Araştırma Makalesi
Research Article

Evaluating the efficacy of therapeutic plasma exchange in the management of HELLP syndrome: A single-center experience

HELLP SENDROMUNUN YÖNETİMİNDE TERAPÖTİK PLAZMA DEĞİŞİMİNİN ETKİNLİĞİNİN DEĞERLENDİRİLMESİ: TEK MERKEZ DENEYİMİ

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ABSTRACT

Introduction and Objectives: HELLP syndrome is a severe pregnancy-related complication characterized by hemolysis, elevated liver enzymes, and low platelet count. Complement dysregulation contributes to the etiopathogenesis of HELLP syndrome. Therapeutic plasma exchange (TPE) removes abnormal complement pathway components and replaces them with normal physiological components. This study aimed to evaluate the impact of TPE on disease progression in HELLP syndrome patients unresponsive to supportive therapy and corticosteroids.

Materials and Methods: This retrospective study involved 13 patients diagnosed with Class 1 HELLP syndrome based on the Mississippi system. These patients underwent TPE in the postpartum period between 2012 and 2015.

Results: Of the thirteen patients, three succumbed to multiorgan failure. After TPE, hemoglobin and platelet counts increased, while AST, ALT, and LDH levels decreased. These changes were statistically significant ($p<0.05$). In patients who died after TPE, the duration between hospital admission and TPE initiation was longer.

Conclusion: TPE is an effective treatment strategy that improves clinical outcomes in patients with complex postpartum HELLP syndrome who do not respond to conservative management. Early diagnosis and the role of TPE in disease management are increasingly important in such cases.

Keywords: HELLP syndrome, Therapeutic plasma exchange (TPE) , Pregnancy-related complication, Complement dysregulation ,Disease management

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ÖZ

HELLP sendromu, hemoliz, yüksek karaciğer enzimleri ve düşük trombosit sayısı ile karakterize, gebelikle ilişkili ciddi bir komplikasyondur. Kompleman düzensizliği, HELLP sendromunun etiyopatogenezine katkıda bulunur. Terapötik plazma değişimi (TPE), anormal kompleman yolu bileşenlerini ortadan kaldırır ve bunları normal fizyolojik bileşenlerle değiştirir. Bu çalışma, destekleyici tedavi ve kortikosteroidlere yanıt vermeyen HELLP sendromlu hastalarda TPE'nin hastalığın ilerlemesi üzerindeki etkisini değerlendirmeyi amaçladı.

Gereç ve Yöntem: Bu retrospektif çalışma, Mississippi sistemine göre Sınıf 1 HELLP sendromu teşhisi konan 13 hastayı içermektedir. Bu hastalara 2012-2015 yılları arasında doğum sonrası dönemde TPE uygulandı. On üç hastadan üçü çoklu organ yetmezliğinden öldü. TPE sonrası hemoglobin ve trombosit sayıları artarken AST, ALT ve LDH seviyeleri azaldı. Bu değişiklikler istatistiksel olarak anlamlıydı ($p<0,05$). TPE sonrası ölen hastalarda hastaneye yatış ile TPE uygulanması arasındaki süre daha uzundu.

Sonuç: TPE, konservatif tedaviye yanıt vermeyen kompleks doğum sonrası HELLP sendromlu hastalarda klinik sonuçları iyileştiren etkili bir tedavi stratejisidir. Bu tür vakalarda erken tanı ve TPE'nin hastalık yönetimindeki rolü giderek önem kazanmaktadır.

Anahtar Kelimeler: HELLP sendromu, terapötik plazma değişimi, klinik sonuçlar

HELLP syndrome, an obstetric complication, is characterized by hemolysis, elevated liver enzyme levels, and low platelet counts. It affects 0.5 to 0.9% of all pregnancies and 10-20% of severe preeclampsia cases (1). Regarded as an extreme form of preeclampsia, HELLP syndrome presents symptoms such as headache, blurred vision, nausea, fatigue, edema, right upper abdominal pain, epistaxis, and seizures. It can lead to fatal consequences, including disseminated intravascular coagulation (DIC), postpartum hemorrhage, acute renal failure, and multiorgan failure (2).

Therapeutic plasma exchange (TPE) is employed in the treatment of various microangiopathies, including postpartum hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Systemic inflammation and complement cascade dysregulation are known to be crucial in the etiopathogenesis of HELLP syndrome (3). Following the discovery that women with mutations in complement regulatory proteins may develop severe preeclampsia (4), TPE has been utilized in treating HELLP syndrome. TPE in HELLP syndrome has been successfully tested and is recommended by the American Society of Apheresis (ASFA) guidelines (5).

