Pregnancy Hypertension 17 (2019) 158–164

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Dexamethasone for the treatment of class I HELLP syndrome: A double-blind, placebo-controlled, multicenter, randomized clinical trial

Javier E. Fonseca[a,*], Juan C Otero[b], Clara Messa[c]

[a] Universidad del Valle, Department of Gynecology and Obstetrics (MUGER research group) and Hospital Universitario del Valle, Calle 5 # 36-08. Cali, 760042, Colombia
[b] Universidad Industrial de Santander and Hospital Universitario de Santander, Carrera 33 # 28, 126, Bucaramanga 680001, Colombia
[c] Universidad CES and Hospital General de Medellín, Carrera 48 # 32, 102., Medellin 050001, Colombia

1. Introduction

HELLP syndrome, characterized by hemolysis, elevated liver enzymes and low platelet count, is one of the most severe complications of preeclampsia; it is associated with increased frequency of complications such as death, eclampsia and acute renal failure, and a longer hospital stay. Women affected by HELLP syndrome may be classified by the degree of thrombocytopenia into class 1 HELLP syndrome (≤50,000 platelets/mm^3); class 2 HELLP syndrome (between 50,000 and 100,000 platelets/mm^3); and class 3 HELLP syndrome (between 100,000 and 150,000 platelets/mm^3) [1].

Since 1994, several clinical trials have suggested that corticosteroids, mainly dexamethasone therapy, can ameliorate and stabilize the disease in the antepartum period, and accelerate recovery after delivery [2–5]. Two clinical trials in contrast, one published in 2005 (which included pregnant and postpartum women), and another published in 2008 (which only included postpartum women) [6,7], did not support the use of dexamethasone for the treatment of HELLP syndrome, because their authors did not find differences in duration of hospitalization, time to recovery of laboratory tests, recovery of clinical parameters, need for blood transfusion, or frequency of complications. However, we found in an unplanned analysis [6], stratified according to the severity of HELLP syndrome, that the platelet recovery time was heterogeneous when the cases were stratified for HELLP class at the time of enrollment (Mantel –cox test, chi squared 4.76; P = 03) [6]. In this analysis we found that in patients with HELLP 1 who received dexamethasone therapy, the conditional probability of platelet recovery was higher (HR 3.4; 95%CI 1.3–8.5), and the duration of hospitalization was shorter (means 4.6 vs 10.4). Based on these findings, we decided to conduct a study aimed to determine the efficacy of using dexamethasone, only for the treatment of women affected by HELLP syndrome class 1.

2. Material and methods

This was a double blind, placebo controlled, multicenter randomized clinical trial involving pregnant and postpartum women admitted to three institutions: Hospital Universitario del Valle in Cali, Colombia; Hospital General del Medellin in Medellin, Colombia and Hospital Universitario de Santander in Bucaramanga, Colombia between October 2009 and November 2012. Pregnant women over 20 weeks of gestation or during the first 3 days of puerperium were asked to participate in the study, if they developed hypertension during pregnancy or the puerperium and met the criteria for complete class 1 HELLP syndrome, as defined by Sibai [8]: platelet count ≤50,000/mm3, aspartate aminotransferase (AST) ≥70 U/L and lactate dehydrogenase (LDH) ≥ 600 U/L. The recruited patients signed informed consent. Exclusion criteria included: oral temperature > 37.5 °C, diabetes diagnosis and contraindication to steroids. Because of the potential for spontaneous platelet recovery, postpartum women were excluded if randomization was not accomplished during the first 24 h after diagnosis. The study was approved by the Institutional Review Boards of the participating Hospitals and the Medical Schools (Universidad del Valle, approval certificate N 017-08); and it was registered in ClinicalTrial.gov with number NCT 01138839.

Pregnant and postpartum women were randomly assigned in a 1:1 ratio to treatment or placebo groups, using a randomized stratification (by center and the status of the patient at the time of admission to the trial, pregnant or postpartum women); randomization was performed in permuted blocks of varying size (4 or 6), and by a person external to this research. The assignment was kept inside consecutively numbered opaque envelopes labeled as pregnant or postpartum, which were opened after obtaining informed consent. Pregnant women in the experimental group received 10-mg doses of dexamethasone sodium phosphate, intravenously, every 12 h until delivery; and 3 additional doses after delivery. Postpartum women received three 10-mg doses after delivery. The same schedule was used for the control group, who were administered sterile water as placebo. Dexamethasone and placebo were packed in identical vials, in sealed boxes that were labeled with the corresponding treatment codes. Codes were not broken until the end of the univariate analysis. Treatment was to be discontinued if oral temperature rose above 37.5 °C

* Corresponding author.
E-mail address: javier.fonseca@correounivalle.edu.co (J.E. Fonseca).

https://doi.org/10.1016/j.preghy.2019.06.003
Received 24 March 2019; Received in revised form 10 June 2019; Accepted 16 June 2019
Available online 17 June 2019

