EFFECTS OF ANTENATAL BETAMETHASONE AND DEXAMETHASONE IN PRETERM NEONATES

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SUMMARY

Objective: This study was undertaken to investigate the effects of antenatal betamethasone and dexamethasone and to determine which is superior for preterm neonates.

Materials and Methods: This prospective, randomized, clinical investigation compared the effects of antenatal betamethasone and dexamethasone in neonates born before 37 weeks of gestation between December 20, 2001 and September 10, 2003. Pregnant women with symptoms and signs of preterm labor at 24–34 weeks of gestation or preterm premature rupture of membranes at 24–32 weeks of gestation were randomly divided into two groups receiving either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone given intramuscularly 12 hours apart. We compared the complications of preterm neonates, such as respiratory distress syndrome (RDS), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and neonatal sepsis in the two groups.

Results: A total of 140 mothers were included in our study and 157 preterm neonates were surveyed, of whom 81 were exposed to antenatal betamethasone and 76 to antenatal dexamethasone. No significant differences were found between the two groups in the incidence of RDS, severe IVH, PVL, NEC, ROP, and neonatal sepsis. However, compared with a complete course of antenatal corticosteroids, the incidence of RDS was significantly increased after an incomplete course (odds ratio, 2.48; 95% confidence interval, 1.04, 5.93; $p = 0.04$).

Conclusion: In our study, no significant differences between antenatal betamethasone and dexamethasone were found in complications of preterm neonates. Incomplete courses of antenatal corticosteroids were associated with an increased incidence of RDS compared with complete courses. [*Taiwanese J Obstet Gynecol* 2005;44(3):247–251]

Key Words: betamethasone, dexamethasone, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, periventricular leukomalacia, respiratory distress syndrome, retinopathy of prematurity

Introduction

Antenatal corticosteroid administration is known to reduce the incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and even necrotizing enterocolitis (NEC) in preterm neonates [1–3]. However, complications in neonates and mothers may occur when antenatal corticosteroids are given, including maternal or neonatal infection, sepsis, and maternal pulmonary edema. The National Institutes of Health (NIH) Consensus Development Conference recommends treatment regimens of either two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart between 24 and 34 weeks of gestation in pregnancies at risk for preterm delivery [4]. The benefits are most apparent when the corticosteroids are administered between 24 hours and 7 days before

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delivery. In principle, antenatal steroid therapy should not be routinely repeated in patients with preterm labor. For preterm premature rupture of membranes (PPROM) at less than 30–32 weeks of gestation, antenatal corticosteroids are also suggested as long as there is no evidence of infection. Our study followed the recommendations of the NIH consensus panel and compared the complications in preterm neonates between those exposed to antenatal betamethasone and dexamethasone.

Materials and Methods

This prospective study was conducted at Mackay Memorial Hospital between December 20, 2001 and September 10, 2003. Pregnant women with symptoms and signs of preterm labor between 24 and 34 weeks of gestation or PPROM between 24 and 32 weeks of gestation were admitted and included in the study. These women were randomly divided into two groups, receiving either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone given intramuscularly 12 hours apart. Data were excluded for intrauterine fetal death, immediate expiration after delivery, delivery after 37 weeks of gestation, or delivery not at our hospital, or if no postnatal data were available. We compared complications in the preterm neonates, including RDS, severe IVH (grade 3 and 4), PVL, NEC, retinopathy of prematurity (ROP), and neonatal sepsis. In addition, infants from the two groups were compared for birth weight, head circumference, and 5-minute Apgar score. Differences in neonatal complications were compared between incomplete and complete courses of antenatal corticosteroids.

Preterm labor was diagnosed when persistent uterine contractions 6–8 times/hour or four contractions in 20 minutes were accompanied by dilation and/or effacement of the cervix detected via speculum examination. PPROM was diagnosed in the presence of a gush of fluid from the vagina followed by persistent, uncontrolled leakage, or pooling of fluid on speculum examination with positive nitrazine testing. The diagnosis of RDS was based on a combination of clinical features (tachypnea, nasal flaring, subcostal and intercostal retractions, cyanosis, and an expiratory grunt), exclusion of other causes of respiratory distress, and characteristic radiographic appearance (a diffuse reticulogranular pattern, giving the classic "ground-glass appearance", in both lung fields with superimposed air bronchograms). Cranial ultrasound was performed at least twice to survey for IVH and PVL within the first week of neonatal life and 6 weeks later. IVH was graded according to severity of hemorrhage into the ventricular system; grade 3 is IVH with ventricular dilatation and grade 4 is IVH with associated parenchymal hemorrhage [5]. PVL was defined as hyperechoic lesions (cysts or hollow places) in the periventricular white matter. NEC was diagnosed by clinical symptoms, physical examination, and abdominal radiography. ROP was defined as the abnormal growth of blood vessels within the retina and vitreous humor and was diagnosed by ophthalmologic examination. Neonatal sepsis was diagnosed from blood or cerebrospinal cultures.

