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The Role of Plasma Exchange in HELLP Syndrome

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Summary: Plasma exchange therapy has been successfully used in selected patients with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome who have organ failure or refractory to treatment. There is no prospective study regarding plasma exchange and its effect in HELLP syndrome. The aim of this study was to investigate the effects of early postpartum use of plasma exchange in patients with HELLP syndrome on outcomes. The mortality rate and the recovery times were compared in patients with HELLP syndrome treated with plasma exchange and historic control group of patients treated conservatively. During a 3-year period (between April 2000 and December 2003), 29 consecutive patients with HELLP syndrome were treated with single or multiple plasma exchange by using fresh-frozen plasma at post-partum period. The control group consist of 26 patients with HELLP syndrome treated between 1993 and 1999. Maternal mortality rate was 23.1% in the control group; there was no death in plasma exchange group; and the mortality rate was significantly higher in the control group ($p=0.006$). The length of stay at the intensive care unit was shorter in the plasma exchange group ($p<0.0001$). Rapid improvement of the platelet, aspartate aminotransferase, alanine aminotransferase, and lactic dehydrogenase levels were observed in the plasma exchange group. This study showed that postpartum early plasma exchange therapy improves treatment outcomes in patients with severe HELLP syndrome.
Key Words: HELLP syndrome—Plasma exchange—Treatment.

In 1982, Weinstein described a group of preeclamptic women who had hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) (1). It occurs in approximately 0.2% to 0.6% of all pregnancies (2,3). HELLP syndrome has been considered a multisystemic disorder that is characterized by loosening of the normal relationship between the blood vessels and blood (4). Thrombocytopenia is one of the most definitive features of this syndrome. Another feature is microangiopathic hemolytic anemia, which is characterized by reduced hemoglobin levels, and increases in un-conjugated bilirubin and lactic dehydrogenase enzyme activity (LDH) (2). In 1990, Martin and colleagues (5) described three risk categories of HELLP syndrome according to platelet count. Maternal mortality in HELLP syndrome changes between 1% and 25%, and it is usually due to the severity of disease, delayed diagnosis, presence of infection, and acute renal failure (6). Most maternal deaths occur among women with class 1 HELLP syndrome (7). Treatment of HELLP syndrome consists of supportive care, and most of the patients improve with this therapeutic approach. However, some patients may not respond to this treatment. Plasma exchange therapy was successfully used in patients who have organ failure or refractory to treatment. At least according to our knowledge, there is no report regarding the effect of plasma exchange on mortality and progression of disease in HELLP syndrome.

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The aim of this study was to investigate the effects of plasma exchange started within the first 2 postpartum days in patients with HELLP syndrome. We compared mortality rate, complications, and the recovery times in patients with HELLP syndrome treated with plasma exchange and historic control group of patients treated conservatively.

MATERIALS AND METHODS

Study Design

During a 3-year period (between April 2000 and December 2003), 29 consecutive patients with HELLP syndrome were observed in Erciyes University School of Medicine, Medical Intensive Care Unit (ICU). All patients were treated with single or multiple plasma exchange by using fresh-frozen plasma during the postpartum period. The study was approved by the Ethical Committee of Erciyes University School of Medicine, and written informed consent was obtained from the patients or their relatives. Twenty-six patients with HELLP syndrome treated conservatively between 1993 and 1999 were chosen as a control group. HELLP syndrome was defined by the presence of all three of the following criteria: hemolysis (characteristic peripheral blood smear and serum lactate dehydrogenase levels ≥ 600 U/L), serum aspartate aminotransferase levels 70 U/L or greater, and platelet count less than 150,000/μL.

Shortly after delivery, all the patients were admitted to the intensive care unit (ICU) of Erciyes University Hospital until laboratory and clinical evidence of HELLP syndrome improved. To prevent and control seizures, all patients routinely received magnesium sulfate as a 6-g intravenous loading dose followed by 2 g intravenously per hour. Antihypertensive drugs, such as calcium channel blockers and angiotensin-converting enzyme inhibitors, were used in patients with hypertension. All patients were routinely treated with dexamethasone in a dosage of 10 mg every 12 hours until the platelet count was greater than 100,000/μL. Discharge from the ICU was indicated if the vital functions were stable without life support and no longer require monitoring or intensive care treatment, if nursing the patient in the ward was possible, if continuation of the plasma exchange was no longer worthwhile, if the patient no longer consented to the treatment, and if the benefit of a treatment no longer outweighed its negative effects.

