Prognostic Factors of the Efficacy of High-dose Corticosteroid Therapy in Hemolysis, Elevated Liver Enzymes, and Low Platelet Count Syndrome During Pregnancy

A Meta-analysis

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Abstract: The aim of this study was to identify the factors which can affect the efficacy of corticosteroid (CORT) therapy in the management of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

Research articles reporting the efficacy of CORT therapy to HELLP syndrome patients were searched in several electronic databases including EMBASE, Google Scholar, Ovid SP, PubMed, and Web of Science. Study selection was based on predefined eligibility criteria. Efficacy was defined by the changes from baseline in HELLP syndrome indicators after CORT therapy. Meta-analyses were carried out with Stata software.

Data of 778 CORT-treated HELLP syndrome patients recruited in 22 studies were used in the analyses. Corticosteroid treatment to HELLP syndrome patients was associated with significant changes from baseline in platelet count; serum levels of aspartate aminotransaminase, alanine transaminase, and lactic dehydrogenase (LDH); mean blood pressure; and urinary output. Lower baseline platelet count predicted higher change in platelet count after CORT therapy. Lower baseline platelet count and lower baseline urinary output predicted greater changes in LDH levels after CORT therapy. There was also an inverse relationship between the change from baseline in LDH levels and intensive care duration. Higher CORT doses were associated with greater declines in the aspartate aminotransaminase, alanine transaminase, and LDH levels. Incidence of cesarean delivery was inversely associated with the gestation age. The percentage of nulliparous women had a positive association with the intensive care stay duration.

High-dose CORT therapy to HELLP syndrome patients provides benefits in improving disease markers and reducing intensive care duration, especially in cases such as mothers with much lower baseline platelet count and LDH levels.

INTRODUCTION

Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is a potentially lethal consequence of gestational hypertension. Pathological dynamics of the syndrome, that is, microangiopathic hemolytic anemia, liver dysfunction, and thrombocytopenia are not easier to understand at the earliest and therefore diagnosis is often late.1-4

Three main options for the management of HELLP syndrome are as follows: immediate delivery at 34 weeks’ gestation or later; delivery within 48 hours after evaluation and stabilization of the maternal clinical condition and corticosteroid (CORT) treatment during 27 to 34 weeks of gestation; and conservative management for more than 48 to 72 hours in pregnant women before 27 weeks’ gestation.5

Use of CORT in the management of HELLP syndrome is frequent. Data generated in the past 2 decades suggest that the CORT treatment to HELLP patients is associated with improvements in biological markers including platelet count, serum aspartate aminotransaminase (AST), alanine transaminase (ALT), and lactic dehydrogenase (LDH) levels, without affecting overall morbidity and mortality.6,7 It is important to know which factors can affect the efficacy of CORT in improving HELLP syndrome markers to identify subgroups of patients that can be benefitted with CORT treatment. We therefore carried out a systematic review and metaregression analysis to identify the factors affecting the efficacy of CORT therapy by using data generated in the studies, which evaluated the efficacy of CORT therapy in HELLP patients.

METHOD

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are followed for carrying out the present study.8 Eligibility criteria for the selection of studies are presented in Table 1. Ethical approval is not required for a meta-analysis.
Between-study variance was tested with tau² and the percentage of between-study heterogeneity was assessed with I² index. For the identification of the predictors and prognostic factors of the efficacy of CORT therapy, the analyses were carried out systematically by testing each of the dependent variables including the number of patients in a study, CORT total dose, mother’s age, nulliparity, gestation week at the time of CORT treatment, baseline platelet count, baseline mean blood pressure, baseline urinary output, baseline ALT levels, baseline ALT levels, and baseline LDH levels. A P value of less than 0.1 was considered to show a significant relationship.

For the assessment of publication bias, Begg funnel plot and Egger precision plot were studied, and trim and filled method was applied to estimate missing number of studies.