Statistical analysis was performed using Student's *t* test for continuous variables and the Chi-squared test for categorical data. Fisher's exact test was used to examine neonatal complications numbering five or less. Logistic regression was used to examine the influence of incomplete courses of antenatal corticosteroids. A p value of less than 0.05 was considered to be statistically significant. For continuous variables, the results are presented as mean ± standard deviation.

Results

During the study period, a total of 168 mothers received antenatal corticosteroids. Fifteen delivered after 37 weeks of gestation and eight delivered at other hospitals. One intrauterine fetal death was noted, and four neonates expired immediately after delivery so no postnatal data were available. The remaining 140 mothers were included in our study and 157 preterm neonates (17 sets of twins) were surveyed, of whom 81 (51.6%) were exposed to antenatal betamethasone and 76 (48.4%) to antenatal dexamethasone. Mean maternal age was higher in the betamethasone group (31.3 ± 5.3 vs 29.1 ± 5.5 years; $p = 0.01$). No significant differences were noted between the two groups with regard to gestational age at delivery, parity, gender, multiplicity, mode of delivery, birth weight, head circumference, and low 5-minute Apgar score (Table 1). In addition, no statistically significant differences were found between the two groups in the incidence of RDS, severe IVH, PVL, NEC, ROP, and neonatal sepsis (Table 2). Logistic regression adjusted for gestational age showed that the incidence of RDS was significantly increased after incomplete courses of antenatal corticosteroids compared with complete courses (odds ratio, OR, 2.48; 95% confidence interval, CI, 1.04, 5.93; $p = 0.04$). There were no significant differences in the incidence of severe IVH, PVL, NEC, ROP, and neonatal sepsis between incomplete and complete courses of antenatal corticosteroids (Table 3).

Table 1. Perinatal characteristics

	Betamethasone (*n* = 81)	Dexamethasone (*n* = 76)	*p*
Maternal age (yr)*	31.3 ± 5.3	29.1 ± 5.5	0.01
Gestational age (wk)*	31.2 ± 2.9	30.9 ± 3.2	0.59
Parity, *n*	1.68	1.45	0.23
Male infant, *n* (%)	43 (53.1)	42 (55.3)	0.91
Multiple pregnancy, *n* (%)	31 (38.3)	30 (39.5)	0.99
Cesarean delivery, *n* (%)	58 (71.6)	47 (61.8)	0.26
Birth weight (g)*	1,662 ± 578	1,613 ± 674	0.62
Head circumference (cm)*	28.7 ± 3.2	28.2 ± 3.5	0.35
5-min Apgar score < 7, *n* (%)	9 (11.1)	9 (11.8)	0.89

**Mean ± standard deviation.*

Table 2. Neonatal complications according to corticosteroid treatment

	Betamethasone (*n* = 81)	Dexamethasone (*n* = 76)	*p*
RDS, *n* (%)	44 (54.3)	39 (51.3)	0.64
IVH (grade 3 or 4) , *n* (%)	3 (3.7)	2 (2.6)	1.00
PVL, *n* (%)	1 (1.2)	2 (2.6)	0.62
NEC, *n* (%)	4 (4.9)	3 (3.9)	1.00
ROP, *n* (%)	6 (7.4)	5 (6.6)	0.96
Neonatal sepsis, *n* (%)	7 (8.6)	11 (14.5)	0.40

RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity.

Table 3. Neonatal complications according to completion of corticosteroid course

	Incomplete course (*n* = 35)	Complete course (*n* = 122)	*p*
RDS, *n*	24	59	0.04
IVH (grade 3 or 4) , *n*	1	4	0.89
PVL, *n*	1	2	0.54
NEC, *n*	1	6	0.65
ROP, *n*	0	11	0.78
Neonatal sepsis, *n*	3	15	0.73

RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity.

