Mini Review

iMedPub Journals
http://www.imedpub.com

Critical Care Obstetrics and Gynecology

2016
Vol. 2 No. 1:10

The Effect of Dexamethasone on the Pre-Eclampstic Process - A Brief Reprieve up to Day 4

Yves Muscat Baron

Department of Obstetrics and Gynaecology, Mater Dei Hospital, Malta

Corresponding author:
Yves Muscat Baron

Department of Obstetrics and Gynaecology, Mater Dei Hospital, Malta

yambaron@go.net.mt

Tel: +356 2545 0000

Summary

A literature review was carried out on the evolution of Pre-eclampstic Toxaemia Syndrome before and after dexamethasone administration. Following the literature review, a case series of three patients who had high blood pressure and proteinuria in pregnancy, in connection with the administration of dexamethasone was reported.

Keywords: Pre-eclampstic, Toxaemia, Proteinuria, Pregnancy

Received: December 15, 2015; **Accepted:** January 22, 2016; **Published:** January 27, 2016

Literature Review

Pre-eclampsia is the consequence of an initial placental trigger, which initially has no adverse effect on the mother. As the pre-eclampstic process progresses, a maternal systemic inflammatory reaction results presenting the clinical signs and symptoms of the syndrome [1]. Although pre-eclampsia is associated with a failure of the normal invasion of trophoblastic cells, leading to maladaptation of maternal spiral arterioles [2] it can also be associated with hyper placentation disorders such as diabetes, hydatidiform mole, and multiple pregnancy.

The maternal arterioles are the source of blood supply to the fetus, and maladaptation of these vessels can interfere with normal villous development. In some cases, compensation can occur, but, in others, poor villous development results in placental insufficiency [3]. Secondary damage, such as fibrin deposition and thrombosis, can then occur within the placenta. These features are found in cases of placental insufficiency whether pre-eclampsia is present or not [3]. Not all women with the potential placental trigger develop pre-eclampsia; consequently the maternal response must be the decisive factor in development of systemic disease.

Although pre-eclampsia is considered primarily to be a vascular endothelial disorder [4], it presents as a multisystem disorder with various manifestations. This variation could be due to different vascular beds being affected to varying degrees, however research has shown that there is a differential maternal inflammatory response [5]. The maternal syndrome of preeclampsia has previously been ascribed to generalized maternal endothelial cell dysfunction. Recent research is suggesting that the endothelial dysfunction is a part of a more generalized intravascular inflammatory reaction involving intravascular leukocytes as well as the clotting and complement systems [6] Pre-eclampsia may be a final common pathway response to inflammatory stimuli such as infection [7].

A possible interpretation of these observations suggests that the anti-inflammatory impact of dexamethasone may attenuate the inflammatory cascade involved in the pre-eclampstic process. Up to day 4, dexamethasone appears to moderate the progression of pre-eclampsia, reducing the blood pressure and leading to significant gain in gestational age. These finding begs the question - Would a repeat administration of dexamethasone in pre-eclampstic patients at day 3-4 gain a further reprieve from the pre-eclampstic process and consequently increase the gain in gestational age?

In a limited capacity other anti-inflammatory drugs such as aspirin given early in pregnancy have been associated with an attenuation of the pre-eclampstic process [8]. Conversely nonsteroidal anti-inflammatory drugs have been linked with exacerbation of hypertension especially in the postpartum period [9].

The evaluation of the impact of antepartum administration of corticosteroids on the course of the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) in pregnancies at 24 to 37 weeks' gestation has been initially attempted by Magann et al. [10]. A small prospective, randomized study was undertaken in 25 antepartum patients with atypical severe preeclampsia expressed as HELLP syndrome. Twelve pregnant women were randomized to receive double-dose dexamethasone (10 mg intravenously every 12 hours) until delivery, and 13 women were randomized to the control arm. Management and delivery decisions for all patients were based on a common protocol, with delivery undertaken for a deteriorating maternal or fetal condition.

In the corticosteroid-treated group the maternal platelet count significantly increased (p = 0.006), whereas lactic dehydrogenase and alanine aminotransferase significantly decreased over time (p = 0.03 and p = 0.005) in comparison to the 13 women who did not receive corticosteroids. Maternal urinary output after entry into the study was significantly increased within hours after steroid administration versus the control group (p = 0.0006). The study entry-to-delivery interval (41 ± 15 hours) was significantly longer in the group of steroid-treated women (p = 0.0068) [10].

