Treatment of Postpartum Hemorrhage With Blood Products in a Tertiary Hospital: Outcomes and Predictive Factors Associated With Severe Hemorrhage

Emilia Guasch, MD, PhD[1], and Fernando Gilsanz, MD, PhD[1]

Abstract

Postpartum hemorrhage (PPH) remains a leading cause of maternal mortality and morbidity worldwide. This retrospective observational study describes patient characteristics and hemostatic therapies administered to 352 parturients experiencing PPH and analyzes risk factors for developing severe PPH. During the study period, bleeding was controlled in all cases and 99.4% survived. The majority (98%) of patients received packed red blood cells. The most frequent hemostatic therapies administered were fibrinogen concentrate (56%), fresh frozen plasma (49%), and platelets (30%). A total of 124 (35%) women experienced severe PPH. Significant independent predictors for evolution to severe PPH were age, obstetric comorbidity, and plasma fibrinogen concentration. The latter was based on records from 267 (76%) patients. Plasma fibrinogen concentration before labor was the only modifiable prepartum risk factor independently associated with severe PPH, indicating that fibrinogen monitoring is warranted in these patients.

Keywords

gynecology and obstetrics, bleeding, blood coagulation factors

Introduction

Postpartum hemorrhage (PPH) is a major contributor to maternal death and severe maternal morbidity, leading to increased therapeutic intervention, mechanical ventilation, hysterectomy, and hospital stay.[1-4] An increase in the prevalence of PPH has been reported in several developed countries between 1991 and 2006.[5-7] Despite the potentially severe outcomes of PPH, clinical management is not evidence based and varies considerably between centers. Protocols have been proposed for PPH management[8-11] but as yet there is little data reporting on their impact.

Postpartum hemorrhage can rapidly evolve to severe PPH, variously defined as estimated total blood loss >1500 mL,[12] >2000 mL,[11] or >2500 mL[13] within 24 hours of birth; transfusion of $\geq$4 units[12] or $\geq$5 units[13] of blood; or a decrease in hemoglobin levels $\geq$4 g/dL.[12] A number of risk factors for PPH have been identified,[14] but few have been specifically linked to the evolution of severe PPH. However, plasma fibrinogen levels have been linked to both the incidence and the severity of PPH.[15-17] The identification of prepartum characteristics that highlight patients at risk of severe PPH before it occurs could be clinically useful, although there is still some uncertainty whether prepartum fibrinogen levels or any other prepartum factors can predict evolution of PPH to severe PPH. For example, one study found no association between elevated prepartum fibrinogen levels and a reduced risk of PPH.[18]

Here, we present our experience of managing PPH in a Spanish tertiary hospital with the main aim of describing patients' baseline characteristics and comorbidities, delivery and hemorrhage characteristics, and hemostatic therapies administered in line with our standardized treatment protocol, which was carried out in cases of severe or massive hemorrhage. In addition, we use our data to explore clinically important outcomes in patients where PPH evolved to severe PPH and patients where it did not. We also investigate prepartum characteristics associated with the evolution of PPH to severe PPH.

Materials and Methods

Study Design and Patient Population

This was a retrospective, observational analysis of information obtained from the general statistical data at La Paz University Hospital, Madrid, between July 1, 2005, and December 31,

[1] Anesthesia and Intensive Care Department, Hospital Universitario La Paz, Madrid, Spain

Corresponding Author:
Emilia Guasch, Anesthesia and Intensive Care Department, Hospital Universitario La Paz, P° Castellana, 261. 28046-Madrid. Spain.
Email: emiguasch@hotmail.com

2011. La Paz University Hospital is a tertiary referral hospital with 9000 deliveries yearly, more than 25% of which are high-risk parturients. All parturients experiencing PPH were eligible for inclusion. The analysis was not designed as a case–control study; data from parturients experiencing PPH were compared with the general parturient population.