The patients' characteristics including age, numbers of pregnancy and abortion, methods of delivery, blood pressure, condition of consciousness, and epileptic attacks were recorded. Additionally, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), phosphorus (P), bilirubins, lactic dehydrogenase (LDH), total protein, albumin, hemoglobin (Hb), leukocyte and platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers, and fibrinogen levels were determined daily and the initial values were used for statistical comparison. The use of blood products such as erythrocytes, platelets, and fresh-frozen plasma were recorded. Patients received platelet concentrates either the patients have had clinically important bleeding or platelet count less than 20,000/μL. Patients who underwent cesarean section also received platelet concentrates if their platelet count was less than 50,000/μL. Fresh frozen plasma or erythrocytes were used to correct coagulation disorders or anemia as needed. Mortality rate, causes of death, complications including renal failure, dialysis requirement, hepatic impairment, disseminated intravascular coagulopathy (DIC), and infections (pregnancy-related or catheter-related), citrate intoxication, or others were noted.

The diagnosis of DIC was based on the association of three criteria among the following: low platelets (<100,000/μL), low fibrinogen (<300 mg/dL), D-dimers (>500 μg/L), or prolonged prothrombin (≥ 14 seconds) and partial thromboplastin (≥ 40 seconds) times. Acute renal failure was defined by a recent decline in creatinine clearance to 20 mL/min or less (8).

Patients were classified as previously described: class 1 HELLP syndrome was defined by a perinatal platelet nadir 50,000/μL or less, class 2 was defined by a perinatal platelet nadir greater than 50,000 but 100,000/μL or less, and class 3 was defined by a perinatal platelet nadir greater than 100,000 but 150,000/μL or less (9).

Plasmapheresis was used to treat all of the class 1 patients. Other patients who had two or more organ failure including DIC, hepatic, or renal failure were also included in the study.

All plasma exchange procedures were performed with Fresenius AS 204 cell separator in the postpartum period. No sooner had sufficient amount of fresh-frozen plasma obtained than plasmapheresis was performed. Plasma exchange procedure was started at the day of delivery in 10 patients, on the first postpartum day in 16 patients and on the second postpartum day in three

patients. One total plasma volume was exchanged daily until platelet count was greater than 100,000/μL and/or normal LDH level (<500 IU) was reached. All adverse effects that developed during plasma exchange were recorded.

Patient charts were also reviewed according to variables described previously in historic control group. Twenty-six of 32 patients were eligible for study.

Statistical Analyses

Maternal complications, mortality rate, and recovery time were the main outcomes in this study. Data are presented as the mean ± SD. Statistical comparisons were performed with independent sample *t* tests and chi-square tests. Patients who died were excluded from comparison of the recovery times and the length of stay at ICU. Survival was shown in Kaplan-Meier curves and the statistical significance was assessed by the log-rank test. A p value less than 0.05 was considered significant.

RESULTS

Characteristics of the Plasma Exchange Group

Vaginal delivery was performed in 17 patients, cesarean section in 11 patients, and one patient underwent total abdominal hysterectomy. Nine patients were primigravid and 20 patients were multigravid. HELLP syndrome developed during the postpartum period in 11 patients (38%). Mean gestational ages were 35.2 ± 4.96 weeks (range; 20–40 weeks). Three patients previously had hypertension. Eleven patients have had preeclampsia or eclampsia. Coagulation test results were consistent with DIC in three patients. Twenty-six patients received red blood cell transfusion, 18 patients received platelets, and 15 patients received additional human plasma. Acute renal failure existed at diagnosis in five patients (17.2%). Other maternal complications were: subcapsular liver hematoma in one patient, intraabdominal abcess in one patient, acute respiratory distress syndrome in one patient, and intraabdominal bleeding in two patients.