This study aims to evaluate the effects of TPE on the progression of HELLP syndrome in patients unresponsive to supportive therapy and corticosteroids.

MATERIALS AND METHODS

Thirteen patients, diagnosed with Class 1 HELLP syndrome as per the Mississippi system, underwent TPE in the postpartum period between 2012 and 2015 at Çukurova University Faculty of Medicine and were included in the study.

All postnatal patients received magnesium sulfate to prevent or treat convulsions. Antihypertensive drugs were administered to patients with blood pressure >140/90 mmHg. All patients were given dexamethasone 10 mg IV every 12 hours to increase platelet count. No patients responded to corticosteroid and supportive treatment during the postnatal period. Consequently, therapeutic plasma exchange was carried out using fresh frozen plasma in single or multiple numbers and a 1:1 volume, based on

clinical and laboratory status. Complications encountered during plasma exchange were documented.

HELLP syndrome diagnostic criteria included hemolysis (abnormal peripheral blood smear, bilirubin level > 1.2 mg/dl, lactate dehydrogenase level > 600 IU/L), elevated liver enzyme levels (SGOT level ≥ 70 IU/L), and a platelet count below 100,000 (6).

Patients' ages were recorded. A complete blood count was conducted to determine hemoglobin and platelet count. Additionally, aspartate aminotransferase (AST), alanine aminotransferase (ALT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen level, D-dimer level, albumin level, LDH, total bilirubin, conjugated bilirubin, uric acid, blood urea nitrogen (BUN), creatinine, and procalcitonin (PCT) levels were assessed. These parameters were recorded in the case report forms. Hemoglobin, platelet, AST, ALT, and LDH values were compared at the time of TPE decision and 24 hours after the completion of TPE.

Statistical Analysis

Categorical measurements were summarized as number and percentage, and numerical measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary). To compare two dependent groups, Wilcoxon signed-rank test was used to determine that the groups were different from each other by looking at the differences between the rankings in the two groups. IBM SPSS Statistics Version 20.0 package programme was used for statistical analysis of the data. Statistical significance level was taken as 0.05 in all tests. SPSS reference: IBMCorp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

A total of 13 patients were included in the study. All patients were class 1 patients according to Mississippi classification. After TPE, platelet count, liver enzyme levels and hemolysis findings rapidly improved in 10 of 13 patients. The mean age and number of TPE performed were higher in the group of patients who deceased after TPE. In the group of patients who deceased after TPE, the time elapsed from the day of admission to the hospital to the day of TPE was longer. The mean hemoglobin and platelet levels were higher in the patient group who recovered after TPE. The mean ALT, AST, total bilirubin, direct bilirubin, LDH, INR, D-dimer, creatinine and procalcitonin levels of the patient group who deceased after TPE were higher than those of the patient group who recovered after TPE. Hemoglobin, platelet count and albumin levels were lower in the patient group who deceased after TPE (Table 1).

Table 1: Characteristics of patients who recovered after TPE and patients who deceased after TPE

	Patients recovering after TPE (n=10)	Patients who have died after TPE (n=3)
Age (years)	29.5± 4.3	35.7±4.7
Time from hospital admission to apheresis (days)	3.3±1.1	5.6±0.6
Number of TPE sessions	3.4±1.7	6.0±4.6
Hemoglobin (g/dL)(12-16)	7.9±1.7	6.6±0.5
Platelet (μL)(150-400)	30300±11804	21333±8447
ALT (U/L) (0-55)	489±274	623±241
AST (U/L) (5–35)	1212±478	1428±586
Total bilirubin (mg/dL)(0.2-1.2)	6.4±1.9	8.7±3.2
Direct bilirubin (mg/dL) (0- 0.5)	2.4±1.7	3.2±2.1
LDH (U/L) (120–250)	869±235	1036±452
INR (0.8–1.2)	1.6±0.4	2.2±0.8
D-dimer (mg/L)(0-0.5)	19.0±14.0	25.4±13.1
Creatinine (mg/dL)(0.7–1.2)	2.9±2.4	4.2±1.7
Procalcitonin (ng/mL) (0-0.5)	4.4±3.6	13.5±9.6
Albumin (g/dL) (3.4 -5.4)	2.3±0.9	2±0.3

Hemoglobin, platelet, AST, ALT and LDH levels before TPE and hemoglobin, platelet, AST, ALT and LDH values after TPE treatment were compared. Hemoglobin and platelet counts were found to be higher and AST, ALT, total bilirubin, direct bilirubin and LDH levels were found to be lower after TPE treatment (Table 2).