Critical Management of PPH

Patients were treated according to the multi-faceted, standardized hospital protocol developed by us and described in Guasch et al[19] for use in severe or massive hemorrhage only, as determined by the anesthesiologist. Following diagnosis, surgical or medical control of the hemorrhage was initiated by the consultant obstetricians. Blood samples were taken, and 4 units of packed red blood cells (pRBCs) were administered immediately, followed by 4 g of fibrinogen concentrate, and 4 units of fresh frozen plasma (FFP). The decision to administer pRBC and FFP was taken when bleeding appeared uncontrollable, despite surgical attempts and when coagulopathy was evidenced by analytical values or was suspected during the hemorrhagic episode. If hemorrhage control was still insufficient, 4-factor prothrombin complex concentrate was administered following consultation with a hematologist; with ongoing life-threatening bleeding, activated recombinant factor VII could also be administered. The decision was also taken as to whether further steps to control the hemorrhage were required, for example, embolization, laparotomy, hysterectomy, or other surgical resource. Patients were divided into nonsevere (defined as transfusion with <5 units pRBC) and severe PPH (requiring ≥5 units pRBC). It was decided to base the definition on transfusion, rather than blood loss, as bleeding measures are frequently inaccurate.

Data Collection and Statistical Analyses

A broad range of demographic and pre-, peri-, and postpartum data were collected from all parturients experiencing PPH until discharge from the hospital. Prepartum coagulation measurements were made using blood drawn directly before start of labor, and the distributions were analyzed. Coagulation parameters were also recorded after hemorrhage and following hemostatic therapy. Postoperative complications were identified as follows: acute kidney failure was defined as serum creatinine levels greater than 1.2 mg/dL; acute pulmonary edema was assessed by radiologic criteria and clinical features; acute myocardial ischemia or infarction was identified by transient or permanent electrocardiogram changes plus laboratory-measured troponin I increase; urinary tract injury was defined as damage to the ureter and/or bladder secondary to surgery; and coagulopathy was measured by an activated partial thromboplastin time and/or international normalized ratio greater than 1.5.

Categorical variables are summarized as the number observed in each category (percentage of total population). Continuous variables are presented as mean values (± standard deviation) if normally distributed and median values (interquartile range) otherwise. Fisher exact test was used to compare outcomes between the nonsevere and the severe PPH groups. Univariate and multivariate analyses were performed to identify prepartum characteristics associated with evolution to severe PPH. Two multivariate analyses were carried out: Model 1 used only variables for which data were available for ≥85% of patients (and so did not include ethnicity, where the patient was referred from, fibrinogen levels, or abnormal coagulation), while Model 2 included variables with larger proportion of missing data (data included as for Model 1, with the addition of fibrinogen levels and abnormal coagulation).

Results

Patient Characteristics

A total of 56 984 women gave birth in our center during the study period, of which 352 (0.62%) women were treated for PPH; bleeding was controlled in all cases, and 99.4% of the patients with PPH survived. Two fatalities were reported; the first died after hepatic failure, while the second died following acute respiratory distress syndrome arising due to an influenza A H1N1 infection. The majority of patients with PPH were referred from the delivery room (45%), other maternal hospital ward (21%), the patient's home (17%), the intensive care unit (ICU; 9%), other hospitals (4%), or postdelivery wards (3%).

The baseline characteristics and comorbidities for patients with PPH are summarized in Table 1. The number of multiple births was relatively high in the PPH population (11% vs 3% in the general parturients population), with a 4.3 times increase in relative risk of multiple births in the PPH population (P < .001).

Delivery and hemorrhage characteristics are described in Table 2. Almost 50% of patients with PPH required an emergency cesarean delivery, with an increased relative risk of 2.0 (P < .001) in the PPH population compared to the general parturients population. The most common reasons for emergency cesarean section were fetal distress, placenta previa, or repeat cesarean delivery. In comparison, 23% of patients with PPH required instrumental delivery, with the most common reasons being a long second stage or fetal distress. The gestational age was recorded for 336 patients and was found to be full term in the majority of cases (236 deliveries, 70%), but preterm (24-36 weeks) in 68 (20%) patients, puerperal in 13 (4%) patients, and not viable (<24 weeks) in 19 (6%) patients. Prematurely ruptured membranes (>24 hours) were observed in 11 (3%) of 352 patients.

In the majority (92%) of patients, hemorrhage occurred following delivery but was also observed prenatally (10%), and during the first (6%), second (6%), and third (10%) stages of labor.

Coagulation Tests and Hemostatic Management

Patients were treated according to a standardized protocol; the therapies administered for hemostatic management are summarized in Table 3. The association between the amount of

Table 1. Patient Baseline Characteristics and Comorbidities.

