Impact of Postpartum Dexamethasone on Postpartum Disease Stabilization in Women with HELLP Syndrome

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ABSTRACT

OBJECTIVE: To investigate the impact of postpartum corticosteroid therapy on maternal disease in women with HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome.

STUDY DESIGN: Thirty-eight patients diagnosed with HELLP syndrome were randomly assigned to treatment (n= 19) and control (n=19) groups. Patients in the treatment group were administered dexamethasone 8 mg, 4 mg and 2 mg IV twice daily, on the postoperative days 1, 2 and 3 consecutively. The first dose was given immediately postpartum. Mean arterial pressure, platelet count , aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels were determined every 6 hours. Duration of intensive care and urinary output were also investigated.

RESULTS: Relative to the control group, the mean arterial pressure became significantly decreased at 42 hours in the steroid-treated group (p = 0.0035), the platelet count increased significantly by 24 hours (p<0.05), and AST and ALT decreased significantly by 24 and 18 hours respectively (p=0.02 and p = 0.01, respectively). Treatment group had higher mean platelet count for all time intervals and the difference between the groups was significant after the postpartum 42nd hour (p=0.03).

CONCLUSION: We observed a rapid resolution of the laboratory and clinical parameters in patients with HELLP syndrome treated with corticosteroids postpartum. We postulate that use of this therapeutic approach could result in reduced overall maternal morbidity and mortality, shorter intensive-care unit stay, with reduced medical care costs.

Keywords: Preeclampsia, HELLP, Corticosteroids

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Introduction

Hypertension complicates around 5-10% of pregnancies and is the most common obstetric challenge[1] HELLP (hemolysis, elevated liver enzymes and low platelets) is the severe form of preeclampsia or eclampsia with hemolysis, elevated liver enzymes, and a low platelet count and its incidence ranges between 2-18% among patients with preeclampsia.[2,3] Patients with HELLP syndrome are at increased risk for infection, disseminated intravascular coagulation, renal failure, adult respiratory distress syndrome, hepatic failure and rupture, and even cardiopulmonary insufficiency.[4] Maternal mortality in HELLP syndrome may be as high as 24% although it's reported to be 1-2 % in tertiary care centers with considerable experience.[5]

Classically, the management of patients with HELLP syndrome essentially consisted of two main approaches; to accelerate delivery and terminate the pregnancy associated stimulus or conservative management while waiting for spontaneous recovery.

However, active management of antepartum or postpartum HELLP syndrome has been suggested by several studies with the use of corticosteroids.[4,5,6,7,8] These studies suggest that dexamethasone therapy has a positive impact on several maternal and perinatal outcomes including blood pressure, platelet count, liver enzymes and neonatal respiratory distress syndrome.

The purpose of the present study is to investigate the impact of postpartum corticosteroid therapy on maternal disease in women with HELLP syndrome.

Material and Method

This prospective randomized study was done in High Risk

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Pregnancy Unit in Zekai Tahir Burak Women's Health Education and Research Hospital. It was approved by the Institutional Review Board and the Central Ethics Committee of the Ministry of Health, and informed consent of all participants were obtained.

Thirty-eight patients diagnosed with HELLP syndrome were recruited in the study. Diagnostic of the HELLP syndrome was made according to the criteria by Sibai:[9]

1. Hemolysis; documented by abnormal peripheral smear, elevated bilirubin (≥1,2 mg/dL), or LDH ≥ 600 U/L
2. Elevated liver enzymes (AST (aspartate aminotransferase) ≥70 U/L, ALT (alanine aminotransferase) ≥50 U/L)
3. Low platelets (≤100.000/mm^3)
4. Other clinical and laboratory evidence of preeclampsia and eclampsia (uric acidemia, etc)

Patients were randomly assigned to treatment (n=20) and control (n=20) groups. One patient from the treatment group and one patient from the control group was excluded because they were transferred to a multidisciplinary center. Finally there were 19 patients in each group. Patients in the treatment group were administered dexamethasone (Dekort 2 mL. 8 mg ampul, Deva İlaç., İstanbul, Turkey) 8 mg, 4 mg and 2 mg IV twice daily, on the postpartum days 1, 2 and 3 consecutively. The first dose was given immediately postpartum.