All recruited patients received 1–1.5 gm/hour of magnesium sulfate intravenously. Nifedipine, 10 mg orally every six hours, was administered to women with diastolic blood pressure > 100 mm Hg; other antihypertensive drugs (clonidine, labetalol, prazosine and amlodipine) were administered if the diastolic pressure remained elevated. In addition, patients received 80–125 ml/hour of normal saline solution during hospitalization. If the urinary output remained below 30 ml/hour, an additional amount of 500 ml of normal saline were given during one hour; if oliguria persisted, 20 mg of furosemide was administered intravenously. Renal failure was diagnosed if serum creatinine was > 1.2 mg/dl; and pulmonary edema was diagnosed by physical examination and chest X-ray. When C-section was indicated, 8 units of platelets were given to women with platelet counts < 50,000/mm^3 at time of incision. The same amount of platelets was also given if the platelet count was ≤20000; or there was presence of bleeding gums, hematuria or bleeding from venipuncture sites. Since the standard of care is interruption of pregnancy after diagnosis of HELLP, induction of labor or C-section were performed depending on the maternal and fetal condition. If the gestational age was between 26 and 34 weeks, betamethasone (12 mg IM) was given every 24 h for up to 2 doses before delivery. Withholding steroids was considered unacceptable by the investigators.

Duration of hospitalization was measured from randomization to discharge. The duration of hospitalization for the two maternal deaths was excluded of the calculation of the mean and median values, but included and treated as censored data in survival analysis. Criteria for discharge included a platelet count > 100,000/mm^3, regardless of AST or LDH levels. However, if evidence of organ damage or other clinical complications were present, the patients remained hospitalized until recovery.

Measurements of blood pressure and urine output were carried out every two hours. Baseline and follow up laboratory studies included platelet count, AST, LDH and serum creatinine measurements every 12 h. Platelet counts were performed by automated counting, while LDH and AST were processed at 25 °C with a reference pattern of 120–240 and 0–18U/L (Roche Laboratories), respectively.

Medical personnel were trained on protocol procedures for enrollment and follow-up of patients. Quality checks of clinical and laboratory forms were carried out before data entry. Data were obtained from residents of gynecology and obstetrics in each institution; they were manually recorded, twice, in the data collection format, and in an electronic sheet. In order to validate the information, the obtained data were compared; and the inconsistencies were corrected, based on medical records.

Sample size was calculated [9] using two main outcomes: conditional probability of discharge and composite morbidity (acute renal failure, pulmonary edema, infections, eclampsia and death). We assumed for discharge an expected hazard ratio of 2.56 (according to our previous publication) [6], with 95% confidence and a power of 80%, requiring a sample size of 60 subjects per group. After performing the calculation with maternal morbidity, and assuming a risk in the placebo group of 36% and in the experimental group of 24% (according to the proportion of complications in patients with HELLP 1 in our previous study -unpublished data) [6], with a power of 80% and 95% confidence, 72 subjects per group were required. Finally, it was decided to include 144 patients, according to calculations made with maternal morbidity.

An intention to treat analysis was carried out. A planned subgroup analysis was performed according to pregnant and postpartum strata. We carried out an interim analysis of a sample size of 50 individuals, according to the method recommended by O'Brien-Fleming, with no differences in the final results. Continuous variables were analyzed with unpaired *t*-test or Mann-Whitney test, according to their distribution. Time to recovery of laboratory parameters (platelets, LDH and AST) and duration of hospitalization were analyzed by Kaplan-Meier. Categorical variables were compared by Chi square or Fisher exact test. Multivariate analysis was correspondingly performed using logistic or Cox regression. In addition to treatment (i.e.; the exposure of interest), other variables were considered in the final model if their P values were below 0.2 in the univariate analysis [10–12]. Antepartum use of betamethasone up to 2 weeks prior to randomization was also considered during modeling. Where appropriate, results are presented as relative risk (RR) with 95% CI, Odds Ratio (OR) and Hazard Ratio (HR).

3. Results

Ninety-five patients were considered eligible and invited to participate in the study. Two were excluded because of fever, 3 declined to participate; in addition, 3 postpartum women were not allocated to treatment during the first 24 h following diagnosis, so they were also excluded. As a result, there were left 87 women eligible for randomization, being assigned 42 to management with dexamethasone and 45 with placebo. Twenty-one were pregnant and 66 postpartum women; two postpartum patients received only 1 dose of placebo, one of them because of death, and the other one because she withdrew from the study. One pregnant women received only one dose of placebo, and none in the puerperium because of death during C-section secondary to hemorrhagic stroke. (Fig. 1).

Mean age of enrolled women was 25.78 years (range 13–48), mean gestational age was 33.85 weeks (range 21–41), and the mean parity was 1.08 (range 0–7 pregnancies). Platelet counts ranged from 16,000 to 49,000/mm^3, with mean and median values of 40,204/mm^3 and 41,500/mm^3, respectively. The mean LDH was 2,497 U/L, with a median of 1,589 (range 615–28,821); while mean AST was 560 U/L, with a median of 344 (range 70–6139). Baseline characteristics according to study groups were similar (Table 1).