Variable	Number of Patients Variable Recorded	Mean (SD) or Number (%)
Age, years	348	32.9 (6.0)
BMI, kg/m^2	315	27.7 (4.7)
Ethnic group	226	
White		115 (51%)
Hispanic		58 (26%)
Black		19 (8%)
Asian		18 (8%)
North African		11 (5%)
Other		5 (2%)
Parity	348	
1		178 (51%)
2		97 (28%)
3		46 (13%)
4+		27 (8%)
Multiple births	352	38 (11%)
In vitro fertilization	350	34 (10%)
Previous PPH	349	12 (3%)
Previous cesarean section	352	64 (18%)
Medical comorbidities	351	
Hypertension[a]		58 (17%)
Gestational diabetes[b]		29 (8%)
Previous abdominal surgery		24 (7%)
Others[c]		74 (21%)
Hematological comorbidities[d]	351	28 (8%)
Bleeding comorbidities[d]		21 (6%)
Thrombotic comorbidities[e]		7 (2%)
Jehovah's witness[f]	351	2 (0.6%)
Obstetric comorbidities	352	
Dead fetus		23 (7%)
Myoma or malformation		21 (6%)
Others[g]		41 (12%)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PPH, postpartum hemorrhage; SD, standard deviation.
[a]Includes gestational hypertension, preeclampsia, chronic hypertension.
[b]Diagnosis of glucose intolerance after week 24, which needs insulin for glycemic control.
[c]Includes respiratory, endocrine pathology, hepatitis B/C infection, pregestational diabetes, psychiatric, cardiac pathology, HIV infection, nephrotic syndrome, lupus, HELLP syndrome, hepatic failure, obesity, H1N1 infection, syphilis, multiple sclerosis, polytraumatized, myotonic dystrophia.
[d]Includes prepartum coagulopathy, thrombocytopenia, LMWH treatment, von Willebrand, aplastic anemia, thalassemia.
[e]Includes previous DVT, FV Leiden, Family DVT.
[f]Although Jehovah's witness patients refused transfusion, they are included as transfusion was recommended by the anesthesiologist.
[g]Includes placenta previa, provoked abortion, curettages, APP (previous tocolytic therapy), conization, chorioamnionitis, cervical cancer.

Table 2. Delivery and Hemorrhage Characteristics.

Variable	Number of Patients Variable Recorded	Number (%)
Controlled pregnancy[a]	351	232 (92)
Start of labor	329	
Spontaneous		236 (72)
Induced		93 (28)
Elective cesarean scheduled	340	5 (1)
Emergency cesarean performed	340	167 (49)
Eutocic delivery[b]	340	101 (30)
Instrumental delivery	340	77 (23)
Intrapartum oxytocin[c]	218	91 (42)
Primary cause of hemorrhage	228	
Atony		68 (30)
Vaginal tears		46 (20)
Placental abruption		16 (7)
Retained placenta		45 (20)
Placenta previa		15 (7)
Placenta accreta		15 (7)
Uterine rupture		13 (6)
Other[d]		10 (4)

Abbreviations: DIC, disseminated intravascular coagulation; IQR, interquartile range.
[a]Defined as women who attended prenatal clinic on a regular basis.
[b]Defined as delivery in the delivery suite without additional obstetric help, for example, forceps, vacuum, and so on.
[c]Defined as oxytocin use during labor for labor augmentation or induction.
[d]Includes uterine inversion, wall hematoma, DIC, gastric ulcer.

8.2–35.2) % posthemorrhage, and 27.9 (3.3, 20.7-39.2) % following therapy; platelet levels were 225 (80, 15-484) c/mL before labor, 153 (73, 5-489) c/mL posthemorrhage, and 154 (70, 41-766) c/mL following therapy; fibrinogen levels were 555 (146, 126-1000) mg/dL before labor, 327 (127, 80-756) mg/dL posthemorrhage, and 440 (140, 151-945) mg/dL following therapy.