Stabilization and significant improvement in the laboratory and clinical parameters associated with HELLP syndrome occurred in women who received high-dose antenatal corticosteroids, as measured by maternal platelet count, urinary output, lactic dehydrogenase, alanine aminotransferase, and postponement of delivery. The findings of this investigation suggest that this therapeutic approach could enhances maternal-fetal care by postponing delivery of some previable fetuses, reduce the need for maternal transfusion of blood products, reduce neonatal morbidity or mortality from multiple systemic effects, and facilitate a safer transfer of the ill mother to a tertiary care site for optimal peripartal care [10].

A different research group (Tompkins et al.) found similar beneficial findings of glucocorticoids on the pre-eclampstic process [11]. The study group consisted of 93 patients between 24 and 34 weeks' gestation diagnosed with HELLP syndrome. All patients were given intramuscular injections of either betamethasone or dexamethasone. The three most common regimens used were 12mg of intramuscular betamethasone administered twice 12 hours apart, 12mg of intramuscular betamethasone administered twice 24 hours apart, and 6mg of intramuscular dexamethasone administered 4 times 6 hours apart. Precorticosteroid and postcorticosteroid platelet counts and liver function test results were compared. The differences in improvement in hematologic abnormalities among the three corticosteroid regimens were also analyzed [11].

The hematologic abnormalities seen in the 93 patients with HELLP syndrome improved after the administration of corticosteroids. The platelet count increased by 23.3 x 10(3)/microL (P <.001). A statistically significant decrease was seen in liver enzyme levels. The alanine aminotransferase decreased by 31.6 IU/L, the aspartate aminotransferase decreased by 52.1 IU/L, and the alkaline phosphatase decreased by 7.6 IU/L. Of the three regimens used, 2 doses of 12mg of intramuscular betamethasone given every 12 hours improved the liver function to the greatest degree.

This study demonstrated that corticosteroids produce a significant improvement in the hematologic abnormalities associated with HELLP syndrome. Two doses of betamethasone given 12 hours apart were found to be the most effective corticosteroid regimen [11].

The effect of steroids on the pre-eclampstic process has differentiated into the type of glucocorticoid which is best suited for attenuating the syndrome by Isler [12]. A study was undertaken to determine whether dexamethasone or betamethasone is superior for the antepartum treatment of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. This prospective randomized clinical investigation compared intravenously administered dexamethasone and intramuscularly administered betamethasone in the treatment of pregnant women with HELLP syndrome. Efficacy end points included laboratory values (platelet count, lactate dehydrogenase activity, aspartate aminotransferase activity) and clinical parameters (mean arterial pressure, urinary output) [12].

Forty patients were enrolled in the study, 19 in the dexamethasone arm and 21 in the betamethasone arm. The adjusted time-averaged changes from baseline were significant for aspartate aminotransferase activity (dexamethasone, -20.4 ± 9.6 U/L; betamethasone, 9.9 ± 8.9 U/L; P =.029), mean arterial pressure (dexamethasone, -15.6 ± 1.4 mm Hg; betamethasone, -8.1 ± 1.4 mm Hg; P <.001), and urinary output (dexamethasone, 12.9 ± 8.6 mL/h; betamethasone, -11.9 ± 8.2 mL/h; P =.043).

Intravenously administered dexamethasone appears to be more effective than intramuscularly administered betamethasone for the antepartum treatment of mothers with HELLP syndrome [12].

The above findings confirmed the superiority of dexamethasone to betamethasone in another study by the same research group. The prospective, mixed randomized/non-randomized clinical investigation of patients with postpartum HELLP syndrome was carried out. Treatment with either dexamethasone or betamethasone was continued until there was evidence of disease recovery [13].

Baseline characteristics of both the dexamethasone (n=18) and betamethasone (n=18) groups were similar. Although the time to discharge from the obstetrical recovery room was not statistically significant between groups, reduction in mean arterial blood pressure was more pronounced in the dexamethasone group as compared with the betamethasone group (-15.3 ± 1.4 mmHg vs. -7.5 ± 1.4 mmHg, respectively, P<0.01). Patients in the dexamethasone group required less antihypertensive treatment than the betamethasone group (6% vs. 50%, P=0.01) and also had a decreased need for readmission to the obstetrical recovery room (0% vs. 22%, P=0.03). This study supports the use of dexamethasone as the superior glucocorticoid to use for patients with postpartum HELLP syndrome (Isler) [12].

The Cochrane Pregnancy and Childbirth Group's Trials Reviewers went through the throes of initially refuting the use of glucocorticoids in attenuating the pre-eclampstic process [12] and recently has supported that there is a beneficial effect [14]. Initial Cochrane Review (2004) did not appreciate glucocorticoid effects even though a significant gain in gestational age was obtained. The mean interval (hours) to delivery (41 ± 15) versus (15 ± 4.5) (p = 0.0068) in favor of women allocated to dexamethasone [15].