3.1. Duration of hospitalization

The mean duration of hospitalization was longer among patients who received steroids; however, this difference was not statistically significant. Median and interquartile ranges (IQR) were not different either (Table 2). The conditional probability of discharge was similar between groups (H.R. 0.92 95% CI 0.53–1.59) (Table 3 and Fig. 2 panel A) in univariate analysis.

There were no differences in the multivariate analysis (H.R. 0.90 95% C.I. 0.52 – 1.58), after adjusting for use of steroids 2 weeks prior to delivery, delivery route and presence of pulmonary edema at time of admission.

3.2. Morbidity

There were 14 cases of composite morbidity, six in the dexamethasone group and eighth in the placebo group, without statistical differences (Table 4). In the separate analysis of each of the complications (acute renal failure, pulmonary edema, infections, eclampsia and death), there were not found differences. There were 2 maternal deaths, both in the placebo group during the first 12 h of study entry; one death was secondary to a cerebrovascular accident during C-section, and the other death occurred in a patient with liver failure and severe hemolysis at enrollment, with AST and LDH of 3870 and 11,351 U/L, respectively. There were no cases of hepatic rupture.

After adjustment, maternal composite morbidity was significantly higher in association with C-section (O.R. 7.84 95% CI 1.53–40.07), but this association was not found in the analysis when using dexamethasone (O.R. 0.95 95% CI 0.27–3.35).

3.3. Time to recovery of laboratory tests

There was no statistical difference between dexamethasone-treated and placebo-treated patients with respect to the time required to achieve a platelet count > 100,000/mm^3 (Fig. 2, panel B, and Table 3).

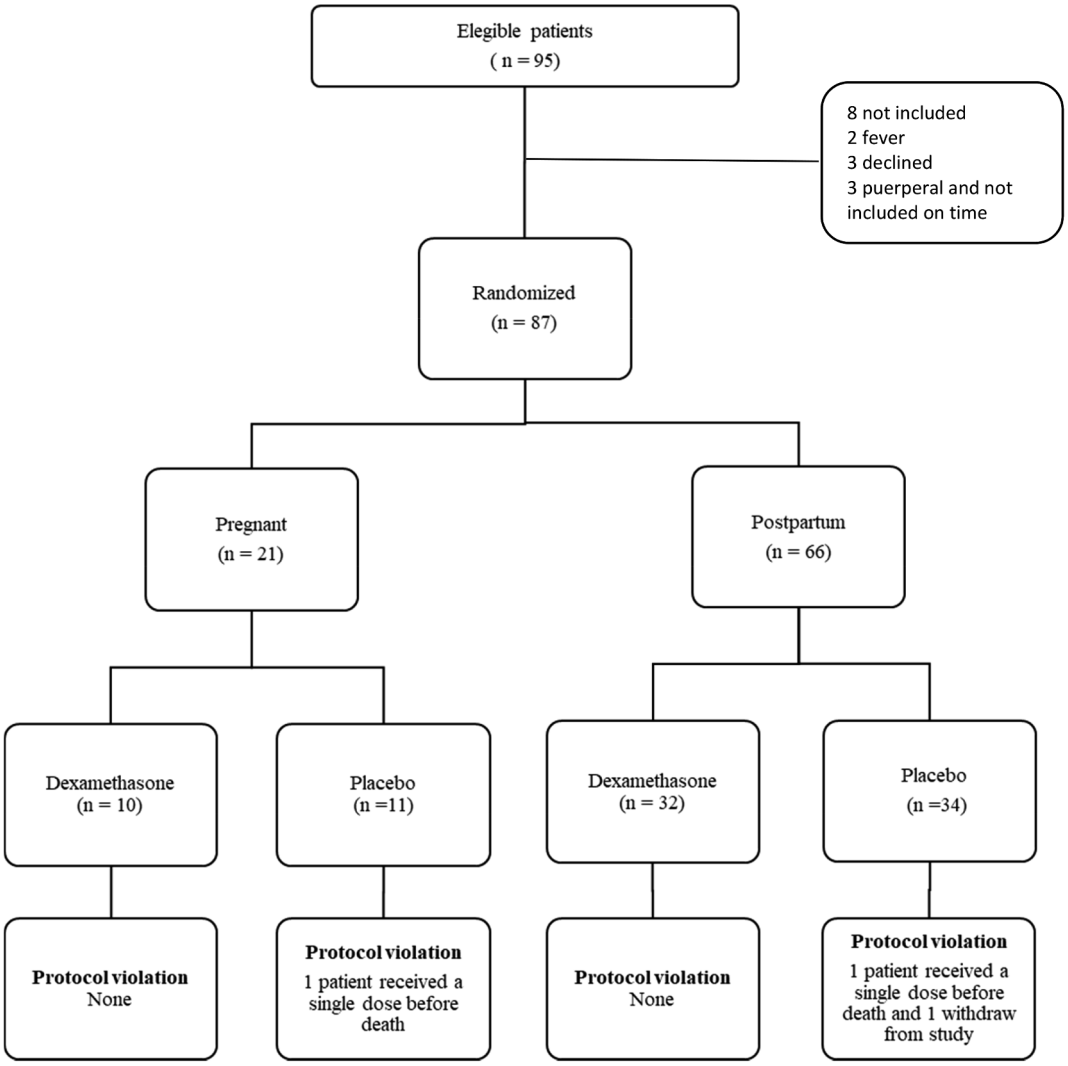

Fig. 1. Trial profile.