Evolution of PPH to Severe PPH

A total of 124 (35%) women experienced severe PPH (requiring ≥5 units pRBC). The key clinical outcomes for patients with severe versus nonsevere PPH are listed in Table 4. The results indicate that severe PPH is more likely to require a change from regional to general anesthesia and is associated with a more than 8-fold increase in patients requiring embolization as well as a more than 5-fold increase in the incidence of hysterectomy. Patients with severe PPH also had a 50% longer median stay in the ICU (36 [24-58] hours vs 24 [12-30] hours in the nonsevere PPH group). Before labor, mean (median, range) values for fibrinogen levels in all parturients were 555 (554, 126-1000) mg/dL and 568 (561, 204-1000) mg/dL and 527 (547, 126-952) mg/dL in patients with nonsevere and severe PPH, respectively.

Analyses were carried out to identify any prepartum risk factors linked to the evolution of severe PPH. A univariate analysis was performed to identify prepartum variables associated with increased odds of severe PPH (Table 5). A 5-year

colloid and/or crystalloids administered and the occurrence of renal failure was examined, and no relationship was found. Coagulation parameters were recorded just before labor, after hemorrhage (lowest values pre-transfusion), and after hemostatic therapy (Figure 1). The mean (standard deviation, range) values observed were as follows: hemoglobin levels were 11.7 (1.7, 5.9-16.2) g/dL before labor, 6.7 (1.3, 2.9-11.1) g/dL posthemorrhage, and 9.4 (1.1, 7.1-13.1) g/dL following therapy; hematocrit was 35.1 (4.8, 3.6-49.3) % before labor, 19.8 (3.7,

Table 3. Volume Replacement, Transfusions, and Hemostatic Therapies Administered.

	Median (IQR) or Number (%)	
Therapy Administered	All patients With PPH (N = 352)	Patients With Severe PPH (N = 124)
Crystalloid (Ringer's solution)		
Patients treated	290 (82%)	102 (82%)
Volume administered, mL	1500 (1000, 2500)	2000 (1500, 4000)
Colloid (HES: hydroxyethyl starch)		
Patients treated	250 (71%)	95 (77%)
Volume administered, mL	1000 (500, 1000)	1000 (500, 1500)
pRBC		
Patients treated	346 (98%)	124 (100%)
Dose administered, units	4 (2, 6)	8 (6, 11)
FFP		
Patients treated	173 (49%)	119 (96%)
Dose administered, units	4 (3.5, 6)	6 (4, 7.5)
Platelets		
Patients treated	106 (30%)	83 (67%)
Dose administered, units	2 (1, 3)	2 (1, 3)
Fibrinogen concentrate		
Patients treated	196 (56%)	115 (93%)
Dose administered, g	4 (3, 4)	4 (4, 6)
Tranexamic acid		
Patients treated	6 (2%)	3 (2%)
Dose administered, g	1 (1, 5.5)	1 (1, 2.5)
4-factor PCC		
Patients treated	36 (10%)	31 (25%)
Dose administered, units	1500 (1000, 1500)	1500 (1000, 1500)
rFVIIa		
Patients treated	29 (8%)	28 (23%)
Dose administered, mg	4.8 (4.0, 6.0)	4.8 (4.0, 6.0)

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; N, number of patients with data available; PCC, prothrombin complex concentrate; PP, postpartum hemorrhage; pRBC, packed red blood cells; rFVIIa, activated recombinant factor VII.

increase in age was associated with a 29% increased odds ratio for severe PPH, obstetric comorbidity was associated with a 2.4 times greater odds ratio of severe PPH, and coagulation diagnosed as "abnormal" increased the odds ratio of severe PPH by 2.8-fold. Conversely, a 50 mg/dL increase in fibrinogen level resulted in a 10% reduction in the odds ratio of severe PPH.

Multivariate analyses were also performed (Table 6). In each case, age and obstetric comorbidity were still significant independent predictors for evolution of PPH to severe PPH. Plasma fibrinogen concentration directly before labor also remained associated with severe PPH. However, abnormal coagulation was not independently associated with severe PPH.