Discussion

Preterm birth occurs in 7–10% of all pregnancies, and complications of prematurity account for most perinatal mortality and morbidity [4]. In the USA, prematurity-related disorders cause more than 70% of fetal and neonatal deaths [6]. Many randomized or controlled trials have demonstrated that antenatal corticosteroids reduce the risk of RDS, IVH, PVL, and even NEC of premature infants [1–3]. Effects of antenatal corticosteroids on the developing lung include increased tissue and alveolar surfactant, increased compliance and maximal lung volume, decreased vascular permeability, more mature parenchymal structure, enhanced clearance of lung water, enhanced response to surfactant treatment, and improved respiratory function [7]. Corticosteroids can also induce brain germinal matrix microvasculature maturation and make these vessels more resistant to rupture, thus decreasing the risk of IVH [8,9]. The physiologic effects of antenatal corticosteroid in PVL prevention include accelerated cytodifferentiation, greater maturity of cerebrovascular endothelial cells and autoregulation of cerebral perfusion, and increased activity of antioxidant enzymes [3]. Results vary in studies examining the effect of antenatal steroid administration on the incidence of NEC. Some conclude that antenatal corticosteroids reduce the incidence because they consider that steroids may accelerate intestinal maturation, but others did not demonstrate a decreased risk [10–13]. The

fluorinated steroids, betamethasone and dexamethasone, are generally the preferred corticosteroids because of their beneficial effect on fetal organ development. Both of these agents can cross the placenta largely in biologically active form and have a long half-life (3–5 hours) and duration of activity (36–54 hours), identical biologic effects, little mineralocorticoid activity, and relatively weak immunosuppressive activity [4]. They are almost identical in structure, differing only in α versus β orientation of the methyl group at position 16. The dexamethasone regimen leads to a lower peak level but a longer time to biologic activity and a rapid passage through the blood–brain barrier compared with the betamethasone regimen. Some reports reveal that dexamethasone with sulfites may generate neurotoxicity [14,15]. In 1994, the NIH recommended either two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone given intramuscularly 12 hours apart, between 24 and 34 weeks of gestation [4]. Our study compared the complications in preterm neonates exposed to betamethasone or dexamethasone in the antenatal period and found no significant difference between the two groups in RDS, severe IVH (grade 3 and 4), PVL, NEC, ROP, and neonatal sepsis. Bar-Lev et al carried out a retrospective study to assess the incidence of short-term outcomes in 550 low birth weight infants (≤ 1,750 g) exposed prenatally to either betamethasone or dexamethasone [16]. They also found no difference in the incidence of premature complications. However, Baud et al published a retrospective study of 883 infants with gestational ages between 24 and 31 weeks and found that betamethasone was associated with a lower risk of PVL than dexamethasone [17]. Whitelaw and Thoresen reviewed the literature and recommended betamethasone rather than dexamethasone for the immature brain [18]. Larger prospective clinical studies and larger sample sizes are needed to obtain more authoritative conclusions.

In our study, compared with complete courses of antenatal corticosteroids, the incidence of RDS was significantly increased in neonates exposed to incomplete courses, and most of the mothers with incomplete courses delivered within 24 hours after corticosteroid administration. This finding is in agreement with the NIH Consensus Statement, which considers that optimal benefits of antenatal corticosteroids begin 24 hours after initiation of therapy and last up to 7 days [4]. Most neonates were exposed to an incomplete course of antenatal corticosteroids due to imminent preterm delivery. On the other hand, in a study to assess the effectiveness between incomplete courses of antenatal corticosteroids and no antenatal corticosteroids on preterm perinatal outcomes, Elimian et al found that even an incomplete course of antenatal corticosteroids was associated with a reduction in the rate of IVH and neonatal death [19]. It was suggested that even an incomplete course of corticosteroid therapy should be administered to a mother in danger of immediate delivery.

In conclusion, our prospective study indicates that there is no difference between antenatal betamethasone and dexamethasone in the incidence of RDS, severe IVH, PVL, NEC, ROP, and neonatal sepsis. It showed no advantage with betamethasone over dexamethasone as antenatal corticosteroid therapy in preterm neonates. Further larger prospective clinical studies are necessary to support our results. In addition, a complete course of antenatal corticosteroids is better than an incomplete course in decreasing the risk of RDS.

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