After adjusting for characteristics at the time of enrollment, no differences were found in platelet recovery, neither in the univariate analysis nor in the multivariate analysis. Platelets counts did not reach levels above 100,000/mm^3 in any of the two maternal deaths.

Before discharge, 37 patients (20 experimental and 17 control patients) did not reach LDH levels below 600 U/L, including the 2 maternal deaths and 35 patients who were discharged when their platelet counts were above 100,000 /mm^3. There was no statistically significant difference between treated and control patients who reached an LDH below 600 U/L before discharge, regarding their time to recovery in univariate and multivariate analysis (Fig. 2, panel C and Table 3). Interestingly, there was a faster recovery of LDH in women with eclampsia at enrollment after adjusting by prior exposure to steroids, treatment (dexamethasone or placebo), and pulmonary edema at enrollment (O.R. 4.19 95% IC 1.24–14.13).

39 patients (22 experimental and 17 control patients) did not reach AST levels below 70 U/L, including two of the maternal deaths and 37 who were discharged once their platelet counts reached > 100,000/mm^3. There was no statistically significant difference between treated and control patients who reached an AST below 70 U/L before discharge, regarding their time to recovery in univariate and multivariate analysis (Fig. 2, panel D and Table 3).

3.4. Blood transfusion

More blood products (platelets, plasma and red blood cells) were needed for women in the placebo group; however, this was not significant (Table 5). Median (IQR) transfused platelets was 6 (6–12) in both the placebo and dexamethasone group. Median (IQR) transfused plasma was 5 (4–7) in the placebo group, and 5 (1–7) in the dexamethasone group. And median (IQR) transfused red blood cells was 2 (2–4) in the placebo group, and 2.5 (2.0–3.5) in the dexamethasone group. None significant difference was found (P > 0.05).

3.5. Subgroup analysis by pregnant and postpartum patients

Stratified analysis of pregnant and postpartum groups showed no differences in the occurrence of complications, recovery of laboratory parameters, transfusion need, composite morbidity or duration of hospitalization. Among postpartum women, the mean duration of hospitalization was similar (but not identical) in those receiving placebo and in those receiving dexamethasone (4.0 vs. 4.2 days); however, this difference was not significant. Median duration of hospitalization was 3 days in both groups; and the interquartile ranges were 2–4 and 3–4 days for dexamethasone and placebo, respectively. Incidence of composite morbidity was 17.86% and 20.69% for dexamethasone and placebo (P = 1.00), respectively.

Among pregnant women, mean duration of hospitalization tended

Table 1
Baseline characteristics.

Characteristic	Dexamethasone (n = 42)	Placebo (n = 45)
Age (Y)*	24.24 ± 7.20	27.22 ± 7.94
Gestational age (weeks)*	34.11 ± 4.79	33.60 ± 4.97
Parity n(%)		
1	22 (52.38)	21 (46.67)
2–4	19 (45.24)	20 (44.44)
> 4	1 (2.38)	4 (8.89)
Ethnicity n(%)		
Afro-Colombian	10 (23.81)	9 (20.00)
Indigenous	4 (9.52)	4 (8.89)
Other	28 (66.67)	32 (71.11)
Platelets (n/mm^3)*	39,295 ± 6995	41,054 ± 6670
ALT (U/L)+	177 (47–1247)	199 (59–1900)
AST (U/L)+	314 (70–1185)	359 (70–6139)
LDH (U/L)+	1412 (631–8774)	1654 (615–28,821)
Creatinine (mg/mL)+	0.79 (0.5–1.4)	0.70 (0.49–2.09)
Acute renal failure at enrollment n(%)	4 (9.52)	2 (4.44)
Eclampsia n(%)	2 (4.76)	4 (8.89)
Pulmonary edema at enrollment n(%)	1 (2.38)	2 (4.44)
Qualitative protein in urine n (%)		
Positive	32 (76.19)	32 (71.11)
Negative	1 (2.38)	5 (11.11)
Unknown/unavailable	9 (21.43)	8 (17.78)
Systolic pressure (mmHg)*	135 ± 16.72	137 ± 27.16
Diastolic pressure (mmHg)*	88 ± 1.50	88 ± 2.98
Steroid use up to 2 weeks before delivery n(%)		
Yes	10 (23.81)	9 (20.00)
No	32 (76.19)	35 (77.78)
Unknown/unavailable	0 (0.00)	1 (2.22)
Patient's condition at enrollment n(%)		
Pregnancy	10 (23.81)	11 (24.44)
Puerperium	32 (76.19)	34 (75.56)
Delivery n(%)		
Vaginal	18 (42.86)	16 (35.56)
C-section	24 (57.14)	29 (64.44)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
* Mean (SD).
+ Median (RIQ)

Table 2
Duration of hospitalization according to treatment.