Discussion

In this study, we have presented our experience with 352 cases of PPH, including 124 cases of severe PPH. Hemostasis was restored in all cases and 99.4% of patients survived. Our therapeutic approach combined standard transfusion practice and coagulation factor concentrate-based therapy. This may have improved the appropriateness of therapy received by each patient and possibly explains the correction of hemostatic parameters observed posttherapy. However, new algorithms for the effective management of PPH are under development, and it is critical that these algorithms are widely tested, reported, disseminated, and applied in order to ensure the most appropriate standardized practice.[14]

In our study, a small number of patients received tranexamic acid (TXA); however, TXA was only introduced to our protocol in 2011, although it was occasionally administered prior to this date at the hematologist's discretion. Mounting evidence suggests that TXA is useful for prevention and treatment of PPH,[20-22] and a global, multicenter, randomized, controlled trial (the WOMAN trial) is underway to test the effects of TXA on mortality and incidence of hysterectomy due to PPH.[23]

One-third of all cases evolved to severe PPH, which was associated with a significantly higher rate of complications. Several of these complications (eg, use of general anesthesia) carry additional risks for the patient as well as incurring significant hospital costs. Additionally, hysterectomy means the absolute loss of reproductive potential as well as being a major surgical intervention. As such, the early identification and treatment of women at risk of severe PPH may help minimize the economic and psychological/socioeconomic costs associated with severe PPH.

The results of this retrospective analysis helped us identify risk factors that may be used in the prepartum period to recognize patients at risk of evolution of PPH to severe PPH. Interestingly, some well-established risk factors for PPH, including high parity, multiple births, previous cesarean section, and anemia, were not significantly associated with the evolution of PPH to severe PPH. The major risk factor for severe PPH was the presence of an obstetric comorbidity; the most common prepartum obstetric comorbidities in our population were dead fetus, myoma, placenta previa, medically induced abortion, and history of curettages in prior pregnancy. Physicians managing patients with these conditions should prepare for rapid deterioration of PPH to severe PPH and the need for intervention to prevent hysterectomy. Age was the next factor most strongly associated with severe PPH. As the average age of parturients is increasing, the proportion of PPH episodes that evolve to severe PPH may also increase.

Our findings build upon previous studies showing that low prepartum fibrinogen is associated with increased incidence of PPH, and low fibrinogen during PPH is associated with evolution to severe PPH. The association of reduced levels of fibrinogen with PPH severity indicates that fibrinogen replacement therapy may be a suitable addition to PPH management. Data are limited, but fibrinogen concentrate (in conjunction with other therapies) has been used as an effective therapy for controlling PPH associated with low fibrinogen levels.[24,25] A trial is ongoing to evaluate whether early treatment with fibrinogen concentrate reduces the need for blood transfusion in women with severe PPH,[26] and
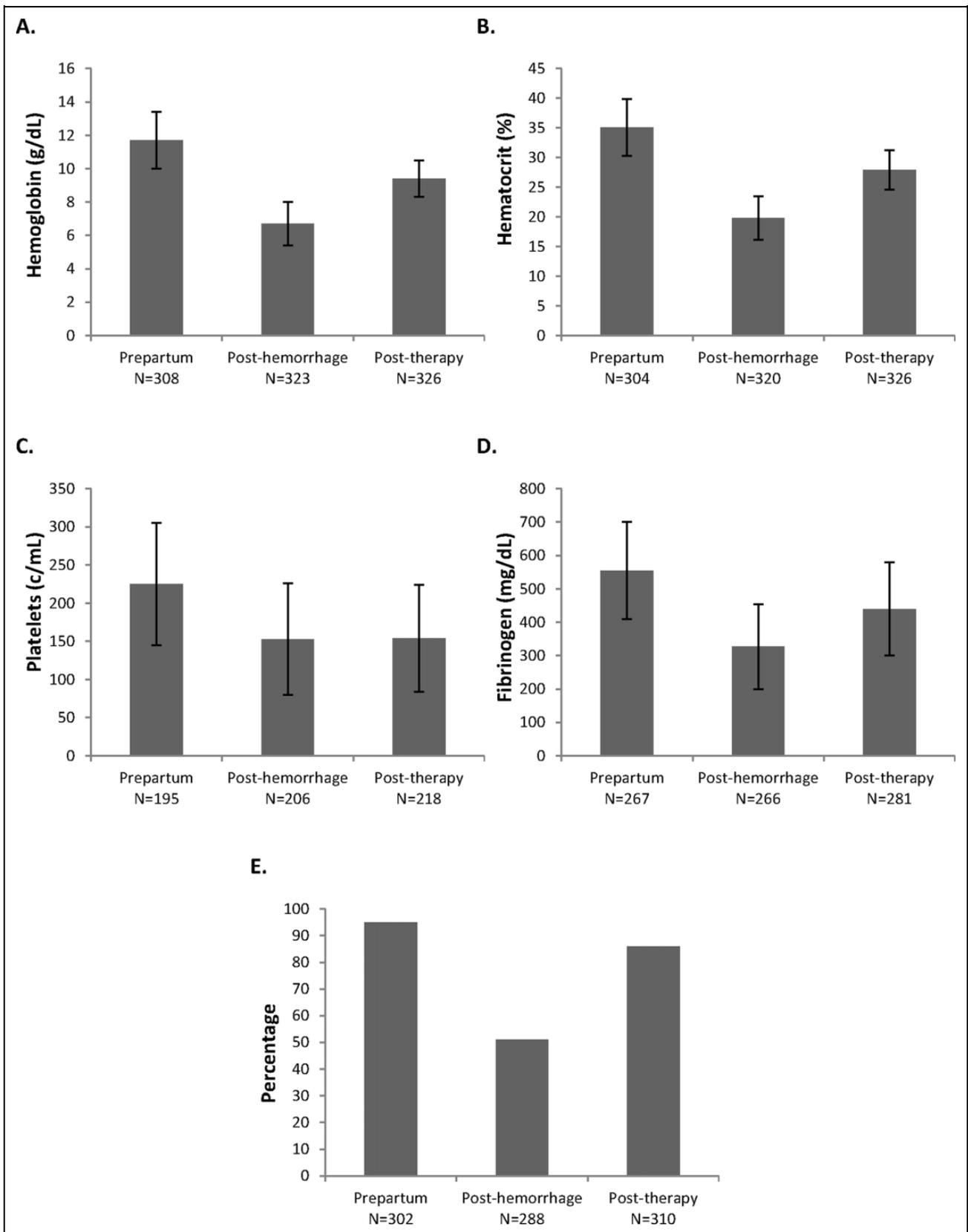
Figure 1. Hematology and coagulation variables: Mean levels of (A) hemoglobin, (B) hematocrit, (C) platelets, and (D) fibrinogen and (E) percentage of patients with normal coagulation[a]. [a]Normal coagulation defined as INR $\leq$ 1.5 and aPTT <1.5 times normal; N, number of patients with data available. aPTT indicates activated partial thromboplastin time; INR, international normalized ratio; N, number of patients with data available.