Patients in both groups received magnesium sulphate for seizure prophylaxis when indicated and antihypertensive agents when arterial pressure exceeded 160/100 mmHg. Patients in the treatment group were not supplied with blood or blood products postpartum unless the platelet count was below 20.000/ mm^3. All patients were followed in the intensive care unit with strict control of blood pressure and urine output.

Platelet count, AST, ALT, hemoglobin and fibrinogen levels were determined every 6 hours.

Kolmogorov-Smirnov test was used to determine distribution characteritics. Mann Whitney U test and Wilcoxon Matched pairs signed ranks tests were used for the statistical analysis of the data. Results were expressed as mean ± standard deviation. A p value <0.05 was considered significant.

Results

Groups were similar in terms of maternal age, gestational age and parity. Mean arterial pressure (MAP), liver enzymes, platelet count, hematocrit and fibrinogen levels at the time of initiation of the therapy were again similar. The percentage of patients delivered by Cesarean section were similar in the treatment and control groups (63% vs 73% respectively, p=0.36) Demographic characteristics and baseline laboratory values are expressed in table 1.

In the treatment group, MAP was found to be at or below 160/100 mmHg by 36 hours postpartum and after that moment MAP taken every 6 hours of the treatment group was significantly lower than the control group (p=0.0035 and p= 0.009 for postpartum 42nd and 48th hours respectively). The behavior of the MAP of the groups during the postpartum 48 hours is represented in figure 1.

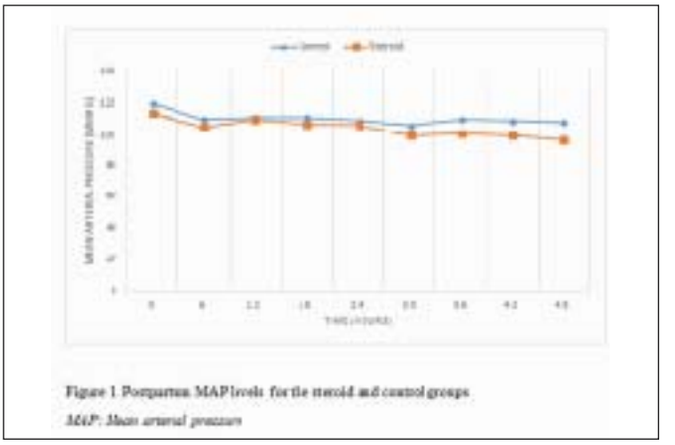

Figure 1 Postpartum MAP levels for the steroid and control groups
MAP: Mean arterial pressure

Table 1: Demographic and admission criteria of the study population

	Dexamethasone group n= 19	Control group n= 19	p
Age (years)	26.0±5.8	28.6±8.2	0.26
Gestational age (weeks)	32.23±4.5	32.7±3.5	0.70
Gravida (n)	2.5±2.6	3±2.2	0.41
MAP (mmHg)	114.6±17.9	120.3±8.2	0.08
AST (U/L)	327.3±252.6	471.3±277.3	0.07
ALT (U/L)	237.0±174.3	321.3±190.0	0.08
Platelet count (/mm^3)	77.9±46.2	76.7±29.7	0.73
Htc (%)	34.4±6.0	34.3±7.3	0.55
Fibrinogen	382±141.6	349.7±128	0.41
C/S delivery	63%	73%	0.36

MAP: Mean arterial pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Htc: hematocrit, C/S: Cesarean Section

