THE EFFECT OF DEXAMETHASONE TREATMENT ON MATERNAL OUTCOME IN HELLP SYNDROME

HELLP SENDROMUNDA DEKSAMETAZON TEDAVİSİNİN MATERNAL SONUÇLAR ÜZERİNE ETKİSİ

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ABSTRACT

INTRODUCTION: There are still controversies in the literature regarding the role of corticosteroids in the treatment of HELLP syndrome. The aim of this study is to investigate the effect of dexamethasone treatment on maternal outcome.

MATERIALS AND METHODS: The study included 20 patients who were followed in ICU with the diagnosis of HELLP syndrome. Data regarding the age, gestational age, Mississippi class, APACHE II score, hematologic and biochemical measurements, mortality and length of ICU stay were analyzed retrospectively.

RESULTS: Two patients died due to the multiple organ failure. Twelve patient received dexamethasone treatment (Group 1) and eight patients did not receive steroid treatment (Group 2). There was not any statistically significant difference in the length of ICU stay, mortality, and transfusion requirements between the groups. The patients receiving dexamethasone treatment showed an increased improvement in platelet count; however the difference was not statistically significant.

CONCLUSIONS: Dexamethasone treatment did not result in any improvement in mortality, length of ICU stay, and in the platelet counts in patients with HELLP syndrome.

Key words: *HELLP, Dexamethasone, Corticosteroid, Platelet*

ÖZET

AMAÇ: Literatürde HELLP sendromunun tedavisinde kortikosteroid kullanımı ile ilgili çelişkili bilgiler bulunmaktadır. Bu çalışmanın amacı deksametazon tedavisinin maternal sonuçlar üzerindeki etkisinin araştırılmasıdır.

YÖNTEMLER: Çalışmaya HELLP sendromu tanısı ile yoğun bakım ünitesinde izlenen 20 hasta dahil edilmiştir. Hasta yaşı, gestasyonel yaş, Mississipi sınflandırması, APACHE II skoru, hematolojik ve biyokimyasal ölçümler, mortalite ve yoğun bakım yatış günü gibi parametreler analiz edilmiştir.

BULGULAR: Hastalardan ikisi çoklu organ yetmezliğine bağlı olarak ölmüştür. On iki hastaya deksametazon tedavisi verilmiş (Grup 1), 8 hasta ise kortikosteroid tedavisi almamıştır. Gruplar arasında yoğun bakım yatış süresi, transfüzyon gereksinimi ve mortalite açısından anamlı fark saptanmamıştır. Deksametazon tedavisi verilen grupta trombosit sayılarında artış daha fazla gerçekleşmiştir ancak bu artış istatistiksel fark yaratacak düzeyde olmamıştır.

SONUÇ: HELLP sendromu tedavisinde dekzametazon kullanımı mortalite, yoğun bakım yatış günü ve trombosit sayılarında anlamlı bir fark yaratmamaktadır.

Anahtar kelimeler: *HELLP, dekzametazon, kortikosteroid, trombosit*

INTRODUCTION

HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome is a severe manifestation of pre-eclampsia with significant morbidity and mortality for pregnant women and their fetus (1). Pathogenesis of HELLP syndrome is unclear and according to some authors HELLP syndrome is a different disease from preeclampsia (2, 3). When considered as a form of severe preeclampsia, it is proposed to originate from abnormal placental development and function. However, apart from preeclampsia, excessive hepatic inflammation and coagulation activation has a role in the pathogenesis of HELLP syndrome (4, 5). Since the first definition by Weinstein in 1982, many treatment and management strategies have been investigated (6).

Depending on the laboratory abnormalities, HELLP syndrome is grouped into different subtypes by the Mississippi and Tennessee classifications. Tennessee classification divides HELLP syndrome into two groups as complete and incomplete. The diagnostic criteria are elevated LDH levels, (> 600 u/l) and hemolysis, AST >

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70, and platelet count < 100.000. If all three parameters are positive it is defined as complete HELLP. When one or two parameters are positive, it is defined as incomplete HELLP syndrome. Mississippi classification states three groups according to platelet counts. Class1: Platelet count ≤ 50.000/mm3, Class2: Platelet count: 50.000 - 100.000, Class3: Platelet count ≥ 100.000 (6).

In HELLP syndrome differential diagnosis should be made from acute fatty liver of the pregnancy, hepatitis, the immune thrombocytopenia (ITP), systemic lupus erythematosus, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) (6, 7).
Corticosteroids (CS) have been widely used in the treatment of HELLP syndrome (6, 8). Small observational studies, randomized trials, and some metaanalyses have suggested that CS use provides fast recovery in the clinical and laboratory parameters (9 - 11). However, these findings were not supported by randomized double-blind, placebo-controlled studies and metaanalyses, and CS administration has not found to be significantly associated with better maternal mortality (7, 12). In the present study, we aimed to investigate the effects of dexamethasone in Intensive Care Unit (ICU) patients with the diagnosis of HELLP syndrome.