Table 4. Outcomes Observed in Patients With Nonsevere Versus Severe PPH.

Variable	Nonsevere PPH, < 5 units pRBC (N = 228)	Severe PPH, ≥5 units pRBC (N = 124)	P Value
Change from regional to general anesthetic, n (%)	12 (5%)	28 (23%)	<.001
Embolization, n (%)	6 (3%)	32 (26%)	<.001
Hysterectomy, n (%)	18 (8%)	52 (42%)	<.001
Tracheal intubation[a], n (%)	5 (2%)	44 (35%)	<.001
Time in ICU, hours; median (IQR)	24 (12–30)	36 (24-58)	<.001
Postoperative complications, n (%)			
Free from complications	191 (84%)	76 (61%)	<.001
Any complications	37 (16%)	48 (39%)	<.001
Acute pulmonary edema	5 (2%)	12 (10%)	.003
Acute kidney failure	9 (4%)	17 (14%)	.001
Acute myocardial ischemia or infarction	3 (1%)	15 (12%)	<.001
Others (including urinary injury)	25 (11%)	38 (31%)	<.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range; N, number of patients with data available; PPH, postpartum hemorrhage; pRBC, packed red blood cells.
[a]Defined as postoperative ventilation.

Table 5. Univariate Analysis of Effects of Baseline Characteristics on Evolution of Severe PPH (≥ 5units pRBC).[a]