Alanine aminotransferase and AST levels of the two groups were similar on admission (p=0.07, p=0.08 respectively). In the treatment group AST levels were significantly lower in the first 24 hours postpartum (p=0.02, p=0.009, p=0.01 and p=0.02 for the 6th, 12th, 18th, and 24th hours postpartum). Similarly, ALT levels of the treatment group are significantly lower than the controls in the first 18 hours (p=0.01 and p=0.07 for 12th and 18th hours postpartum, respectively). Although ALT levels were lower during the rest of follow up period the difference was not statistically significant. In the treatment group liver enzymes tended to decrease by the 6th postpartum hour. Changes of serum AST and ALT levels of the groups versus time are shown in figures 2 and 3 respectively.

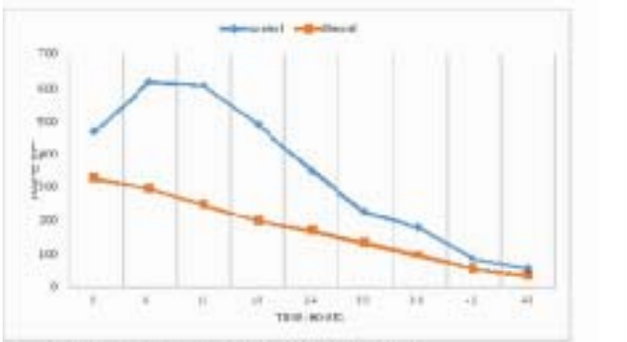

Figure 2. Postpartum AST levels of the steroid and control groups
AST: Aspartate aminotransferase

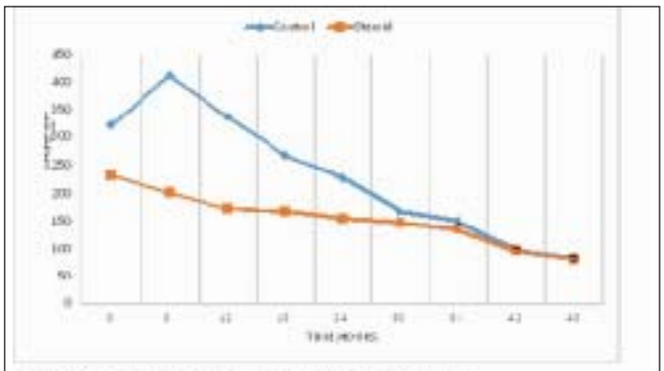

Figure 3. Postpartum ALT levels of the steroid and control groups
ALT: Alanine aminotransferase

Treatment group had higher mean platelet count for all time intervals and the difference between the groups was significant after the postpartum 42nd hour (p=0.03 and p=0.006 for postpartum 42nd and 48th hours respectively). In the steroid treated group, the platelet count was more than 50.000/mm^3 after postpartum 12 hours and started to increased steadily after 18th hour.

Mean platelet count of the control group displayed a continuous decline in the first 24 hours and was more than 50.000/ mm^3 only after 30 hours postpartum. Behavior of mean platelet counts with time are represented in figure 4. Hematocrit and fibrinogen levels of the two groups were not different for any time interval.

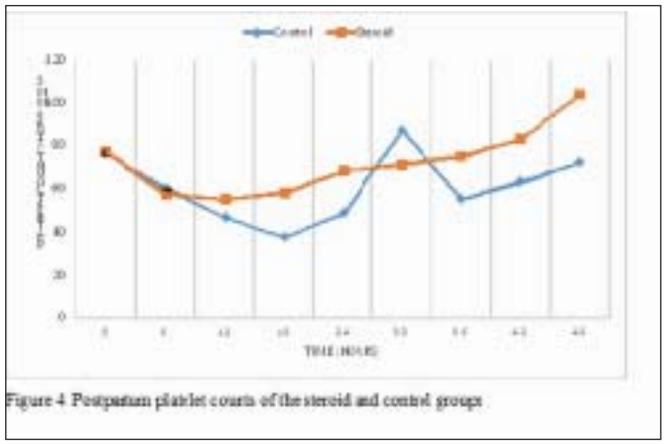

Figure 4. Postpartum platelet counts of the steroid and control groups

Time spent in the intensive care unit was similar (30.4±10.3 and 38.9±17.5 hours, p=0.79) for the treatment and control groups respectively.

