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Factors Affecting Blood and Blood Product Replacement in Patients Admitted to the Intensive Care Unit due to Postpartum Hemorrhage

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Abstract

Objective: In this study, we aimed to determine the factors affecting the blood and blood product replacement by examining patients who were admitted to the intensive care unit due to postpartum hemorrhage.

Material and methods: The present study was conducted by retrospective analysis of 374 patients' records who were admitted to the intensive care unit due to postpartum hemorrhage. Patients were divided into two groups: those who were not transfused with blood and blood product (Group 1) and those who were transfused (Group 2). The groups were compared in terms of age, blood type, comorbidities, gravidity, parity, gestational age, type of delivery, the status of the fetus, hemoglobin levels, hematocrit levels, platelet levels, and duration of stay in the intensive care unit.

Findings: There was no need for replacement in 169 patients (Group 1) while 205 patients received a replacement (Group 2). Patients' hemoglobin and hematocrit levels in Group 2 were lower than those of Group 1 (p values, respectively: <0.001, <0.001). The mean duration of stay in the intensive care unit for the patients in Group 2 was found to be significantly higher than those in Group 1 (p<0.001). Patients who had comorbidity (p=0.009) and patients who developed postpartum hemorrhage after vaginal delivery (p<0.001) were found to receive more blood and blood product replacement. Patients who underwent caesarean delivery under general anesthesia received more blood and/or blood products replacement (p=0.017). Patients admitted to the intensive care unit due to placental abnormalities, placental abruption, and uterine rupture required more blood and/or blood products replacement (p=0.01).

Conclusion: Patients who had low hemoglobin and hematocrit levels, comorbid diseases (such as anemia), vaginal delivery, caesarean delivery under general anesthesia, placental abnormalities, placental abruption, and uterine rupture require more blood and blood product replacement.

Keywords: Postpartum hemorrhage; Blood transfusion; Intensive care units

Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality in low income countries and affects approximately 2% of all women giving birth [1]. PPH is the leading cause of maternal mortality worldwide as well. It is a serious condition affecting mother's health due to excessive blood loss which may lead to shock, organ dysfunctions, disseminated intravascular coagulation (DIC) and long-term problems [1-3]. Many risk factors have been identified for PPH including advanced maternal age, the presence of a history of postpartum hemorrhage, multiple pregnancies, anemia, macrosomia, labor induction, intra-uterine fetal death, operative vaginal deliveries, and emergency cesarean delivery [4-7]. Although many risk factors have been identified in this patient group, unexpected, sudden and very severe bleeding may occur in some patients. Therefore, follow-up and treatment of this patient group are very important in terms of maternal morbidity and mortality.

An emergency and multidisciplinary approach is essential for patients with postpartum hemorrhage. In case of bleeding, emergency surgical intervention, application of medical treatments (administration of uterotonics and prohemostatic agents) and rapid supply and replacement of necessary blood and blood products are important steps in treatment [3]. The surgical approach includes arterial ligation, uterine balloon tamponade, and hysterectomy in case of unpreventable bleeding [3]. The World Health Organization (WHO) stated that, among the medical therapies, the use of oxytocin should be the first choice in the third stage of labor for prevention of PPH in all women giving birth [1]. Other uterotonic agents other than oxytocin are ergometrine, methergine, misoprostol (PGE1), PGE2 and 15-methyl-PGF2 [8,9]. Tranexamic acid and recombinant active factor VII (rFVIIa) are used as hemostatic drugs in difficult hemorrhages that do not respond to treatment to reduce blood loss [3].

In addition to the treatments mentioned above, transfusion of blood and blood products in patients with PPH is one of the

most substantial steps of treatment. Protocols on obstetric hemorrhages do not include high quality data on transfusion. The existing protocols are mostly based on the recommendations from trauma studies [7].

In our study, the patients admitted due to PPH were examined. We aimed to determine the factors affecting blood transfusion in this patient group by comparing the patients who were given blood and blood products and the patients who were not given. Thus, in order to determine the required transfusion level for patients, we aimed to contribute to the formation of proper treatment protocols for these patients.

Materials and Methods

After the approval of the ethics committee, the records of 396 patients who were admitted to the intensive care unit (ICU) of the anesthesia department in our hospital due to PPH between 01.01.2017-01.01.2019 were retrospectively reviewed. 22 patients who did not have sufficient information in the hospital registry system were excluded from the study.