Duration of hospitalization (days)	Dexamethasone (n = 42)	Placebo (n = 43)
Mean ± SD	4.59 ± 4.91	3.93 ± 2.78
Median (IQR)	3 (2–4)	3 (3–4)
Range	1–26	1 – 17
Difference of mean: 0.67 (−2.38–1.05) P = 0.46 (Wilcoxon rank-sum test)		

to be lower in those receiving placebo than in those receiving dexamethasone (3.6 vs. 6.0 days), but this difference did not reach statistical significance. Median duration was 3 days in both groups, and the interquartile ranges were 2–10 and 2–4 days for dexamethasone and placebo, respectively. Incidence of composite morbidity was 14.29% and 22.22% for dexamethasone and placebo (P = 1.00), respectively.

In addition, there were no differences between the two groups (dexamethasone and placebo) in the time for recovering platelets, AST and LDH.

4. Discussion

Several controlled clinical trials have demonstrated the positive effects of dexamethasone in patients with HELLP syndrome. The initial studies[2–5] demonstrated beneficial effects on recovery times for laboratory studies, less need for blood products transfusion, less hospital days both ante- and post-partum; however, the strength of these findings is limited due to the small sample size and the lack of blindness in the studies; in addition, some of the studies did not report the results of all included patients; and even in the studies that included patients with HELLP 2 syndrome, the mean platelet count in one of them was > 100,000.

Two meta-analysis concluded that steroid administration in HELLP syndrome resulted in improvement in both platelet count and transaminases levels; and less hospital days. However, these meta-analysis included both retrospective and prospective studies with high heterogeneity (I^2 = 99%), which limits their validy [13,14].

Three controlled clinical trial have been published since 2005 [6,7,15]; two of these studies did not show any benefit with the use of steroids. Our unplanned subgroup analysis, using as criteria the severity of the disease (based on class), showed that in patients with HELLP 1 syndrome, there were less number of hospital days and the time required to reach a platelet count > 100,000 in patients receiving steroids. However, this analysis should be taken with caution and should be confirmed with additional studies [16].

In this clinical trial, intended to assess the value of using dexamethasone, only in patients affected by HELLP syndrome class 1, no differences were found in any of the primary parameters that were studied, including days of hospitalization and a composite of maternal morbidity. The duration of hospitalization was used as a primary outcome under the assumption that this outcome variable reflects the development of complications, and the rate of recovery of clinical and laboratory variables. In addition, it is a useful indicator for patients and clinicians; and for the composite maternal morbidity, in order to increase the power to the study in relation to the analysis of each complication, individually.

The mean and median duration values of hospitalization in this study were similar in the dexamethasone group (4.15 and 3 days, respectively), compared to the placebo group (4.44 and 3 days, respectively). This findings contrast with the unplanned subgroup analysis that we performed, in which there were found significant differences in hospital days. This difference could be due to the fact that the initial study did not take into account the severity of HELLP syndrome at the moment of planning the study, because there was no evidence at that time suggesting that the response to dexamethasone would be different, based on the severity of the condition; for this reason, the randomization did not consider the stratification based on HELLP syndrome types. Our current study included only class I HELLP syndrome patients; in addition, it performed randomization by blocks, which reduced the risk of bias selection and increased the validity of internal results.

There were no significant differences in the composite of maternal morbidity in patients receiving dexamethasone, compared to the ones receiving placebo (17.4% vs 21.05%); in addition, there were no differences in any of the complications (that were) individually analyzed; however, the frequency of renal failure was lower in patients receiving steroids (2.7%), compared to the ones receiving placebo (14.29%), but this difference did not reach significance. This could be due to the under power of our study, because it did not reach the size of recruitment that was initially planned for; which also might explain the lower frequency of expected maternal complications, individually or in composite (expected 36%, real 19.18%).

Similarly, regarding primary outcomes, there were no differences for any of the secondary outcomes (time to platelet recovery, LDH, transaminases and need for blood products) by univariate analysis or thereafter, after controlling for potential confounders, including exposure to steroids for fetal lung maturity two weeks prior to starting the study. On the contrary, in the group exposed to steroids, the recovery times for laboratory parameters were longer: platelets (H.R. 0.97 CI95% 0.58–1.61), LDH (H.R. 0.70 CI 95% 0.38–1.30) and AST (H.R. 0.76

Table 3
Determinants of hospitalization, composite morbidity and platelets, AST, LDH recovery.