Median four apheresis procedure (range: 1–15) were performed. Fresh-frozen plasma was used for replacement. The most common complication was chills in 12 patients (41.4%). Other adverse effects including urticaria (8 patients, 27.6 %), catheter insertion–related hematoma (5 patients, 17.2%), and paresthesias (4 patients, 13.7%) were mild and easily treated.

Characteristics of the Control Group

All information was obtained from patients' charts and/or computer-based records. Gestational ages were between 23 and 40 weeks (mean 34.65 ± 4.83). HELLP syndrome developed at postpartum period in 13 patients (50%). Nine patients were primigravid and 17 multigravid. Vaginal delivery was performed in 17 patients (73.9%), cesarean section in 7 patients (30.5%), and two patients (8.6%) underwent total abdominal hysterectomy. Nine patients previously had hypertension (35%). Nineteen patients (73.1%) had preeclampsia or eclampsia. Three patients had experienced an epileptic attack before hospital admission. Acute renal failure was existed at the time of diagnosis in six patients (23%). Coagulation test results were consistent with DIC in four patients.

Six of 26 patients died within 30 days after diagnosis. The causes of mortality were infection in two patients, acute renal failure in two patients, brain edema in one patient, and adult respiratory distress syndrome (ARDS) in one patient. Mean duration of hospitalization in the ICU was 10.5 days in patients who survived. Eighteen patients received red blood cell transfusion, 22 received fresh-frozen plasma, 13 received platelet concentrates, and two patients received antithrombin-III.

Comparison of Parameters, Complications and Mortality

Mean age and the laboratory parameters including LDH, BUN, Cr, albumin, AST, ALT, bilirubins, Hb levels, the rate of patients who had undergone surgical procedures, and the percentage of class 1 patients were not statistically different in two groups (Table 1). Mean platelet values were lower in the plasmapheresis group than the control group (Table 2).

The maternal mortality rate was 23% (6/26) in the control group; there were no deaths in the plasma exchange group. All deaths were in patients with class 1 disease, and the mortality rate was significantly higher than that in the plasma exchange group (Fig. 1) (p=0.006). Six of 26 patients (23%) in the control group and five of 29 (17%) patients in the plasma exchange group required hemodialysis. Chronic renal failure developed in three (10%) of the plasmapheresis group and four (15%) of the control group patients. However, there were no differences in dialysis requirement and development of renal failure, statistically.

TABLE 1. Patients Classification According to Platelet Count

Classification	Plasmapheresis Group (n=29)	Control Group (n=26)
Class I (platelet count ≤ 50,000/μL)	23 (82.6%)	16 (61.6%)
Class II (platelet count >50,000/μL but ≤ 100,000/μL)	6 (17.4%)	7 (26.9%)
Class III (platelet count >100,000/μL)	0 (0%)	3 (11.5%)

TABLE 2. Basic Characteristics in Patients with HELLP Syndrome

Parameters	Plasmapheresis Group (n=29) (mean ± SD)	Control Group (n=26) (mean ± SD)	p
Platelet count, cells/μL	37.41 ± 22.56	55.31 ± 33.45	0.023
Age (yr)	28.72 ± 5.45	28.08 ± 7.79	NS
Hb, g/dL	8.5 ± 1.49	8.62 ± 1.89	NS
LDH, U/L	4501.83 ± 2726.02	3491.42 ± 2831.28	NS
AST, U/L	846.07 ± 950.62	882.31 ± 659.10	NS
ALT, U/L	340.66 ± 359.74	493.96 ± 480.66	NS
Total bilirubin, mg/dL	5.84 ± 5.43	7.51 ± 7.35	NS
Conjugated bilirubin, mg/dL	4.12 ± 5.24	3.45 ± 4.57	NS
BUN, mg/dL	22.04 ± 10.25	22.62 ± 13.56	NS
Cr, mg/dL	1.31 ± 0.70	1.54 ± 1.36	NS
Albumin g/dL	2.90 ± 0.36	2.72 ± 0.48	NS

NS: None significant.

The length of stay at the ICU was shorter in the plasma exchange group. In addition, platelet, serum AST, ALT, and LDH improvement rapidly occurred in plasma exchange group (Table 3).