Age, blood type, comorbidities, gravidity, parity, gestational age, type of delivery, the status of the fetus, hemoglobin, hematocrit, platelet values, amount of blood and blood products needed, and the duration of stay in the intensive care unit were recorded.

In addition, indications for patients who underwent cesarean delivery, the type of anesthesia applied to these patients and emergency or elective operation were recorded. The patients were divided into two groups as those who were not provided with blood and blood product replacement (Group 1) and those who were provided (Group 2).

SPSS 16.0 for Windows was used for statistical analysis. Statistically, numerical data was expressed in the form of mean and standard deviation while categorical data was expressed in the form of frequency and percentage. Kolmogorov-Smirnov test was used to determine whether non-categorical data follows the normal distribution. Student-t-test was used to compare the data following the normal distribution. The Mann-Whitney U test was used to compare the data that did not follow the normal distribution, and the results were expressed as Median ± Minimum-Maximum. The comparison of categorical data obtained from groups was performed by chi-square test and the results were expressed as % n. $p<0.05$ was considered significant in all comparisons.

Results

Over the course of study, it was found that 396 patients were followed up in our intensive care due to PPH. Since there was insufficient data for 22 of these patients, the study was completed by examining the remaining 374 patients' data. It was determined that 10 of the patients were referred to an external center due to the need for advanced intensive care follow-up and the rate of referral to an external center was 2.52%. Maternal mortality rate was found to be 0.252%. The only exitus was in a patient who had no pre-pregnancy follow-up, had a primipara, had excessively bleeding after normal delivery, and had a severe replacement and this patient was transferred to an external center. Intra-uterine fetal deaths were present in 23 (6.1%) of the patients. The patients' demographic data were given in **Table 1**. The patient who stayed in the ICU for the longest was followed for 14 days because of HELLP syndrome and then transfer to the obstetric clinic.

Table 1 Basic characteristics of the patients and laboratory values (Mean ± SD[1], Min-Max[2]).

Features and laboratory values	Mean ± SD	Min-Max
Age (years)	28.9 ± 6.68	16-47
Gravidity (times)	3.23 ± 1.96	1-13
Parity (times)	2.77 ± 1.65	0-9
Gestational week at delivery (weeks)	35.8 ± 4.38	24-42
Hemoglobin (mg/dl)	8.69 ± 1.89	3.2-14
Hematocrit (%)	27.06 ± 5.53	9.2-42.3
Platelet count (× 10^9/L)	189.9 ± 81.15	11-485
Days in intensive care unit	1.88 ± 1.01	1-14
[1]Mean ± Standard Deviation; [2]Minimum-Maximum values		

63 of the patients (16.84%) had comorbidity. The most common comorbidity was anemia (39 patients). 94 (25.1%) of the patients had PPH after vaginal delivery, and 280 of them (74.9%) had postpartum hemorrhage after cesarean delivery. The most common indication for cesarean delivery was found to be recurring cesarean delivery (**Figure 1**) with a rate of 28.2% (79 patients). Among the patients who had a cesarean delivery, 252 patients (90%) were under spinal anesthesia and 28 patients (10%) were under general anesthesia. In 216 patients, PPH occurred after emergency caesarean surgery while it occurred after elective cesarean surgery in 64 patients (**Table 2**).

Patients were divided into two groups according to whether they were provided with blood and blood product replacement. During the follow-up in the intensive care unit, 169 patients did not need replacement (Group 1) and 205 patients received a replacement (Group 2). Patients in Group 2 were administered an average of 2.54 ± 1.53 units of erythrocyte suspension (RBC), 1.48 ± 1.64 units of fresh frozen plasma (FFP), 0.23 ± 0.96 units of apheresis platelets, and 0.02 ± 0.24 units of whole blood (**Table 2**). In addition to blood and blood products, 46 patients were administered tranexamic acid and 37 patients transfused with fibrinogen. 5 of the patients underwent surgical intervention used uterine balloon tamponade and 5 of them had a hysterectomy.

The groups were compared in terms of age, blood groups, Rh factor, comorbidity, gravidity, parity, gestational age, type of delivery, indications in those who had caesarean delivery, type of anesthesia and surgery (emergency or elective), status of fetus, hemoglobin levels, hematocrit levels, platelet levels, and

transfused blood and blood products. The results are shown in **Table 2**.