The more recent Cochrane Pregnancy and Childbirth Group's Trials reviewed eleven trials (550 women) comparing corticosteroids with placebo or no treatment. There was no difference in the risk of maternal death (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.28 to 3.21), maternal death or severe maternal morbidity (RR 0.27, 95% CI 0.03 to 2.12), or perinatal/infant death (RR 0.64, 95% CI 0.21 to 1.97) [15].

The only clear effect of treatment on individual outcomes was improved platelet count (standardized mean difference (SMD) 0.67, 95% CI 0.24 to 1.10). The effect on platelet count was strongest for women who commenced treatment antenatally (SMD 0.80, 95% CI 0.25 to 1.35). Two trials (76 women) compared

dexamethasone with betamethasone. There was no clear evidence of a difference between groups in respect to perinatal/infant death (RR 0.95, 95% CI 0.15 to 6.17) or severe perinatal/infant morbidity or death (RR 0.64, 95% CI 0.27 to 1.48). Maternal death and severe maternal morbidity were not reported. With respect to platelet count, dexamethasone was superior to betamethasone (MD 6.02, 95% CI 1.71 to 10.33), both when treatment was commenced antenatally (MD 8.10, 95% CI 6.23 to 9.97) and postnatally (MD 3.70, 95% CI 0.96 to 6.44) [15].

The authors conclude that there was no clear evidence of any effect of corticosteroids on substantive clinical outcomes. Those receiving steroids showed significantly greater improvement in platelet counts which was greater for those receiving dexamethasone than those receiving betamethasone. There is to date insufficient evidence of benefits in terms of substantive clinical outcomes to support the routine use of steroids for the management of HELLP. The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile [15].

Case Reports

In the first case, hypertension and proteinuria were noted at 27 weeks of gestation in a 32 year old primigravida. The blood pressure progressively rose to levels as high as 160/105 mmHg. Urine analysis showed three plus protein, the 24 hour urine collection indicated a total of 2.5 g of protein. Compared to the booking visit at 22 weeks gestation, the platelet count decreased by 56 x 10(3)/microL, alanine aminotransferase increased by 71.6 IU/L and the aspartate aminotransferase increased by 62.1 IU/L.

Antihypertensive treatment in the form of 400 mg labetolol three times a day was administered and the mean arterial blood pressure decreased to safer levels. Two doses of dexamethasone 12 mg were administered twelve hours apart to encourage fetal lung maturity. On day 4 the blood pressure readings surged again and persisted to 170/120 mmHg necessitating abdominal delivery. Following the abdominal delivery a live 1.2 Kg fetus was delivered and cared for at the Neonatal and Pediatric Intensive Care Unit. The mother was discharged seven days post operation while the child was discharged two and a half months after.

The second case had a similar scenario the pathological process initiating at 26 weeks gestation in a 34 year old primigravida. Blood pressure readings progressively rose to levels as high as 150/100 mmHg while the urinalysis showed three plus protein. The 24 hour urine collection indicated a total of 3g of protein lost over 24 hours. Labetolol as antihypertensive treatment in the form of 400 mg twice times a daily was administered. The mean arterial blood pressure decreased to safer levels 140/85 mmHg. Fetal lung maturity was accelerated with two doses of dexamethasone 12 mg were administered twelve hours apart. On day 4 the blood pressure readings surged again and persisted to 180/120 mmHg. The patient complained of dyspnea with signs of pulmonary oedema, requiring delivery of the fetus. Following the Caesarean section a live 1 Kg fetus was delivered and managed in the Special care Baby Unit. The mother was discharged seven days post operation while the child was discharged three months later.

The third patient was a 21 year old primigravida, admitted at 24 weeks gestation complaining of dysuria, and pyrexia. A positive renal punch was elicited. Antibiotics were started with apparent resolution of symptoms.

The next day the patient complained of sudden dyspnea, resistant to oxygen delivered via mask. A medical consultation ventilation/perfusion scan excluded pulmonary embolism. A diagnosis of Adult Respiratory Distress Syndrome was made and the patient was transferred to the Intensive Therapy Unit.

Blood cultures were positive for Proteus mirabilis and meropenem 12 gram three times a day was initiated. In view of the possibility of premature delivery dexamethasone 12 mg BD was administered.