MATERIALS AND METHODS

The study included 20 patients who were followed in ICU with the diagnosis of HELLP syndrome between July 2013 and August 2014. The patient records were analyzed retrospectively. Data regarding the age, parity, gestational age at admission, neonatal prognosis, Mississippi class, APACHE II score, arterial blood pressure, hemoglobin and platelet counts, liver enzymes, LDH, serum bilirubin, and length of ICU stay were analyzed. All patients underwent ultrasonographic examination in order to determine any possible complication of liver hematoma. Cranial computed tomography was performed if needed. Ethical Committee of our hospital approved the study (ANEAH.EH.2014/46, Chair: Prof. Dr. OKA). Statistical analysis was performed using the SPSS 15. Nonparametric Mann–Whitney U test was used to assess the differences between continuous data. Descriptive data were presented as mean ± SEM (Standard error of mean).

RESULTS

Table I summarizes the patients' characteristics. In terms of gestational week, 5 patients were greater than 34 week pregnancy, and remaining patients were smaller than 34 gestational week. Mean platelet count was 89.405 ± 41.372 /uL (17000 - 144.000). Six patients were Mississippi class 1, 13 patients were class 2 and 1 patient were class 3. Six patients needed mechanical ventilation. Antihypertensive medications were commenced on with nitroglycerin, esmolol and/or sodium-nitroprusside (which were available in the institute) in case of resistant hypertension. Seven patients had eclamptic convulsions before admission to ICU. Acute renal failure occurred in one patient. Two patients who had eclampsia and did not response to the treatment died due to the multiple organ failure, one in each group. Eighteen patients were discharged uneventfully. Two intrauterine, and one premature mortality occurred. Two of the cases had the diagnosis of postpartum HELLP after spontaneous vaginal delivery. All other patients were delivered by emergency cesarean sections with general anesthesia, upon diagnosis of HELLP syndrome. Twelve patient (60 %) received dexamethasone treatment (2 × 10 mg iv) (Group 1) while eight patients (40 %) did not receive (Group 2).

Table 1: Descriptive statistics of the patients

	N	Min	Max	Mean	SEM
Age (year-old)	20	18.00	46.00	31.55	±1.89
Gestational age (weeks)	20	26.00	39.00	33.10	±0.73
Gravida	20	1.00	6.00	2.85	±0.39
BMI (kg/m2)	20	24.50	33.30	29.80	±0.63
LOS-ICU (days)	20	1.00	9.00	4.70	±0.45
Mechanical ventilation (days)	6	1.00	9.00	3.00	±1.26
APACHE II score	20	3.00	29.00	9.15	±1.38

BMI: Body mass index
LOS-ICU (Intensive care unit length of stay)
SEM: Standard Error of Mean

The patients in Group 1 was administered 10 mg dose of intravenous dexamethasone just after anesthesia induction, and 2 additional same doses of dexamethasone in every 12 hours after delivery.

The distribution of HELLP classes according to Mississippi classification of the patients between groups was shown in **table 2.** There was not any statistically significant difference in variables, except APACHE II scores on admission, between the groups **(Table 3).** Any of the patients did not receive platelet transfusion, except two patients who had died because of multiple organ failure. When the groups were compared in terms of improvement in the platelet counts from the first day to the third day of treatment, a trend towards an increase in platelet count in group 1 was observed, but the difference did not reach to the statistical significance (**Table 3 and Figure 1**).

DISCUSSION

The HELLP syndrome usually develops between 28 - 36 weeks of gestation. Its etiology and pathogenesis are still not well understood. The pathogenesis of HELLP is considered to result from aberrant development, function and ischemia of the placenta which in turn cause endothelial damage with loss of pregnancy-induced vascular relaxation, release of proinflammatory cytokines and vasoconstrictors, and platelet activation. A microangiopathic thrombotic hemolysis occurs consequently. Thrombocytopenia results mainly from increased consumption and destruction of platelets (7, 13).

In the treatment of HELLP, urgent delivery is indicated when the gestational age is beyond 34 weeks. Earlier delivery should be considered in the presence of fetal stress, or if complications of HELLP syndrome exist such as multiorgan dysfunction, disseminated coagulation, abruptio placenta, acute renal failure, pulmonary edema, and liver hemorrhage (7, 14).

Corticosteroids (CS) should be administered to accelerate the fetal lung maturity if the gestational age is less than 34 weeks in preparation for delivery 48 h later (13, 15). Other than for the indication of improving fetal lung maturity, there is still no consensus regarding CS use aiming to improve maternal outcome. The maternal benefit of CS in the treatment of HELLP was first reported in 1984 (16). As HELLP has been considered as a systemic inflammatory syndrome, anti-inflammatory and immunosuppressive properties of CS treatment have been suggested to result in diminished edema, inhibited endothelial activation and reduced endothelial dysfunction, prevention of thrombotic microangiopathic anemia, and inhibition of cytokine production, and antiangiogenic and inflammatory factors in the HELLP syndrome (6, 17, 18).