Table 2 Comparison of the groups in terms of basic clinical features, laboratory values and length of stay in intensive care unit (Mean SD[1], n, %).

Features and laboratory values	Group 1 (n=169) Mean ± SD	Group 2 (n=205) Mean ± SD	p[2]
Age (years)	29.59 ± 6.68	28.40 ± 6.65	0.084
Gravidity (times)	3.36 ± 2.03	3.13 ± 1.89	0.325
Parity (times)	2.85 ± 1.68	2.71 ± 1.63	0.480
Gestational week at delivery	35.49 ± 4.21	36.09 ± 4.51	0.033
Hemoglobin (mg/dl)	9.87 ± 1.39	7.73 ± 1.701	<0.001
Hematocrit (%)	31.26 ± 12.27	24.40 ± 5.1	<0.001
Platelet count (× 109/L)	189.00 ± 63.35	190.64 ± 93.46	0.846
PRBC3 units(n)	--	2.54 ± 1.53	--
FFP4 units (n)	--	1.48 ± 1.64	--
Platelet transfusion units (n)	--	0.23 ± 0.96	--
Whole blood units (n)	--	0.02 ± 0.24	--
Days in intensive care unit	1.65 ± 0.61	2.08 ± 1.22	<0.001
Features	n (%)	n (%)	p[5]
Blood group			
A	68 (40.2)	88 (42.9)	0.117
B	37 (21.9)	42 (20.5)	
AB	19 (11.3)	10 (4.9)	
0	45 (26.6)	65 (31.7)	
Rh factor			
(+)	150 (88.8)	180 (87.8)	0.776
(-)	19 (11.2)	25 (12.2)	
Comorbidity			
(-)	150 (88.8)	161 (78.5)	0.009
(+)	19 (11.2)	44 (21.5)	
Delivery mode			
Vaginal	19 (11.2)	75 (36.6)	<0.001
Caesarean section	150 (88.8)	130 (63.4)	
Anesthesia			
Regional (Spinal)	141 (94)	111 (85.4)	0.017
General	9 (6)	19 (14.6)	
Mode of cesarean delivery			
Emergency	112 (74.7)	104 (80)	0.289
Elective	38 (25.3)	26 (20)	
Fetal situation			

Live	159 (94.1)	192 (93.7)	0.865
Exitus	10 (5.9)	13 (6.3)	
Total	169 (100)	205 (100)	
1: Mean ± Standard Deviation; 2: Mann Whitney U test result p value; 3: Packed red blood cells; 4: Fresh frozen plasma; 5: Chi-square test result p value			

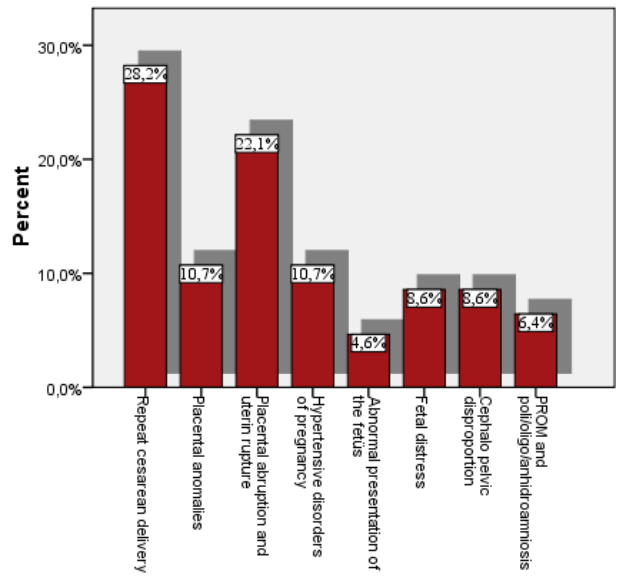

Figure 1 Indications for caesarean section; PROM: Premature rupture of membranes.

Hemoglobin and hematocrit levels of the patients in Group 2 were lower than those of Group 1 (p values: <0.001, <0.001).

The mean gestational age of the patients in Group 2 was higher than Group 1 (p=0.033). The mean duration of stay in the intensive care unit for the patients in Group 2 was found to be significantly higher than Group 1 (p <0.001).

When the patients in the groups were compared in terms of comorbidity and type of delivery, the patients who had comorbidity (p=0.009) and patients who developed PPH after vaginal delivery (p <0.001) were found to receive more blood and blood product replacement.