**RESULTS**

Twenty-two studies, which overall recruited 778 CORT-treated patients, were used for the analyses (Figure 1). Of the included studies, 10 were randomized controlled trials (RCTs), 1 nonrandomized prospective study, and 11 were retrospective analyses. Significant publication bias was observed with the Egger and Begg methods of assessment (Figure 2A and B). The CORT was administered during antepartum period in 9 studies, during postpartum period in 8 studies, and during peripartum period in 5 studies.

Age of the patients as mean ± SD (range) was 26.12 ± 2.64 (23.2 ± 6 to 33.5 ± 4) years. Gestation age at the time of randomization or CORT treatment was 31.6 ± 2.22 (range 27 ± 1–35.1 ± 2.9) weeks. Of these patients, 41.6 ± 31.4% women were nulliparous. Total dose administered to these patients ranged from 30 to 150 mg, with an average of 60.8 ± 45.5 mg (12 studies data). Incidence of cesarean deliveries in CORT-treated HELLP syndrome patients was 68.9 ± 19.4% (range 33.3%–100%).

Important findings of the meta-analysis are presented in Tables 2 and 3, and the results of all systematic metaregression analyses are given in supplementary information file (Tables S1–S7, http://links.lww.com/MD/A855). Corticosteroid treatment to HELLP syndrome patients was associated with significant improvements in the changes from baseline in platelet count, serum levels of AST, ALT, and LDH, mean blood pressure, and urinary output (Figure 3, Table 2, and Figures S1–S5, http://links.lww.com/MD/A855).

**TABLE 1. Study Eligibility Criteria**

| PICOS | Inclusion Criteria | Exclusion Criteria |
|-------|--------------------|--------------------|
| Patients | Pregnant/postpartum mothers who received CORT therapy for the management of with HELLP syndrome | Pregnant mothers receiving CORT therapy for the management of eclampsia or preeclampsia without HELLP syndrome; pregnant mothers receiving CORT therapy for fetal lung maturity primarily |
| Interventions | High-dose CORT therapy to HELLP syndrome patients | CORT therapy in combination with other therapies |
| Controls | Placebo-controlled or comparator-controlled or uncontrolled | None |
| Outcomes | Changes from baseline in platelet count; changes from baseline in serum levels of AST, ALT, and LDH; change in urinary output; cesarean section rate; blood transfusion rate; intensive care duration; incidence of comorbidities | Fetal outcomes (Apgar score, abdominal circumference, end-diastolic flow, birth weight, etc) and obstetric outcomes other than incidence of cesarean delivery |
| Study designs | Retrospective or randomized controlled/nonrandomized prospective | Case reports |

ALT = alanine transaminase, AST = aspartate aminotransaminase, CORT = corticosteroid, HELLP = hemolysis, elevated liver enzymes, and low platelet count, LDH = lactic dehydrogenase.
Change in platelet count from baseline had a significant inverse relationship with baseline platelet count (Figure 4, Table 3). Thus, lower baseline platelet count and lower baseline LDH levels were predicting higher level change in platelet count from the CORT therapy. However, there was also an inverse relationship between baseline LDH levels and the change in platelet count after CORT therapy. Thus, lower baseline LDH levels were predicting higher change in platelet count.

Lower baseline platelet count and lower baseline urinary output also predicted higher changes in LDH levels after CORT therapy as a significant inverse relationship was observed between the changes from baseline in LDH levels and the baseline platelet count or urinary output (Table 3). There was also an inverse relationship between the change from baseline in LDH levels and intensive care duration.

Total CORT dose had significantly positive association with the changes from baseline in AST, ALT, and LDH levels. Thus, higher CORT doses were associated with more declines in these enzyme levels (Table 3).

Incidence of cesarean delivery was inversely associated with the gestation age (Figure 5). The intensive care stay duration was positively associated with the percentage of nulliparous women and the percentage of HELLP syndrome patients with comorbidities (Table 3). None of the other independent variables were significantly associated with the incidence of cesarean delivery (Tables S1–S7, http://links.lww.com/MD/A855).