Characteristic	Hospitalization H.R. (95% CI)	Composite morbidity* O.R. (95% CI)	Platelets H.R. (95% CI)	AST H.R. (95% CI)	LDH H.R. (95% CI)
Treatment					
Placebo+	1	1	1	1	1
Dexamethasone	0.92 (0.53–1.59)	0.78 (0.24–2.51)	0.94 (0.57–1.57)	0.67 (0.36–1.24)	0.71 (0.39–1.29)
Steroid use up to 2 weeks before delivery					
No+	1	1	1	1	1
Yes	0.91 (0.69–1.20)	0.59 (0.12–2.97)	0.64 (0.37–1.11)	0.89 (0.44–1.79)	0.90 (0.46–1.77)
Delivery					
Vaginal+	1	1	1	1	1
C-section	0.72 (0.41–1.28)	5.8 (1.19–28.20)	1.04 (0.62–1.74)	1.14 (0.61–2.13)	1.14 (0.61–2.14)
Ethnicity					
Afro-Colombian+	1	1	1	1	1
Indigenous	1.45 (0.63–3.33)	1.20 (0.16–8.88)	0.81 (0.35–1.85)	1.02 (0.39–2.69)	1.22 (0.45–3.25)
Other	0.83 (0.49–1.41)	0.57 (0.15–2.23)	0.96 (0.57–1.62)	0.57 (0.29–1.09)	0.79 (0.41–1.54)
Acute renal failure at enrollment					
No+	1	–	1	1	1
Yes	0.77 (0.33–1.78)	–	0.77 (0.28–2.10)	1.03 (0.32–3.35)	1.15 (0.41–3.19)
Pulmonary edema at enrollment					
No+	1	–	1	1	1
Yes	1.63 (0.51–5.21)	–	1.76 (0.55–5.61)	1.85 (0.44–7.67)	1.94 (0.60–6.28)
Eclampsia at enrollment					
No+	1	–	1	1	1
Yes	1 (0.43–2.30)	–	0.89 (0.39–2.06)	3.33 (1.38–8.03)	2.03 (0.86–4.78)

H.R, Non-adjusted Hazard Ratio; O.R, Non-adjusted Odd Ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
Composite morbidity included acute renal failure, eclampsia, pulmonary edema, hepatic rupture and death.
* Excluded patients with any morbidity at enrollment.
+ Reference category.

CI95% 0.42–1.36).

One of the strengths of our study is its high compliance, > 95% for the randomization treatment. The study design considered the differences in patient status at time of randomization, and the randomization was done in a blinded way, based on blocks of 4 to 6, which increased the internal validly of the results.

In addition, the analyses for subgroups were similar to the ones for all patients included. The external validity of this study is also high because of the large number of eligible patients who accepted to participate in the study (only 3 declined), the adoption of a widely accepted dose of dexamethasone for the treatment group, in which 100% of patients assigned to the dexamethasone group received 3 postpartum doses, and 8 of the 10 pregnant patients received one dose before the end of pregnancy; and the clinical relevance of the outcome measures.

The limitations of the study include the fact that the initial calculated sample size was not reached because of the long time required to recruit patients, the expiration of the medication supplied by the pharmacy, and the end of financial support by Colciencias; this fact diminishes the power of the study. However, all the results tend to be less favorable with exposure to dexamethasone, with the exception of renal failure. In addition, 19 patients (21.84%) received betamethasone within two weeks prior to entering the study, because of their gestational age < 34 weeks when they developed preeclampsia; however, similar results were found in the multivariate analysis adjusting for this variable, and after analyzing patients who did not receive betamethasone (32 in the group that received dexamethasone and 35 in the placebo group) with an HR = 0.85 IC95% 0.44–1.62.

Several published studies have demonstrated the potential physiologic effects of steroids in patients with HELLP, with a tendency to improve endothelial function. For example, Van Runnard found lower serum levels of interleukin 6 (IL6) in patients with HELLP who received prednisolone, compared to patients who received placebo, which suggests that steroids can stabilize endothelial function; however, the same study did not show any effect of prednisolone for ameliorating hepatic damage, without any change in AST, ALT or glutathione s-transferase alpha 1 (GSTA 1-1), a marker for hepatocyte necrosis [17].

In 2013, Wallace demonstrated that administering 10 mg of intravenous dexamethasone in patients with HELLP syndrome diminished by 32.3% their levels of circulating soluble endoglin after 12 h of administration, and 62.8% by 24 h; there was also a reduction of antiangiogenic factors, such as sFLt-1 by 25%, and 43.6% by 12 and 24 h after steroid administration [18]; similarly, Van Runnard found a diminution of IL6 levels after 24 h of steroid administration, concluding that “dexamethasone administration blunts the release of both antiangiogenic and inflammatory factors that could play a role in the pathophysiology of HELLP syndrome.” In addition, a meta-analysis that included 11 trials found a significant difference (0.67 CI95% 0.24–1.10) for the rate of platelet count change after steroid administration [19]; but in the same revision, no differences in other results were found. So, even though theoretically steroids should be of benefit in patients with HELLP syndrome, as stated by Asher: “the most important thing about a treatment is that it is effective, not merely that it ought to be effective” [20]; unfortunately, since 2005, all clinical assays determined to prove the benefit of dexamethasone in the management of