Table 2: Comparison of laboratory values before and after TPE

	Before TPE	After TPE
Hemoglobin (g/dL) (12-16)	7.6 ±1.6	9.6 ±1.62
Platelet (μL) (150-400)	30538±11730	56615±14268
ALT(U/L) (0-55)	582±216	108±75
AST(U/L) (5–35)	1329± 459	172±103
Total bilirubin (mg/dL)(0.2-1.2)	6.9±2,4	3.1±2.5
Direct bilirubin (mg/dL) (0- 0.5)	2.7±1.9	0.9±0.5
LDH (U/L) (120–250)	1520±829	183±72

Since the number of cases was small, the Wilcoxon signed-rank test was applied by looking at the differences between hemoglobin, platelet, AST, ALT and LDH levels before and after TPE (Table 3). A significant difference was found between the levels after TPE and the levels before treatment. ($p<0.05$)

Table 3: Results of Wilcoxon signed-rank test analysis based on hemoglobin, platelet, AST, ALT and LDH values before and after TPE.

	Hemoglobin	Platelet	AST	ALT	LDH
Z	-3.185[a]	-3.188[a]	-3.180[b]	-3.180[b]	-3.180[b]
Asymp. Sig. (2-tailed)	0.001	0.001	0.001	0.001	0.001

a. Based on negative ranks.

b. Based on positive ranks.

DISCUSSION

HELLP syndrome is a life-threatening complication of pregnancy, with a mortality rate of 1.1% (7). The majority of cases occur before labor, with a very small number of HELLP cases occurring within 48 hours postnatal. HELLP syndrome is considered a complication of hypertensive pregnancy disorders. Early diagnosis and treatment are crucial, as the risk of mortality is high in cases that are recognized late (7). There are two main classification systems for the diagnosis of HELLP syndrome. Sibai proposed strict criteria for the first-used Tennessee classification system (8). For the diagnosis of HELLP syndrome in the Tennessee classification system, intravascular hemolysis, peripheral smear findings including evidence of microangiopathy, elevated serum bilirubin (≥ 20.5 μmol/L or ≥ 1.2 mg/100 mL) and elevated LDH levels (> 600 IU/L) are required (7). The second classification system, the Mississippi system, categorizes patients into three classes according to platelet count, AST or ALT levels, and LDH levels. In this classification system, the lowest platelet count at any time during the course of the disease is important (9). Class 1 is consistent with a platelet count ≤50,000/μL, class 2 with a platelet count of 50,000-100,000/μL, and class 3 with a platelet count of 100,000-150,000/μL. Class 1 HELLP is associated with the highest maternal morbidity and mortality rates and the longest recovery time. The more severe the disease, the longer the postnatal recovery time (10).

Microangiopathic hemolytic anemias (MAHA) describe a group of diseases characterized by the destruction of erythrocytes passing through the platelet-fibrin network in microthrombi in small vascular structures such as capillaries and arterioles. Thrombotic microangiopathies (TMAs) are a group of diseases characterized by platelet-rich fibrin deposition, especially in small vessels. TTP is one of the more common thrombotic microangiopathies. Clinical and laboratory findings in TTP improve rapidly with the application of TPE. Due to the significant reduction in patient mortality, this treatment has been applied to other TMAs. A subset of HELLP syndrome may be associated with thrombotic microangiopathy caused by complement dysregulation and can be treated without the need for rapid delivery of the fetus (11).

The etiopathogenesis of HELLP is still not fully clarified (12). Increased inflammatory response due to complement activation is thought to have an important role in the etiopathogenesis of HELLP syndrome (13). When C5b-9, a membrane attack complex, is used as a marker in serum and urine, upregulation of the alternative complement pathway has been suggested (14). Gene mutations affecting the regulatory factors of the complement system have also been reported to have an important role in the etiopathogenesis of HELLP syndrome (15). TPE removes abnormal complement pathway components and replaces them with normal complement components. In HELLP syndrome, TPE is performed to correct the defect in the complement system.

The ASFA categories of evidence provide guidance to clinicians for apheresis therapies, including TPE, in the treatment of various diseases. In HELLP syndrome, TPE may be used if there is no improvement within 72 hours postnatal. ASFA recognizes postpartum HELLP syndrome as a condition for which the optimal role of TPE has not been determined (16). Therefore, it is classified as category III. TPE in the antepartum period has

no role as delayed labor is associated with maternal and fetal loss. Antepartum use of TPE is considered category IV, as evidence suggests that TPE is ineffective or harmful due to the increased risk of mortality associated with delayed labor (16). HELLP syndrome can be misdiagnosed as viral hepatitis, cholangitis, and other acute diseases that make pregnancy difficult (17). Less common diseases in the differential diagnosis of HELLP, but which may be associated with high maternal mortality in pregnancy, include idiopathic thrombocytopenic purpura, acute fatty liver of pregnancy, HUS, TTP, antiphospholipid antibody syndrome, and systemic lupus erythematosus (18).

