volume of a pregnant woman (80 ml/kg) × weight (kg) × [(Hb.i − Hb.d2)/(Hb.i + Hb.d2)/2] + 500 ml for every erythrocyte unit transfused. (Hb.i=preoperative hemoglobin; Hb.d2=postoperative hemoglobin concentration on the second day).
- Transfusions: data about the blood products administered (RBC, FFP, ratio of FFP/RBC, platelets, and fibrinogen concentrate) as well as complications like transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), renal failure, hypocalcaemia, hyperkalemia, infection, or anaphylaxis.
- Maternal outcomes following massive transfusion: surgical interventions to stop bleeding (embolization, arterial ligation, or hysterectomy), length of stay in ICU, need for catecholamine, need for ventilator >24 h, and final issue (death/survival).

Bias

PPH was managed according to the clinical protocol of our institution, which adheres to the French Society of Anesthesiology and Intensive Care (SFAR) guidelines. (9) Transfusion was indicated to maintain Hb >8 g/dl, prothrombin ratio >50%, fibrinogen >2 g/l, and platelets >50000/mm^3. Hypocalcaemia, acidosis, and hypothermia were prevented systematically. The fibrinogen concentrate was transfused at the dose of 90 µg/kg to treat coagulopathy (when plasmatic fibrinogen concentration was <2 g/l), or earlier when practitioners in charge of the patient estimated that the bleeding may lead to coagulopathy (before the result of the plasmatic concentration of fibrinogen). When fibrinogen concentrate was given, patients were transfused with a ratio of FFP/RBC of 1. When fibrinogen concentrates were not available, we used a higher ratio of FFP/RBC=2.

Quantitative variables

The main outcome of this study was to compare the maternal outcomes of two strategies of massive transfusion in major postpartum hemorrhages. Pa-

tients were divided into 2 groups:

- Group 1: included patients who received 2 g of fibrinogen concentrates during the massive transfusion whatever the timing of its administration associated with a ratio of FFP/RBC of 1.
- Group 2: included patients who received a ratio of FFP/RBC of 2 with no fibrinogen concentrates administration.

The ratio was calculated using the cumulative units of FFP and RBC received during the first 6 hours of management. Then we compared maternal outcomes (surgical hemostasis techniques, massive transfusion-related complications, need for prolonged intensive care, and need for mechanical ventilation and catecholamine) in the 2 groups.

Statistical analyses

All statistical analyses were achieved using the SPSS 23.0 (SPSS, Chicago, IL, USA) statistical package. Continuous variables were presented as means value ± standard deviation in the case of a Gaussian distribution and as medians in the case of a non-Gaussian distribution. The comparison between groups was achieved by Student's t-test and chi-square test for continuous variables and categorical variables, respectively. The Fisher exact test was used when the chi-square test was not applicable. The Mann-Whitney U test was used for non-parametric continuous variables. The significance threshold was set at $p<0.05$.

Results

Participants

Among 29214 deliveries during the study period (3 years), 345 (1.18%) were complicated by postpartum hemorrhage requiring transfusion. Sixty-one patients needed massive transfusions (208 per 100000 deliveries). Nineteen patients were excluded from the study (1 case with congenital hemophilia, 3 cases with suspected amniotic embolism, 7 cases with antenatal diagnosis of placenta accrete, 4 patients did not adhere to the protocol of the study, 3 cases with incomplete data, and 1 patient who received cryoprecipitates). Finally, 42 patients with completed data were included and allocated into one group of the study according to their transfusion strategy. Twenty-three patients were allocated to the fibrinogen group (Group 1, n=23) and 19 patients were allocated to the high ratio of FFP/RBC group (Group 2, n=19).

Descriptive data

Of the 42 patients included, 29 patients delivered by cesarean section (69%), and 13 patients had a vaginal delivery (31%). The emergency context was noted in 38 patients (90.4%). The main causes of severe postpartum hemorrhage were uterine atony in 21 patients (50%), abnormal placentation in 8 cases (19%), and genital tract damage in 13 patients (31%). All of them needed general anesthesia. Severe bleeding was associated with hemodynamic shock needing early introduction of catecholamine in 39 patients (92.8%). Thirty-two patients needed hemostatic hysterectomy (76%). The main postoperative complications were TRALI seen in 16 patients (38%), renal failure seen in 8 patients (19%), and pulmonary embolism seen in 2 patients (4.2%). All patients were referred to the ICU for a stay of 4.2±2 days. Maternal death was noted in 3 patients (7.1%).