When the patients, who were admitted to the ICU due to PPH after cesarean delivery, were examined in terms of the type of anesthesia and surgery (emergency or elective), it has been found that patients under general anesthesia had received more blood and blood product replacement (p= 0.017). However, no difference was found between the groups in terms of the type of surgery (p>0.05).

When the patients were examined according to the indications for cesarean delivery, it was found that the patients admitted to the intensive care unit due to placental abnormalities, placental abruption, and uterine rupture required more blood and blood product replacement (p=0.01) (**Table 3**).

Table 3 Comparison of the groups according to the cesarean indications (n, %)

Indications	**Group 1**	**Group 2**	**p**[1]
Repeat cesarean delivery	49 (32.7)	30 (23.1)	0.01
Placental anomalies	12 (21.9)	18 (13.8)	
Placental abruption and uterin rupture	24 (16)	38 (29.2)	
Hypertensive disorders of pregnancy	12 (8)	18 (13.8)	
Abnormal presentation of the fetüs	9 (6)	4 (3.1)	
Fetal distress	15 (10)	9 (6.9)	
Cephalo pelvic disproportion	16 (10.7)	8 (6.2)	
PROM[2] and poli/oligo/anhidroamniosis	13 (8.7)	5 (3.8)	
Total	169 (100)	205 (100)	
[1]Chi-square test result p value; [2]Premature rupture of membranes			

Age, gravidity, parity, platelet count, blood group, Rh factor and intra-uterine fetal deaths were found to make no significant difference in terms of a replacement (p>0.05) (**Table 2**).

Discussion

The need for a multidisciplinary approach to the treatment of PPH and the need for close follow-up of the patients in ICU increase the significance of the anesthesiologists involved. This

need shows up mainly during the transfusion of blood and blood products, and the treatment of the coagulopathy process which develops as a result of hemorrhage [10].

In patients with hemorrhage, there are liberal and restrictive blood transfusion approaches. In the literature, there are studies that accept different parameters for these approaches [11]. In the liberal approach, the threshold for hemoglobin level is generally considered to be 10 g/dl, whereas, in restrictive approach, a hemoglobin level of 7 g/dl or anemia symptoms is accepted as a threshold. Some of the studies conducted in different patient groups reported that there was no superiority between the two approaches, while others reported that the restrictive blood transfusion approach was relatively better [11-15]. Apart from these approaches, there are some massive bleeding protocols for patients with PPH [10,16,17]. One of these protocols suggests that 6 units of erythrocyte suspension, 4 units of fresh frozen plasma and 1 unit of platelets should be prepared for these patients and used if necessary, with emphasis on the importance of preparation for blood and blood products in patients with postpartum hemorrhage [10]. In another study, according to the severity of PPH, transfusion is recommended while keeping the hemoglobin concentration above 8 mg/dl [16]. For this purpose, administration of 3 units of erythrocyte suspension in the first stage, and 3 units of erythrocyte suspension together with 3 units of fresh frozen plasma in the second stage is recommended [16]. In our clinic, replacement in patients with PPH is performed by taking the patient's clinical status, vital signs (tachycardia, hypotension etc.), and laboratory test results into consideration so that the hemoglobin level remains above 8 mg/dl. At the same time, erythrocyte suspension is given together with fresh frozen plasma. Our practical application usually has a ratio of 1:2 (FFP: RBC), while there are sources in the literature that recommends a ratio of 1:1 or 1:1.5 as well [2,10,17,18]. It is suggested that this ratio may range from 1:1 to 1:2 according to the level of bleeding and the need for transfusion [2].

In our clinic, the patients without active bleeding are transfused with apheresis platelets for platelet counts below 10×10^9/L. In case of massive bleeding, patients with a platelet count of 50×10^9/L are treated with thrombocyte replacement. In the recommendations of the WHO, it is recommended that platelet count should be kept above 10×10^9/L for prophylaxis in non-bleeding, non-infected patients; above 20×10^9/L in infected patients/patients with fever; in case of acute DIC, it is recommended to be kept above 20×10^9/L in the presence of bleeding and thrombocytopenia; and above 50×10^9/L in patients with massive blood transfusion due to dilution thrombocytopenia [19]. The Royal College of Obstetricians and Gynecologists (RCOG) recommend transfusion at rates below 75×10^9/L during PPH [20].