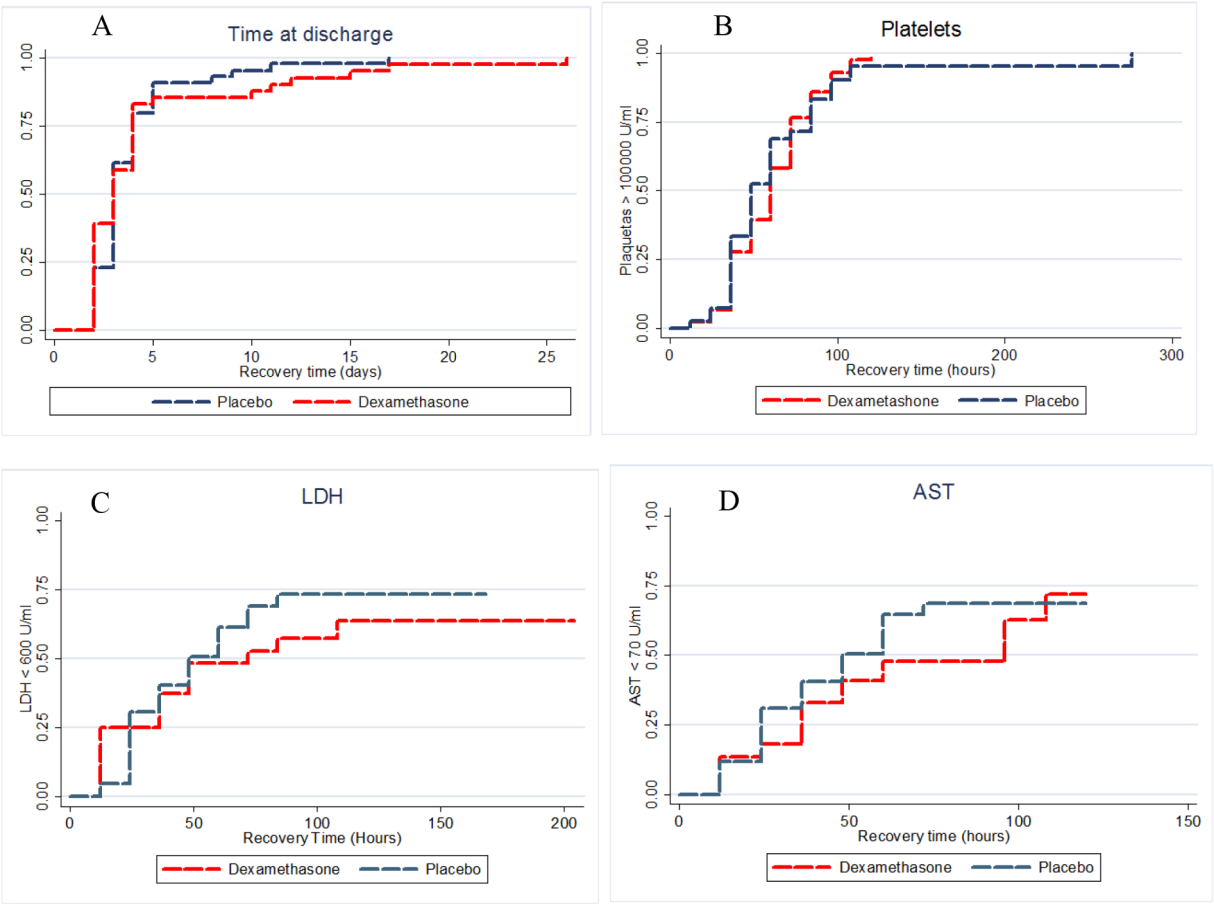

Fig. 2. Cumulative risk of discharge and laboratory parameters recovery Curves showing difference in time to (A) discharge, (B) platelet recovery (count > 100000), (C) LDH recovery (< 600 U/L), and (D) AST recovery (< 70U/L).

Table 4
Complications associated with HELLP I syndrome according to steroids use.

Complication [n/N(%)]*	Dexamethasone	Placebo	p	Relative Risk (95% CI)
Composite morbidity	6/35 (17.14)	8/38 (21.05)	0.67	0.81 (0.31–2.11)
Acute renal failure	1/37 (2.70)	6/42 (14.29)	0.11	0.19 (0.24–1.50)
Pulmonary edema	0/41 (0.00)	1/43 (2.33)	1	0
Infections	4/42 (9.52)	6/45 (13.33)	0.57	0.71 (0.22–2.36)
Eclampsia	2/40 (5.0)	1/41 (2.44)	0.62	2.05 (0.19–21-72)
Death	0/42 (0.00)	2/45 (4.44)	0.49	0

* Only included patients without the event before randomization [women with complication/women at risk (%)].

Table 5
Transfusion according to steroids use.

Blood component	Dexamethasone (n = 42)	Placebo (n = 45)	p	Relative Risk (95% CI)
Platelets	12 (28.57)	15 (33.33)	0.63	0.93 (070–1.24)
Plasma	3 (7.14)	7 (15.56)	0.32	0.91 (0.78–1.06)
Red blood cells	8 (19.05)	14 (31.11)	0.20	0.85 (0.67–1.09)
Any transfusion	16 (38.10)	23 (51.11)	0.22	0.79 (0.54–1.16)

Data are n (%).