**DISCUSSION**

This pooled analysis, followed by the metaregression analyses, has found that the CORT treatment to HELLP syndrome patients significantly improves platelet count; AST, ALT, and LDH levels; and urinary output. Changes in platelet count and LDH levels after CORT therapy were more robust in patients with lower baseline platelet count, and these outcomes were also associated with lesser intensive care duration. However, intensive care duration was also positively associated with nulliparity. Cesarean delivery rate was negatively associated with gestation age.

Class 1 HELLP syndrome is associated with relatively higher maternal mortality and poor prognosis in delayed diagnosis cases. A statistically significant negative association between the change from baseline in platelet count and the baseline platelet count, and also baseline LDH levels observed in the present study suggests that CORT treatment can be more efficacious in patients with lower platelet count and thus CORT therapy to class 1 patients can be more beneficial. In a RCT also, a faster platelet recovery was found in the class 1 subgroup of HELLP patients after CORT therapy. After analyzing HELLP class 1 patients’ data retrospectively, Vigil-De Gracia also...
suggested high-dose CORT therapy for class 1 HELLP syndrome patients.

In the present analysis, we have found that the incidence of cesarean deliveries was inversely associated with the gestation week, and intensive care duration was positively associated with the percentage of nulliparous women in the CORT-treated HELLP syndrome patients. Neither any of the baseline biological marker nor change in the biological markers after CORT therapy was significantly associated with cesarean delivery rate. Recently, Katz et al.,33 after analyzing 500 women with severe preeclampsia, have observed that whereas uncontrolled hypertension was a risk factor for cesarean section, there was no association between cesarean section and HELLP syndrome. Haddad et al.,34 in a retrospective analysis of 183 HELLP syndrome cases, have found that except for the need for blood products transfusion, onset of HELLP syndrome at or less than 28 weeks’ gestation was not associated with an increased risk of adverse maternal or neonatal outcomes when they compared these cases with severe preeclampsia patients without the HELLP syndrome at a similar gestational age.

Haddad et al.,35 in the same 183 HELLP syndrome cases, found that women with nadir platelet counts <50,000 cells/μL were at increased risk for adverse maternal outcomes in comparison with those with nadir platelet counts between 50,000 and 100,000 cells/μL. However, their logistic regression analyses could not identify significant associations between the nadir values of platelet count of <50,000/μL, serum AST level of >150 U/L, or serum LDH level of >1400 IU/L and maternal adverse outcome. There was also no significant association between laboratory markers and the adverse outcomes in a study of 44 HELLP syndrome patients.36 The present study also could not find any significant relationship between baseline platelet count, AST, ALT, or LDH, and the incidence of comorbidities in CORT-treated HELLP syndrome patients. Intensive care duration was negatively associated with gestation week and positively associated with nulliparity and percent patients having comorbidities in HELLP patients, but not with the severity of biological markers per se.

Some of the limitations of the present study may have compromised the overall outcomes to some extent. Firstly, studies with varying designs are included because no particular design could make available sufficient data. Secondly, clinical and methodological heterogeneity of the sample population in the form of factors such as the severity of HELLP syndrome, time of CORT administration, and dosage and duration of CORT administration in recruited patients may have impact on overall outcomes. Another factor to compromise the precision of the outcomes may be the handling of missing data. Statistical procedures used to impute measures of dispersal may also have slight impact as some study reports lacked such data.

**CONCLUSIONS**

Corticosteroid administration to HELLP syndrome patients provides benefits in improving disease markers. Changes in platelet count and LDH levels after CORT therapy are found to be negatively associated with baseline platelet count, and also with intensive care duration in CORT-treated HELLP syndrome patients. Intensive care duration was, in contrast, positively associated with gestational age.