We have also measured the time needed to achieve urinary output of ≥50 cc/hours. It was 5.5 ±5.1 hours for the treatment and 12.4 ±12.1 cc/hours (p=0.04).

Discussion

Diagnosis and management of patients with HELLP syndrome remained one of the major challenges of the obstetric practice. Severity of the disease usually peaks in the 24-48 hours postpartum.[6] How rapidly a patient recovers from a pregnancy complicated by HELLP syndrome depends on various factors including the time of pregnancy termination during the disease process. A small number of such patients suffer from severe multi systemic disease that even discontinuation of the pregnancy is unable to achieve recovery, if at all, and other treatment modalities such as plasma exchange is needed.[10]

A number of patient series and case reports in literature have described the clinical presentations, clinical course, laboratory findings, and maternal/ fetal outcomes of patients with HELLP syndrome. In most of these studies it is suggested that that delivery and conventional medical management of preeclampsia-eclampsia usually led to relatively rapid resolution of the HELLP disease process within 72 hours postpartum. However, more specific information related to postpartum recovery and resolution of this important complication of pregnancy is lacking.[11]

Mean platelet count and liver enzyme levels are laboratory findings best reflective of the severity and the recovery rate of the disease process. Stabilization of the arterial pressure and diuresis are the important clinical criteria for discharging the patient from the intensive care units. In the present study, we have demonstrated that recovery is more rapid in patients with HELLP syndrome treated with corticosteroids.

Corticosteroids have been used for treating women with HELLP syndrome both before and after delivery. Several ob-

servational studies demonstrated improvement of maternal outcomes with administration of dexamethasone or betamethasone and small randomized clinical trials found improvement in laboratory and clinical findings, particularly the platelets count.[4,12,13,14]

Mean arterial pressures and urine outputs of the steroid treated group displayed a faster resolution than the control group which has a major contribution to shorter intensive care stay. Our findings are similar to those of Magann et al.[5] who reported a significant improvement in urinary outputs and MAP by 24 hours with corticosteroid therapy. However, Vigil-De Gracia and Gracia Caceres[7] failed to show a significant difference for these parameters between the two groups.

AST and ALT levels of the control group were significantly elevated in the first 24 hours postpartum but in the steroid treated group they declined from the time of parturition on. In our study, enzyme levels of both groups are similar by 48 hours but in the first 24 hours steroid treated group has significantly lower levels.

Platelet counts stabilized by 12 hours and started to rise by 18 hours in the steroid treated group. Platelet counts of the control group decreased until 24 hours postpartum and the difference between the groups was significant by 42 hours. Magann et al[5] reported a significant difference between the groups from 24 hours on. We restricted the transfusions to steroid group and supplied them with blood or blood products only when the platelet count was <20.000/ mm^3. The control group was free of such restriction. Although significant differences were achieved on the second postpartum day, steroid group had an earlier resolution of the platelet counts without transfusions.

It ıs not exactly known how dexamethasone acts on platelet counts. Probable mechanisms are; decreased platelet adhesion, decreased platelet removal by spleen, a direct endothelial or rheological mechanism, and platelet activation.[4] Rapid resolution of the platelet count in the treatment group led us to the conclusion that the thrombocytopenia in preeclampsia/eclampsia may be immunologically mediated. Sibai[9] also suggested that repeated transfusion in such patients are unnecessary and only have a transient effect.