DISCUSSION

HELLP syndrome is a disorder that affects many systems and causes maternal and fetal mortality (2,3). The main features of HELLP syndrome include thrombocytopenia, hemolysis and liver dysfunction.

Thrombocytopenia is one of the most important findings of HELLP syndrome, and this parameter is used to classify the severity of disorder (5). It was shown that class 1 patients have higher mortality rates than the other patients (4,10). Another finding is hemolysis characterized by high levels of LDH. Martin and colleagues (5) found that the platelet count and LDH serum concentration, as indicators for severity and recovery of HELLP syndrome, were clinically useful parameters. According to their findings, the median platelet recovery time was 11 days in class 1 patients and 6 days in class 2 patients. Another characteristic finding is the increment in liver enzymes. Some studies reported that liver enzymes were higher in class 1 than class 2 and class 3 patients. However, a significant correlation between liver enzyme levels and liver histology was not shown (11).

It is well known that HELLP syndrome is associated with renal failure. It is one of the most

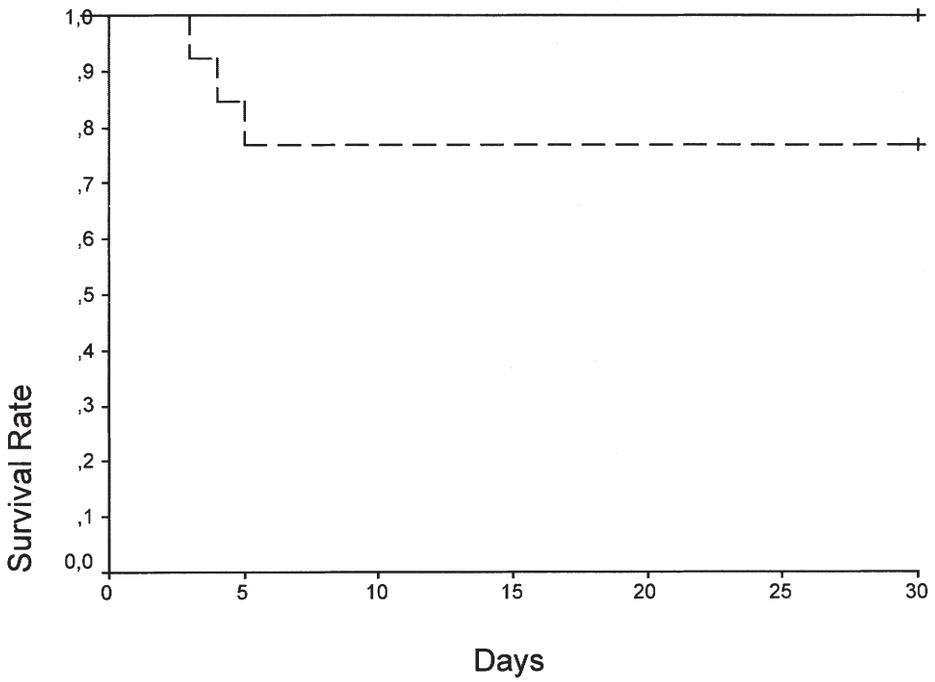


FIG. 1. The mortality rate in the first 30 days was significantly higher in the control group (p = 0.006). —, plasmapheresis group; ----, control group.

TABLE 3. Comparison of the Recovery Times in Two Groups

Time (Day)	Plasmapheresis Group (n=29) (mean ± SD)	Control Group (n=20) (mean ± SD)	p Value
Length of stay at ICU	5.86 ± 4.43	10.55 ± 3.00	0.0001
Platelet recovery time	4.52 ± 2.20	7.00 ± 1.97	0.0001
LDH recovery time	7.48 ± 5.82	11.00 ± 2.99	0.008
AST recovery time	4.04 ± 2.55	6.55 ± 2.82	0.003
ALT recovery time	3.32 ± 2.94	5.80 ± 2.57	0.004

important causes of mortality in these patients (12). In a study, 7.3% of renal failure rate, and 13% of mortality rate were found in patients with HELLP syndrome (6). Martin and colleagues (4) showed a renal failure rate as 1.2% in 777 patients. The incidences of acute renal failure in HELLP syndrome were 3.2% and 7.7% in two different studies (3,13).