Outcome data and main results

The demographic parameters (age, weight, term of pregnancy, mode of delivery, and comorbidities) and preoperative blood analysis were comparable in both groups (**Table 1**). Hemoglobin concentration, prothrombin ratio, platelet level, and fibrinogen concentration just before massive transfusion (at the beginning of severe PPH) were comparable in both groups. Blood loss was estimated to be 4731±991 ml in Group 1 versus 4576±914 ml in Group 2 with p=0.604. The need for RBC was comparable in both groups, but the need for platelet transfusions was lower in Group 2 (p=0.001). The surgical management of severe PPH was also similar in both groups (**Table 2**). The incidence of complications related to transfusion was higher in Group 1 in spite of the reduced ratio of FFP/RBC. We noted 12 cases of TRALI in Group 1 versus 4 cases in Group 2 (p=0.039) and 7 cases of renal failure in Group 1 versus 1 case in Group 2 (p=0.044). We noted no cases of anaphylaxis or hemolysis (**Table 2**).

A high ratio of FFP/RBC (=2) reduced the length of stay in intensive care units from 5.58±2.1 to 3.07±1.6 days (p=0.002). The need for catecholamine infusion more than 24 hours after massive transfusion was seen in 17 patients in Group 1 versus 8 patients in Group 2 (p=0.038).

Even if all maternal deaths (3 cases, 7.1%) in this study were seen in Group 1 with no cases in Group 2, the mortality rates were comparable in both groups with p=0.154 (**Table 3**).

Discussion

Key results

In this study, we showed that massive transfusion with a high ratio of FFP/RBC of 2 had better maternal outcomes in comparison with fibrinogen concentrates administration with a ratio of FFP/RBC of

1. It allowed lower rates of massive transfusion-related complications. It also reduced the length of stay in the ICU and the need for catecholamine.

Interpretation

The incidence of massive transfusion after major postpartum hemorrhage in our population was 208 per 100000 births, which was widely higher than in high-income countries. (10) The elaboration of a transfusion protocol respecting the particularities of our population and our conditions as a low-income country is mandatory, to reduce maternal morbidity and mortality. The key strengths of this study were that it allowed us to compare two different strategies of massive transfusions in our maternity. (1) In dead, we tried to select the patients to include in the study, and we tried to exclude all biases in order to select the best strategy. In our study, the severity of bleeding and the decrease of biological parameters at the beginning of bleeding were comparable in both groups, which meant that the differences found in the maternal outcomes were related to the transfusion strategy.

A 1:1 ratio of RBC, FFP, and fibrinogen concentrates, has been advocated for massive transfusions in trauma hemorrhage. (11,12) The effectiveness of this ratio for postpartum hemorrhage was also proven in vitro. (13) Nevertheless, other clinical studies showed that a higher ratio of 2 FFP per 1 RBC was associated with a lower requirement for advanced interventional procedures, (8) which is consistent with our results.

In major obstetrical bleeding, the decrease in fibrinogen concentration is a predictor of the severity of PPH. (3,5) Early administration of fibrinogen concentrates may help in preventing coagulopathy. (1) Maintaining fibrinogen over 2 g/l is recommended to reduce the need for transfusion, which can be beneficial as it may reduce the infectious risk (14) and the inflammatory response implicated in TRALI. (15) However, this hypothesis, supported by previous studies in trauma patients, (16) was not found in our clinical study. We suggest that FFP can provide both fibrinogen (0.6 g per 300 ml of FFP) and coagulation factors which can help in avoiding coagulopathy. The obstetric patients are characterized by high levels of procoagulants (plasmatic fibrinogen and coagulation factors) but also by rapid consumption processes at the same time, which may lead rapidly to disseminated intravascular coagulation. (17) In our study, the ratio of FFP/RBC of 2 was more efficient in preventing coagulopathy because the need for platelet transfusion (to replace platelets consumed) was lower. In a recent study, (18) assessing the impact of different doses of fibrinogen concentrate and 4-factor prothrombin complex concentrate on clotting time as measured by thromboelastometry in an in-vitro model of dilutional coagulopathy, the dose of prothrombin complex concentrates in hemorrhage might be too high for the obstetric patient. This may explain why a higher ratio of FFP/RBC was more effective. However, the same study showed that after fibrinogen correction alone, several samples required no further correction. (18) We suggest that the dose of 2 g early in major bleeding is not sufficient and higher doses are recommended. Fibrinogen concentrate and prothrombin concentrate are now widely used instead of their traditional sources, such as FFP and cryoprecipitate, (19) in spite of their high cost. However, a high ratio of FFP/RBC seems to be efficient and safe, particularly in obstetric patients, and practical for low-income countries. In our study, the incidence of TRALI and TACO was lower in spite of the high ratio of FFP transfused. This may be explained by the rapidity of transfusion and fluid replacement, which was not assessed in our research, or due to platelet transfusion. (20) Even if fibrinogen concentrates can reduce fluid replacement and the infectious risk, we should mention that we noted 2 cases of thromboembolic events. Previous studies showed that the fibrinogen concentrate did not increase the risk of thrombosis in perioperative patients, (21) but in obstetric patients, the coagulation physiology may be different.