The following day the blood pressure progressively rose to levels as high as 160/110 mmHg. Urinalysis showed three plus protein, the 24 hour urine collection indicated a total of 800mg of protein. Antihypertensive treatment in the form of 400 mg labetolol three times a day was administered and the mean arterial blood pressure decreased to levels of around 140/95 mmHg.

On day 4 following of dexamethasone administration, grade IV pre-eclampsia with a blood pressure of 220/120 mmHg, proteinuria ++++. The patient complained of severe dyspnea the chest signs culminating into pulmonary oedema resistant to diuretic treatment. An abdominal delivery was carried out as an emergency.

Discussion

The above three cases illustrate a common pattern whereby all three primigravida presented with early onset pre-eclampsia which abated for 4 days after treated with anti-hypertensive and dexamethasone. After four days the pre-eclampstic process resurfaced necessitating delivery.

A crucial caveat in the treatment of pre-eclampstic process with glucocorticoids is the timing and form of administration. The maximum benefit of glucocorticoid treatment was noted in those cases where the administration was given early in the pre-eclampstic process. Once the HELLP syndrome sets in, the vicious cycle of the pre-eclampstic process will precede inexorably requiring delivery of the child. Moreover the biological activity of the glucocorticoid on the pre-eclampstic inflammatory process is undoubtedly affected by the mode of administration.

The anti-inflammatory effect of dexamethasone may not only affect the placental bed but its impact may be extrapolated towards the glomeruli, whereby improved renal function may help in retarding the pre-eclampstic cascade. It is obvious that the intravenous route would exert its effect more efficiently than the intramuscular group. One must keep in mind the progress in many pre-eclampstic women is rapid and difficult to predict.

A possible compromise in management of the pre-eclampstic process may be elucidated from our observations. It may well be that instead of the tempestuous application of dexamethasone 10 mg every 12 hours, a more palatable administration would be the early intravenous glucocorticoid treatment given twice daily every 3-4 days just enough to avoid the recrudescence of the pre-eclampstic process and simultaneously avoid the side-effects of high dose steroid therapy.

References

1 Redman CW, Sacks GP, Sargent IL (1999) Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obster Gynecol 180: 499-506.

2 Lyall F (2006) Mechanisms regulating cytotrophoblast invasion in normal pregnancy and pre-eclampsia. Aust N Z J Obstet Gynaecol 46: 266-273.

3 Sheppard BL, Bonnar J (1981) An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol 88: 695-705.

4 Roberts JM, Hubel CA, Taylor RN (1995) Endothelial dysfunction yes, cytotoxicity no. Am J Obstet Gynecol 173: 978-979.

5 Pijnenborg R, McLaughlin PJ, Vercruysse L, Hanssens M, Johnson PM, et al. (1998) Immunolocalization of tumour necrosis factor-alpha (TNF-alpha) in the placental bed of normotensive and hypertensive human pregnancies. Placenta 19: 231-239.

6 López-Jaramillo P, Herrera JA, Arenas-Mantilla M, Jáuregui IE, Mendoza MA (2008) Subclinical infection as a cause of inflammation in preeclampsia. Am J Ther 15: 373-376.

7 Macara L, Kingdom JC, Kaufmann P, Kohnen G, Hair J, et al. (1996) Structural analysis of placental terminal villi from growth-restricted pregnancies with abnormal umbilical artery doppler waveforms. Placenta 17: 37-48.

8 Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, et al. (2014) Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force.Ann Intern Med. 160: 695-703.

9 WHO Pharmaceuticals Newsletter (2004) Nonsteroidal Anti-inflammatory Drugs – Postpartum Administration may cause hypertension. Reactions 980: 2.

10 Magann EF, Bass D, Chauhan SP, Sullivan DL, Martin RW, et al. (1994) Antepartum corticosteroids: disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) Am J Obstet Gynecol 171: 1148-1153.

11 Tompkins MJ, Thiagarajah S (1999) HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome: the benefit of corticosteroids. Am J Obstet Gynecol 181: 304-309.

12 Isler CM, Barrilleaux PS, Magann EF, Bass JD, Martin JN Jr (2001) A prospective, randomized trial comparing the efficacy of dexamethasone and betamethasone for the treatment of antepartum HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol 184: 1332-1339.

13 Isler CM, Magann EF, Rinehart BK, Terrone DA, Bass JD, et al. (2003) Dexamethasone compared with betamethasone for glucocorticoid treatment of postpartum HELLP syndrome. Int J Gynaecol Obstet 80: 291-297.

14 Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T (2010) Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database Syst Rev 8: CD008148.

15 Matchaba P, Moodley J (2004) Corticosteroids for HELLP syndrome in pregnancy. Cochrane Database Syst Rev CD002076.