HELLP syndrome is a potentially life-threatening disease for both mother and fetus. Maternofetal complications are common in HELLP syndrome, and the disease causes 7.0-70.0% perinatal death and 1.0-24.0% maternal death (19). It is known that patients fulfilling Mississippi class 1 diagnostic criteria have the highest perinatal morbidity and mortality rate. Patients with class 1 disease have an incidence of hemorrhage of approximately 13%. The most common autopsy finding is cerebral hemorrhage, with sixty percent of mortality occurring in patients with class 1 disease (20). In this potentially fatal disease, hospitalization is recommended for close follow-up of clinical findings and laboratory parameters. Since HELLP syndrome is known as a severe form of pre-eclampsia, pre-eclampsia should be treated carefully, and effective blood pressure control should be provided with safe drugs such as hydralazine, nifedipine, and labetalol together with magnesium sulfate for seizure prophylaxis. Blood pressure should be kept below 155/105 mmHg (21).

Most of the clinical trials for the management of HELLP syndrome are experimental. Reaching 34 weeks of gestation plays an important role in the treatment decision. Labor is indicated if the disease occurs after 34 weeks of gestation or if fetal and/or maternal conditions worsen. Vaginal birth is preferred (22). If the cervix is not suitable in this patient group, it is recommended to deliver after cervical maturation is achieved. If the mother's condition deteriorates or signs of intrauterine fetal stress are observed before 34 weeks of gestation, labor should be performed without waiting. For fetal lung maturation before the 34th week of gestation, a single course of corticosteroid treatment as 12 mg betamethasone at 24-hour intervals or 6 mg dexamethasone at 12-hour intervals is recommended before labor. High-dose treatment and repeated doses should be avoided for fear of long-term adverse effects on the fetal brain (23). The clinical value of standard corticosteroid therapy in maternal HELLP syndrome is uncertain.

In our study, all postpartum patients with HELLP syndrome were classified as Class 1 according to the Mississippi system. Despite prior treatment with corticosteroids, maternal stabilization, and pregnancy termination, clinical findings did not improve. TPE was conducted in all patients. Two patients experienced tetany due to citrate used for anticoagulation, and one patient had hypotension. A total of three patients died from multiorgan failure. We calculated a 23% mortality rate in this patient group with an unfavorable prognosis. Ten patients whose laboratory parameters and clinical findings improved rapidly after plasma exchange were discharged after full clinical and laboratory recovery.

In HELLP syndrome, albumin levels decrease in response to an increased inflammatory response. In our study, serum albumin levels were low in all patients (Table 2). The albumin level was lower in patients who died after TPE compared to those who survived. Although not statistically significant, this may suggest a connection between lower albumin levels and worse prognosis in patients with HELLP syndrome. Further studies with larger patient populations are required to confirm this relationship.

HELLP syndrome remains a major cause of maternal and fetal morbidity and mortality. Early detection and prompt management are essential to minimize complications. The primary treatment involves delivering the baby and providing supportive care. TPE may be considered in cases of postpartum HELLP syndrome, particularly for patients not showing improvement within 72 hours after delivery. In our study, we found that TPE could be beneficial for a select group of postpartum HELLP patients, with a reduction in mortality compared to the expected rate. However, it is crucial to emphasize that TPE

should be reserved for select cases where conventional treatments have failed, and the risk-benefit ratio should be carefully assessed.

Conclusion

In conclusion, HELLP syndrome is a complex and potentially life-threatening condition with significant maternal and fetal risks. Early detection and appropriate management, including delivery and supportive care, are vital for improving outcomes. In some cases, TPE may be a beneficial adjunct therapy for postpartum HELLP syndrome. Further studies are needed to better understand the role of TPE in managing HELLP syndrome and to establish guidelines for its use.

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İbrahim Halil Açar designed and, performed the experiments and wrote and revised the manuscript; Birol Güvenç provided materials, designed and analyzed the data, and wrote and revised the manuscript.

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Written informed consent was waived in light of the urgent need to collect and report the data.

Data Availability Statement:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest:

The authors declare no conflict of interest

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