Tranexamic acid, an antifibrinolytic drug used to reduce bleeding, acts by inhibiting the activation of plasmin [2,9]. On the use of tranexamic acid in PPHs, the WHO has suggested the use of oxytocin and other uterotonics in unstoppable bleedings or when bleeding is thought to be partly due to trauma.1 In some studies, it has been reported that it decreases bleeding-related deaths without causing an increase in thrombotic events [9,17]. The American College of Obstetricians and Gynecologists (ACOG) stated that tranexamic acid could be used as second line treatment in PPHs when the first line treatment with uterotonics yielded no result [9]. In our study, it was determined that 46 patients with ongoing bleeding who did not respond to first-line treatment were given tranexamic acid. No thrombotic complications developed in these patients.

Fibrinogen, which plays a critical role in the maintenance of hemostasis and the formation of clots, is the first decreasing clotting factor in obstetric hemorrhages.2 Due to the strong correlation between low fibrinogen levels and the severity of bleeding, most authorities recommend keeping fibrinogen levels above 150-200 mg/dL [7,9,20]. In our study, 37 patients with fibrinogen levels less than 200 mg/dl received fibrinogen replacement in addition to blood and blood product replacement.

When the literature is reviewed, there are various publications about the patients' admission to the ICU and follow-up of these patients who developed PPH. Krishna et al. followed 15 of 21 patients in the ICU and used blood and blood products in 12 patients who developed DIC. The mean duration of stay in the ICU was 12.6 ± 5.4 days [21]. Incebıyık et al. examined 41 patients with PPH in 3 years and found that the mean duration of stay in the ICU was 0.83 ± 1.11 days. They stated that 85.4% (35 patients) of the patients needed the transfusion [22]. In our study, the mean duration of stay in the ICU 1.88 ± 1.01 days and 54.81% of the patients (205 patients) had blood and blood product replacement. In our study, a lower percentage in patients who need blood and blood product replacement compared to other studies may be due to the characteristics of our ICU and our hospital. The ICU of our hospital is a intensive care unit and only gynecology cases are followed in our ICU. All patients who have PPH risk are followed up in our ICU for close observation and treatment. Therefore, some patients were admitted only for close observation, while some of them were admitted due to massive blood and blood product replacement. The follow-up period of the patients in the ICU who had blood and blood products replacement might last longer than follow up period of the patients who were kept for observation due to the re-evaluation of the replacement and results.

Previous studies have reported that the presence of various comorbidities is a risk factor for PPH [4-7]. It is also highlighted in the manual of RCOG that proper prenatal investigation and treatment of prenatal anemia is required because it could reduce the morbidity associated with PPH [20]. In our study, the majority of patients with comorbidities (61.9%) were composed of patients with anemia. These patients' need for replacement was higher than the patients without comorbidities. Additional bleeding together with the already low hemoglobin levels in these patients may have led to an increased need for blood and blood product replacement.

In our study, patients who had placental abnormalities (Pl. Accreta, Pl. Previa, etc.), placental abruption, and uterine rupture were found to need more blood and blood product

replacement. It is reported in the literature that these complications are the causes of PPH which can cause rare but severe bleeding and need massive transfusions [2,7]. In their study that covered a ten-year period, Hu et al. reported that placental abnormalities were in an increasing trend due to increased cesarean delivery rates. They found that bleeding control was very difficult especially in patients with placenta accreta and these patients had higher hysterectomy rates compared to other patient groups [23].

Limitations

As our study was retrospective, our data was based on the patient records in the hospital registration system and the epicrisis data in the computer system. The lack of data of some patients was the most important factor limiting our study.

Conclusion

According to our findings, 45.19% of the patients who were admitted to the ICU due to PPH were observed to have first-line PPH treatment while 54.81% of them had blood and blood product replacement. Patients with low hemoglobin and hematocrit levels, comorbid diseases such as anemia, vaginal delivery, caesarean delivery under general anesthesia, placental abnormalities, placental abruption, and uterine rupture need more blood and blood product replacement.

Close follow-up of patients with PPH in ICUs, administration of appropriate blood and blood products in addition to medical and surgical treatment in a timely and rapid manner will contribute to the reduction of maternal mortality and morbidity. The important role of PPHs in maternal mortality and morbidity across the globe indicates the need for broader and more comprehensive studies on the subject.

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