Study limitations

This was a retrospective study and further studies are needed to make conclusions. The second limitation was that we did not assess the long-term safety of the two protocols of transfusions (infectious diseases, alloimmunization, etc.).

Conclusion

In obstetric patients, major bleeding remains the leading cause of maternal morbidity and mortality, particularly in developing countries. (21) It can lead to the rapid onset of coagulopathy that may require massive transfusion. In this study, we showed that a high ratio of FFP/RBC was safe and effective with better maternal outcomes than 2 g of fibrinogen followed by a ratio of FFP/RBC of 1. It seems that FFP provides both the required fibrinogen and coagulation factors. This may overcome the problem of the high cost of fibrinogen or prothrombin concentrates. This study changed our maternity's massive transfusion protocol, but larger studies are needed to assess the impact of this ratio and the role of fibrinogen in massive transfusion on maternal outcomes and transfusion-related complications.

Acknowledgment
All authors contributed to the elaboration of this manuscript and approve this version. No funding for this study and no competing interest for any author.

Table 1. Demographic and preoperative parameters

	Group 1 (fibrinogen) n=23	Group 2 (FFP/RBC=2) n=19	p value
Age (years)	32.5±6.6	35.8±4.4	0.070
Age >40 years	6	3	0.336
Weight (kg)	81.2±5.2	79.8±6	0.215
Term of pregnancy (WG)	35.1±2.9	35.1±2.9	0.950
Multiparity (>2)	10	16	0.051
Previous comorbities	7	3	0.285
Cesarean/vaginal delivery	14/9	16/3	0.092
Preoperative Hb (g/dl)	10.4±1.7	10.6±1.1	0.776

Legend: WG=week of gestation; Hb=hemoglobin concentration; FFP=fresh frozen plasma; RBC=red blood cell.

Table 2. Postpartum hemorrhage management

	Group 1 (fibrinogen) n=23	Group 2 (FFP/RBC=2) n=19	p value
Blood analysis just before massive transfusion			
Hb (g/dl)	5.19±1.1	6.07±0.63	0.058
Prothrombin ratio (%)	68.3±21	66.9±29.3	0.870
Platelets (x10^6)	170.6±73	180.8±62	0.646
Fibrinogen (g/l)	2.1±0.77	1.93±0.75	0.706
Blood loss within the first 48 hour after delivery			
Blood loss (ml)	4731±991	4576±914	0.604
Hemorrhagic shock (n)	23	17	0.199
Total transfusion required			
RBC (units)	5.95±2.4	4.8±1.2	0.078
FFP (units)	6.9±3.6	10.1±6.8	0.060
FFP/RBC ratio	1.1	2.1	-
Platelets (units)	8.5±7.3	2.1±3.8	0.001
Transfusion complications			
TRALI or TACO (n)	12	4	0.039
Renal failure (n)	7	1	0.044
Hemolysis (n)	1	0	0.548
Infection (n)	0	0	-
Anaphylaxis (n)	0	0	-
Hypocalcaemia (n)	0	0	-
Hyperkalemia (n)	0	0	-
Surgical management of severe PPH			
Embolization (n)	2	0	0.199
Hypogastric arterial ligation (n)	7	3	0.230
Hysterectomy (n)	16	16	0.305

Legend: Hb=hemoglobin concentration; RBC=red blood cells; FFP=fresh frozen plasma; TRALI=transfusion-related acute lung injury; TACO=transfusion-associated circulatory overload; PPH=postpartum hemorrhage.

Table 3. Maternal outcomes after massive transfusions

	Group 1 (fibrinogen) n=23	Group 2 (FFP/RBC=2) n=19	p value
Length of stay in ICU (days)	5.58±2.1	3.07±1.6	0.002
Length of hospitalization (days)	5.85±4.2	5.84±3.05	0.995
Need for ventilator >24 h (n)	6	2	0.095
Need for catecholamine >24 h (n)	17	8	0.038
Pulmonary embolism (n)	2	0	0.294
Maternal death (n)	3	0	0.154

Legends: ICU=intensive care unit; FFP=fresh frozen plasma; RBC=red blood cell.

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