In the literature, maternal mortality ranges from 1% to 25%. Martin and colleagues (2) found that maternal mortality was 3.2% in 62 patients with HELLP syndrome. In a large series, consisting of 442 patients, maternal mortality was found 1.1% (13). Another study showed that maternal mortality was 13% in patients with HELLP syndrome and acute renal failure (5).

Mortality rate was found to be 25% in a study had performed in Turkish women with HELLP syndrome (14). These different results may be related to the severity of diseases.

Death was caused by a variety of pathologic conditions. Many of these conditions included hemorrhagic complications, such as intracranial or hepatic hemorrhage and disseminated intravascular coagulopathy. The other major mode of death was a vascular insult to the cardiopulmonary or renal system. Most maternal deaths occur among women with class 1 HELLP syndrome, and delayed diagnosis is associated with mortal consequences. Delayed diagnosis was noted in 51.1% of the maternal deaths in the largest series of the patients (12).

Definitive treatment of HELLP syndrome is controversial. Many therapeutic procedures, including dexametasone, blood products, and magnesium sulfate, had been evaluated. Only a few studies have been reported regarding the use of plasma exchange in HELLP syndrome. In the medical literature, the largest case series reporting the effect of plasma exchange on HELLP syndrome contained 18 patients. That study showed that the postpartum application of plasma exchange therapy was successful for persistent postpartum HELLP syndrome; however, uniformly positive response to this therapy could not be obtained in patients who had additional single or multiple organ injury (15). Most of the other reports are case presentations. Many patients have had organ failure or persistent HELLP syndrome and they had rapid response to plasma exchange therapy (16–19). There are no data regarding the effect of plasma exchange on mortality rate and disease progression in HELLP syndrome.

Plasmapheresis is a therapeutic procedure used for many medical conditions. The main goals of plasmapheresis are the removal of some plasma components, such as antibodies, immune complexes, endogenous and exogenous toxins, and the replacement of some plasma proteins and coagulation factors. During plasmapheresis, colloids, human albumin, and fresh-frozen plasma might be used for the replacement. The mechanism of the effect of plasma exchange in HELLP syndrome is still controversial. HELLP syndrome is a microangiopathic disease and it has similar clinical and laboratory characteristics of thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome. It is possible that plasma exchange removes aggregating and procoagulant factors released from both activated platelets and endothelial cells.

In this study, we reported our intensive care experiences on severe HELLP syndrome. All patients admitted to the ICU for HELLP syndrome treated with supportive care including nutrition, blood products, antihypertensive agents, dialysis, magnesium sulfate, fluid and electrolyte replacement, dexamethasone, and additionally, plasmapheresis was applied in some patients with HELLP syndrome.

Platelet, AST, ALT, and LDH recovery time were found to be shorter in patients treated with plasma exchange. More rapid improvement in platelet count after plasma exchange therapy may be due to decreasing of platelet activation and shortening of thrombotic process. Plasmapheresis may also affect renal functions. In this study, 23% (6/26) of the control group and 17.2% (5/29) of the plasma exchange group presented evidence of renal dysfunction at admission. Although there were no statistical differences, dialysis requirement and development of chronic renal failure were lower in plasma exchange group. It is likely that plasma exchange therapy may improve renal function and shorten the length of stay in the ICU with removing toxic substances. Plasmapheresis may cause some important complications; nevertheless, we did not observe any fatal or infectious complications.

Our results showed that plasma exchange therapy reduced mortality rate in severe HELLP syndrome when performed early. The main causes of mortality were infection, acute renal failure, brain edema, and ARDS in the control group. A longer stay in the ICU may cause infectious complications and ARDS in these patients. Plasma exchange therapy may reduce mortality rate in patients with severe HELLP syndrome by decreasing the rate of renal failure or shortening day of stay at the ICU.

In conclusion, plasma exchange with fresh-frozen plasma may be valuable in patients with severe HELLP syndrome. Plasma exchange may also be considered in patients who are not responding to supportive therapy.

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