Variable	N	Category	Severe PPH, n (%)	Odds Ratio (95% CI)	P Value
Age, years[b]	348	–	–	1.29 (1.07-1.57)	**.009**
BMI[b]	315	–		0.82 (0.62-1.09)	.17
Ethnicity	226	White	45/115 (39%)	1	.15
		Hispanic	14/58 (24%)	0.49 (0.24-1.01)	
		Other	19/53 (36%)	0.87 (0.44-1.71)	
Parity	348	1	55/178 (31%)	1	.10
		2	35/97 (36%)	1.26 (0.75-2.13)	
		3+	33/73 (45%)	1.85 (1.05-3.23)	
Multiple births	352	No	110/314 (35%)	1	.83
		Yes	14/38 (37%)	1.08 (0.54-2.18)	
IVF	350	No	108/316 (34%)	1	.42
		Yes	14/34 (41%)	1.35 (0.66-2.77)	
Previous CS	352	No	100/288 (35%)	1	.67
		Yes	24/64 (38%)	1.13 (0.64-2.00)	
Hypertension	351	No	100/293 (34%)	1	.42
		Yes	23/58 (40%)	1.27 (0.71-2.26)	
Other medical comorbidity	351	No	84/244 (34%)	1	.72
		Yes	39/107 (36%)	1.09 (0.68-1.76)	
Hematological comorbidity	351	No	116/323 (36%)	1	.44
		Yes	8/28 (29%)	0.71 (0.30-1.37)	
Obstetric comorbidity	352	No	84/274 (31%)	1	**.001**
		Yes	40/78 (51%)	2.38 (1.43-3.98)	
Hemoglobin, g/dL	308	–	–	1.00 (0.87-1.15)	.99
Hematocrit, %[b]	304	–	–	1.00 (0.78-1.28)	.97
Platelets, c/mL[c]	195	–	–	0.91 (0.75-1.11)	.36
Fibrinogen, mg/dL[c]	267	–	–	0.90 (0.83-0.99)	**.03**
Coagulation	302	Normal[d]	91/286 (32%)	1	
		Abnormal[d]	9/16 (56%)	2.76 (0.99-7.63)	.05

Abbreviations: aPTT, activated partial thromboplastin time; BMI, body mass index; CI, confidence interval; CS, cesarean section; INR, international normalized ratio; IVF, in vitro fertilization; N, number of patients with data available; PPH, postpartum hemorrhage; pRBC, packed red blood cells.
[a]P values in bold indicate statistically significant values.
[b]Odds ratios given for a 5-unit increase in explanatory variable.
[c]Odds ratios given for a 50-unit increase in explanatory variable.
[d]Normal, INR ≤1.5 and aPTT <1.5 times normal; abnormal, INR >1.5 and aPTT ≥1.5 times normal.

fibrinogen replacement has been recommended as an early intervention for the control of PPH associated with amniotic fluid embolism.[27]

Low fibrinogen concentration directly before labor is the only independent risk factor that we identified for severe PPH that is readily modifiable indicating that early, targeted

Table 6. Multivariable Analyses of Effects of Baseline Characteristics on Evolution of Severe PPH ($\geq$ 5 units pRBC).

Variable	Category	Odds Ratio (95% CI)	P Value
Model 1 (n = 348)			
Age[a]	–	1.28 (1.05-1.56)	.01
Obstetric comorbidity	No	1	
	Yes	2.29 (1.36-3.87)	.002
Model 2 (n = 264)			
Age[a]	–	1.42 (1.11-1.81)	.005
Obstetric comorbidity	No	1	
	Yes	2.56 (1.36-4.82)	.002
Fibrinogen, mg/dL[b]	–	0.91 (0.83-1.00)	.05

Abbreviations: PPH, postpartum hemorrhage; pRBC, packed red blood cells; Ci, confidence interval.
[a]Odds ratios given for a 5-unit increase in explanatory variable.
[b]Odds ratios given for a 50-unit increase in explanatory variable.

fibrinogen replacement therapy may be warranted during severe PPH. Consistent with this, our data show a transfusion pattern in which fibrinogen concentrate is frequently administered during severe PPH. Fibrinogen concentrate was the only available option that could elevate mean fibrinogen levels from 3.3 g/L to 4.4 g/L as observed in our population. As the fibrinogen content of FFP is only $\sim$2 g/L, it would not be suitable to bring about this increase. Cryoprecipitate could be considered as an alternative to increase fibrinogen concentration in this setting, but it was withdrawn from most European countries due to safety considerations.[28]

There are some limitations to this study: the findings are subject to the constraints typically associated with retrospective data analyses, in particular the fact that full data were not available for all patients. For example, we only had fibrinogen data for 267 patients, representing 76% of the total study population. In addition, none of the analyses were prespecified, so a sample size calculation was not performed to assess the statistical power of the study. Moreover, many of the comparative analyses showed striking between-group differences with highly significant *P* values. Generalizability of the findings is also uncertain, given that our hospital is a tertiary referral center, so may receive more serious cases of PPH compared with other hospitals. Additionally, it should be noted that we did not do a precise quantification of the amount of bleeding in our patients with PPH.