There are controversies in the literature regarding the role of CS in the treatment of HELLP syndrome. In general, retrospective and small randomized studies, and case reports suggested that the use of dexamethasone (10 mg, every 12 hours) improved maternal outcome and induced rapid improvement of the platelet counts (6, 8, 19-25). Although improvements in hematologic parameters (Platelet counts) are often seen in patients with HELLP syndrome receiving dexamethasone, maternal morbidity and mortality along with duration of hospital stay and rate of transfusion does not gain benefit (7, 12).

The largest randomized double blind, placebo controlled study in the literature included 132 patients with HELLP syndrome. The study included both antenatal (n = 60) and postnatal (n = 72) HELLP patients (15). Dexamethasone treatment did not reduce maternal complications and length of hospital stay. The rates of platelets and fresh frozen plasma transfusions were not significantly reduced. The authors stated that their results did not support the routine use of dexamethasone in HELLP patients (15).

A recent Cochrane review included 11 trials with 550 patients comparing CS with placebo or no treatment in the HELLP syndrome (26). There was no difference in the risk of maternal death, severe maternal morbidity, or perinatal/infant death. The only clear effect of dexamethasone treatment on individual outcomes was improved platelet count. Authors' conclusions were that there was no clear evidence of any effect of CS on clinical outcomes, and the use of CS might be only justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile.

In the present study, the groups were comparable in terms of variables, except APACHE II scores on admission. The patients in group 2 had increased mean score. However, since the mean APACHE II score is lower than 15, the figure indicating the widely accepted limit for severe physiological condition, we think that this difference did not impair the comparability of the groups. We did not find any significant difference in mortality, length of ICU stay, transfusion requirements, and improvement in the platelet counts between the groups. The patients receiving dexamethasone treatment showed an increased improvement in platelet count; however the difference was not statistically significant.

The major drawbacks of our study are its low patient size, and retrospective design. Most of the reports in the literature investigating the effect of CS use on the maternal outcome in the HELLP syndrome suffer from the same drawbacks.

CONCLUSIONS

Dexamethasone treatment did not result in any improvement in mortality, length of ICU stay, and in the platelet counts in patients with HELLP syndrome.

Prospective, randomized studies with large patient

numbers are needed to clarify the effect of CS treatment on maternal mortality in patients with HELLP syndrome.

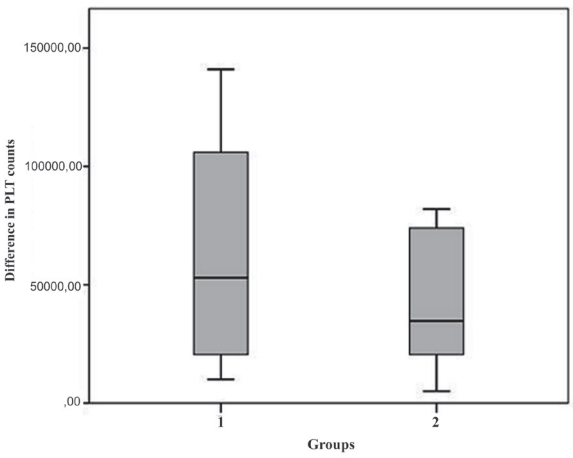
Table 2. HELLP classes of the patients

	Class			Total
	1	2	3	
Group 1	4	8	0	12
Group 2	2	5	1	8
Total	6	13	1	20

Table 3. Comparison of Groups 1 and 2. Data were presented as mean ± SEM

	Group 1	Group 2	P
Age (year-old)	30.58 ± 2.77	33.0 ± 2.35	NS
Gestational age (weeks)	33.42 ± 1.07	32.63 ± 0.92	NS
Systolic BP (mmHg)	188.58 ± 4.37	203.38 ± 8.07	NS
ALT (U/L)	201.25 ± 55.59	224.63 ± 95.16	NS
Bilirubin (mg/dl)	1.18 ± 0.22	2.4 ± 1.43	NS
Hematocrit (%)	29.8 ± 1.92	34.13 ± 1.5	NS
Platelet count on admission (/mm3)	85716 ± 12427	94937 ± 14472	NS
LDH (U/L)	1012.42 ± 171.3	797.88 ± 171.67	NS
LOS-ICU (days)	4.58 ± 0.6	4.88 ± 0.74	NS
APACHE II score	6.25 ± 0.72	13.5 ± 2.7	0.032
Transfusion requirement (N)	3 / 12	2 / 8	NS
Difference in Plt counts (days 1-3)			
(/mm3)	63330 ± 13330	43188 ± 10506	NS
Mortality (N)	1 / 12	1 / 8	NS

LOS-ICU (Intensive care unit length of stay)
Plt: Platelet



Legend for figure 1: The increase in platelet counts between days 1 and 3.

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