In 2004, a systematic Cochrane review about the effects of corticotherapy on maternal and perinatal prognosis in the HELLP syndrome was published. Although there were no statistically significant differences in relation to maternal and perinatal mortality or sub capsular hepatic hematoma, acute pulmonary edema, renal failure, and premature placental detachment, they reported improvement in laboratory parameters after treatment with dexamethasone, compared to both placebo and betamethasone, and some clinical findings including arterial pressure and diuresis after treatment with dexamethasone, compared to betamethasone.[15]

On the other hand, two clinical trials with significant number of cases failed to confirm our findings for treatment with corticosteroids in HELLP syndrome. Fonseca et al.[16] could not demonstrate any difference in the treatment group with regard to length of hospitalization, duration to recovery for laboratory or clinical findings, complications, or requirement for blood transfusion. Another prospective, double-blind, randomized trial that recruited 105 postpartum women with HELLP syndrome where patients were allocated to either treatment or placebo groups, investigated the duration of hospitalization, maternal morbidity, and laboratory and clinical findings . However, their results did not support the use of corticosteroids after delivery for resolution of HELLP syndrome.[8]

An important limitation of these studies, that patients of different degrees of severity of the disease were recruited. Fonseca et al.[16] performed a post hoc analysis and observed that the subgroup of class I patients displayed a faster recovery of platelet counts . Thus it may be concluded that the inclusion of patients with milder forms of the disease may have reduced the impact of corticosteroid therapy.

In conclusion; we observed a rapid resolution of the laboratory and clinical parameters in patients with HELLP syndrome treated with corticosteroids postpartum. This accelerated recovery is very important to avoid the potentially increased maternal mortality and morbidity in this clinical setting. Additionally it shortens the intensive care period which may help reduce overall health costs and we recommend the use of this therapeutic approach in this particular group of patients.

HELLP Sendromlu Hastalarda Postpartum Kortikosteroid Tedavisinin Maternal Hastalığın Stabilizasyonuna Etkisi

ÖZET

AMAÇ: HELLP (hemolysis, elevated liver enzymes and low platelets) sendromlu hastalarda postpartum kortikosteroid tedavisinin maternal hastalığın stabilizasyonuna etkisinin araştırılmasıdır.

GEREÇ VE YÖNTEM: HELLP sendromu tanısı alan 39 hasta tedavi (n=19) ve control gruplarına (n=19) randomize edildi. Tedavi grubundaki hastalara postpartum 1., 2. ve 3. günlerde sırasıyla günde 2 defa IV olmak üzere 8 mg, 4 mg ve 2 mg dexamethasone verildi. İlk doz doğumdan hemen sonra uygulandı. Ortalama arteryel basınç, trombosit sayısı, aspartat aminotransferaz (AST), alanine aminotransferase (ALT) düzeyleri altı saatte bir ölçüldü. Yoğun bakımda kalış süreleri ve idrar çıkışı da takip edildi.

BULGULAR: Steroid alan grupta ortalama arter basıncı postpartum 42. saatte kontrol grubuna göre anlamlı düşük düzeylere ulaştı (p=0,0035), trombosit sayısı postpartum 24. saatte anlamlı daha yüksek (p<0,05), AST ve ALT düzeyleri sırasıyla

24 ve 18. saatlerde anlamlı daha düşük olarak tespit edildi (sırasıyla, p=0,02 ve p=0,01). Tedavi grubu tüm zaman aralıklarında daha yüksek trombosit sayılarına sahipti ve iki grup arasındaki fark postpartum 48. saatten itibaren istatistiki olarak anlamlı bulundu (p=0,03).

SONUÇ: Postpartum kortikosteroid tedavisi alan HELLP sendromlu hastalarda klinik ve laboratuar parametrelerinde hızlı bir düzelme izledik. Sonuçlarımız bu tedavi yaklaşımın maternal morbidite ve mortaliteyi, yoğun bakımda kalış süresini azaltabileceğini göstermektedir. Ayrıca bu durumun genel sağlık harcamalarının azaltılmasına da katkısı olabilecektir.

Anahtar Kelimeler: Preeklampsi, HELLP, Kortikosteroid

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