In conclusion, our data describe successful management of PPH in a tertiary hospital. Over 99% of the patients with PPH survived. In our setting, the application of a multidisciplinary protocol with early administration of fibrinogen and FFP was useful in the absence of point-of-care viscoelastic measurements such as thromboelastometry or thrombelastography. Protocols or guidelines for high-risk parturients are important in this field, and plasma fibrinogen concentration directly before labor was the only modifiable prepartum risk factor independently associated with severe PPH. However, further study of peripartum plasma fibrinogen levels is needed to examine the role of fibrinogen. Close peripartum monitoring of fibrinogen levels (or fibrin-based clotting) is warranted in line with the 2013 European Society of Anaesthesiology guidelines,[8] especially in older parturients with obstetric comorbidities, as the results indicate that these patients are at risk of severe PPH.

References

1. Gayat E, Resche-Rigon M, Morel O, et al. Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. *Intensive Care Med*. 2011;37(11): 1816-1825.
2. Zeeman GG. Obstetric critical care: a blueprint for improved outcomes. *Crit Care Med*. 2006;34(9 suppl):S208-S214.
3. Zhang WH, Alexander S, Bouvier-Colle MH, et al. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. *BJOG*. 2005; 112(1):89-96.
4. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367(9516):1066-1074.
5. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. *Am J Obstet Gynecol*. 2010;202(4):353. e351-e356.
6. Joseph KS, Rouleau J, Kramer MS, et al. Investigation of an increase in postpartum haemorrhage in Canada. *BJOG*. 2007; 114(6):751-759.
7. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy Childbirth*. 2009;9:55.
8. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270-382.
9. Fuller AJ, Bucklin BA. Blood product replacement for postpartum hemorrhage. *Clin Obstet Gynecol*. 2010;53(1):196-208.

10. World Health Organization. *WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage*. Geneva: World Health Organization; 2012.

11. Royal College of Obstetricians Gynaecologists. *Prevention and Management of Postpartum Haemorrhage*. London, UK: Royal College of Obstetricians Gynaecologists; 2011.

12. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ*. 2001; 322(7294):1089-1093; discussion 1093-1084.

13. Wise A, Clark V. Strategies to manage major obstetric haemorrhage. *Curr Opin Anaesthesiol*. 2008;21(3):281-287.

14. Devine PC. Obstetric hemorrhage. *Semin Perinatol* 2009;33(2): 76-81.

15. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost*. 2007;5(1):266-273.

16. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth*. 2012;108(6):984-989.

17. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. *Int J Obstet Anesth*. 2011;20(2):135-141.

18. Peyvandi F, Biguzzi E, Franchi F, et al. Elevated prepartum fibrinogen levels are not associated with a reduced risk of postpartum hemorrhage. *J Thromb Haemost*. 2012;10(7):1451-1453.

19. Guasch E, Viejo A, Martínez B, et al. Hemorragia masiva obstétrica. Protocolo de actuación del Hospital Maternal Universitario La Paz. *Act Anest Reanim (Madrid)*. 2006;16(2):78-83.

20. Ducloy-Bouthors AS, Jude B, Duhamel A, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. *Crit Care*. 2011;15(2):R117.

21. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev*. 2010;(7): CD007872.

22. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. *Expert Opin Pharmacother*. 2011;12(4):503-516.

23. Shakur H, Elbourne D, Gulmezoglu M, et al. The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial. *Trials*. 2010;11:40.

24. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. *Int J Obstet Anesth*. 2010;19(2):218-223.

25. Glover NJ, Collis RE, Collins P. Fibrinogen concentrate use during major obstetric haemorrhage. *Anaesthesia*. 2010;65(12):1229-1230.

26. Wikkelsoe AJ, Afshari A, Stensballe J, et al. The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials*. 2012;13:110.

27. Annecke T, Geisenberger T, Kurzl R, Penning R, Heindl B. Algorithm-based coagulation management of catastrophic amniotic fluid embolism. *Blood Coagul Fibrinolysis*. 2010;21(1): 95-100.

28. Sorensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol*. 2010;149(6):834-843.