HELLP have failed to demonstrate improvement in over 354 patients, and have not been able to replicate earlier findings.

In summary, the results of this study failed to demonstrate the benefit of using dexamethasone in patients with class I HELLP syndrome, similarly to our previous study that included type 1 and 2 patients. There are needed further randomized clinical trials with sufficient power, by using greater patient numbers and meta-analysis with adequate design, in order to determine if steroids should be used in this clinical condition.

5. Financial support

COLCIENCIAS RC No. 334-2008. Dexamethasone was provided by *Tecnoquimicas*; however, they did not participate in the design, planning, execution and analysis of this study; nor did they participate in the preparation of this article.

Declaration of Competing Interest

None.

References

[1] J.N. Martin, P.G. Blake, K.G. Perry, J.F. McCaul, L.W. Hess, R.W. Martin, The natural history of HELLP syndrome: patterns of disease progression and regression, Am. J. Obstet. Gynecol. 164 (1991) 1500–1513.

[2] E.F. Magann, D. Bass, S.P. Chauhan, D.L. Sullivan, R.W. Martin, J.N. Martin, Antepartum corticosteroids: disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP), Am. J. Obstet. Gynecol. 171 (1994) 1148–1153.

[3] E.F. Magann, K.G. Perry, E.F. Meydrech, R.L. Harris, S.P. Chauchan, J.N. Martin, Postpartum corticosteroids: accelerated recovery from the syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP), Am. J. Obstet. Gynecol. 171 (1994) 1154–1158.

[4] P. Vigil-De Gracia, E. Garcia-Caceres, Dexamethasone in the post-partum treatment of HELLP syndrome, Int. J. Gynecol. Obstetrics 59 (1997) 217–221.

[5] O.T. Yalcin, T. Sener, H. Hassa, S. Ozalp, A. Okur, Effects of postpartum corticosteroids in patients with HELLP syndrome, Int. J. Gynecol. Obstetrics 61 (1998) 141–148.

[6] J.E. Fonseca, F. Mendez, C. Cataño, Arias F Dexamethasone treatment does not improve the outcome of women with HELLP syndrome: a double-blind placebo-controlled randomized clinical trial, Am. J. Obstet. Gynecol. 193 (2005) 1591–1598.

[7] L. Katz, M.M. deAmorim, J.N. Figueiroa, et al., Postpartum dexamethasone for women with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a double-blind placebo controlled, randomized clinical trial, Am. J. Obstet. Gynecol. 198 (283) (2008) e1–e8.

[8] B.M. Sibai, The HELLP syndrome (hemolysis, elevated liver enzymes and low platelets): Much ado about nothing? Am. J. Obstet. Gynecol. 162 (1990) 311–316.

[9] S. Piantadosi, Clinical Trials. A methodologic Perspective, First edition, A Wiley-Interscience Publication, U.S.A., 1997.

[10] D. Hosmer, S. Lemeshow. Applied Logistic Regression. Applied probability and Statistics, ed. P.A.M. Statistics. U.S.A. 1989: John Wiley & Sons. 307.

[11] Stata Reference Manual. Release 6. Vol 3. Stata Press, College Station, Texas. 1999;392.

[12] D. Hosmer, S. Lemeshow, Applied Survival Analysis. Regression Modeling of Time to Event Data, Wiley-Interscience, U.S.A., 1999.

[13] M. Mao, C. Chen, Corticosteroid therapy for managament of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome: a meta-analysis, Med. Sci. Monit. 21 (2015) 3777–3833.

[14] L. Yang, C. Ren, M. Mao, S. Cui, 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, Med. 95 (13) (2016) e3203.

[15] S. Mould, F. Paruk, J. Moodley, High-dose dexamethasone in the treatment of HELLP syndrome, Int. J. Gynaecol. Obstet. 93 (2006) 140–141.

[16] S.F. Assmann, S.J. Pocock, L.E. Enos, L.E. Kasten, Subgroup analysis and other (mis) uses of baseline data in clinical trials, Lancet 355 (2000) 1064–1069.

[17] P. Van Runnard, A. Kavelaars, C. Heijnen, W. Peters, et al., HELLP Syndrome is Associated with an increased inflammatory response, which may be inhibited by administration of prednisolone, Hypertension Pregnancy 27 (2008) 253–265.

[18] K. Wallace, J. Martin, K. Tam, et al., Seeking the mechanism(s) of action for corticosteroids in HELLP syndrome SMASH study, Am. J. Obstet. Gynecol. 208 (380) (2013) e1–e8.

[19] D.M. Woudstra, S. Chandra, G.J. Hofmeyr, T. Dowswell, Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy, Cochrane Database Syst. Rev. (9) (2010) CD008148.

[20] R. Asher, Apriority: thoughts on treatment, Lancet 2 (1961) 1403–1404.