**TABLE 2. Effect Sizes (Changes From Baseline) in the Markers of HELLP Syndrome in CORT-treated Patients**

| Outcome Variable   | Datasets | Effect Size (95% CI)       | P        | I²  |
|--------------------|----------|---------------------------|----------|-----|
| Platelet count     | 25       | 38.09 (29.55, 46.6)       | <0.00001 | 99% |
| AST levels         | 18       | -61.08 (–81.59, –40.57)   | <0.00001 | 98.7% |
| ALT levels         | 9        | -51.08 (–86.07, –16.09)   | <0.005   | 94% |
| LDH levels         | 19       | -292.57 (–424.21, –160.93)| <0.00001 | 99% |
| Mean blood pressure| 7        | -14.02 (–14.32, –13.73)   | <0.00001 | 99% |
| Urinary output     | 7        | 44.37 (2.81, 85.92)       | <0.00001 | 100%|

ALT = alanine transaminase, AST = aspartate aminotransaminase, CI = confidence interval, CORT = corticosteroid, HELLP = hemolysis, elevated liver enzymes, and low platelet count, LDH = lactic dehydrogenase.
### TABLE 3. Important Findings of the Metaregression Analyses

| Outcome Variable          | Explanatory Variable    | Coefficient (95% CI)       | P       | Datasets | Tau² |
|---------------------------|-------------------------|-----------------------------|---------|----------|------|
| Change in platelet count  | Baseline platelet count | −0.893 (−1.945, 0.158)      | 0.092   | 21       | 1171 |
| Change in platelet count  | Baseline LDH levels     | −0.053 (−0.098, 0.007)      | 0.027   | 18       | 1017 |
| Change in AST levels      | CORT total dose         | 1.399 (0.415, 2.384)        | 0.013   | 8        | 405  |
| Change in ALT levels      | CORT total dose         | 1.509 (0.327, 2.69)         | 0.027   | 5        | 188  |
| Change in LDH levels      | CORT total dose         | 2.916 (1.362, 4.470)        | 0.004   | 8        | 0    |
| Change in LDH levels      | Baseline platelet count | −10.833 (−22.912, 1.245)    | 0.075   | 16       | 108,663 |
| Change in LDH levels      | Baseline urinary output | −16.61 (−27.803, −5.409)    | 0.012   | 7        | 23,305 |
| Change in LDH levels      | Intensive care stay     | −35.99 (−63.866, −8.131)    | 0.020   | 8        | 69,857 |
| Cesarean delivery rate    | Gestation age           | −0.053 (−0.112, 0.006)      | 0.074   | 19       | 0    |
| Intensive care duration   | Nulliparous percentage  | 0.240 (−0.012, 0.493)       | 0.059   | 7        | 45   |
| Intensive care duration   | % with comorbidities    | 0.787 (0.248, 1.327)        | 0.009   | 11       | 26   |

ALT = alanine transaminase, AST = aspartate aminotransaminase, CI = confidence interval, CORT = corticosteroid, HELLP = hemolysis, elevated liver enzymes, and low platelet count, LDH = lactic dehydrogenase.

**FIGURE 3.** Forest graph showing the meta-analysis of the change from baseline in platelet count in CORT-treated HELLP syndrome patients. CORT = corticosteroid, HELLP = hemolysis, elevated liver enzymes, and low platelet count.
however, positively associated with nulliparity and percentage of patients with comorbidities. Incidence of cesarean delivery was negatively associated with gestation age, but not with any of the biological markers or their changes after CORT therapy. These results favor the use of high-dose CORT therapy to HELLP syndrome patients with greater reductions in platelet count.

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FIGURE 4. Scatter plot showing the relationship between the change from baseline in platelet count after CORT therapy, and (A) baseline platelet count and (B) baseline LDH levels. CORT = corticosteroid, LDH = lactic dehydrogenase.

FIGURE 5. Plots showing the relationship between the incidence of cesarean deliveries and gestation age in the CORT-treated HELLP syndrome patients. CORT = corticosteroid, HELLP = hemolysis, elevated liver enzymes, and low platelet count.
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