Comparison of single versus multiple courses of antenatal betamethasone in patients with threatened preterm labor

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Summary

Purpose of investigation: To compare single versus multiple courses of antenatal betamethasone administration with regards to the morbidity and mortality of preterm neonates. *Methods:* One-hundred and twenty-two women with threatened preterm labor were allocated to three different betamethasone schedules: 1) two doses of betamethasone 12 mg, intramuscularly, 24 hours apart (standard treatment) (n = 41); 2) standard treatment plus a third dose of 12 mg after seven days (n = 41); and, 3) standard treatment plus one dose of 12 mg every seven days until delivery (n = 40). Neonatal morbidity and mortality as well as maternal morbidity were evaluated. *Results:* Neonatal parameters, such as frequency of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis and neonatal mortality were not significantly different among the three groups for both singleton and multiple pregnancies. Similarly, maternal parameters were not significantly different among the three groups. *Conclusion:* The administration of multiple betamethasone courses in threatened preterm labor is not superior to single courses with regards to neonatal morbidity and mortality, as well as to maternal morbidity.

Key words: Betamethasone; Preterm labor; Neonatal morbidity; Neonatal mortality; Maternal morbidity.

Introduction

Preterm birth is a common medical problem with a rising incidence [1]. Neonatal complications associated with preterm birth are respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, neonatal retinopathy, jaundice, hypoglycemia and thermo-regulatory disturbances [2].

The main preventive measure taken against RDS, that is the most common complication in preterm neonates, is prophylactic administration of antenatal corticosteroids. This treatment approach began after the pioneering study of Liggins and Howie in 1972 [3]. The standard treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart [4]. It has been well documented that the maximal benefits of antenatal steroids are achieved within seven days from the initiation of treatment [5]. Since many women remain undelivered for weeks after initial steroid treatment, many clinicians choose to administer repeat steroid courses. There are studies that report reduced incidence and severity of neonatal lung disease with multiple steroid courses [6]. However, there has been great controversy regarding multiple steroid courses, mainly due to the potential adverse effects on neonatal health [7]. Multiple steroid courses may even adversely affect behavioral patterns in childhood [8]. The National Institute of Health in the USA has issued a consensus statement against the practice of repeated antenatal steroid courses outside clinical trials [9].

The aim of this study was to compare single versus multiple courses of antenatal betamethasone administration with regards to the morbidity and mortality of preterm neonates.

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Materials and Methods

The study was a prospective, non-randomized trial. It was carried out in the First Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece. The preterm neonates were evaluated and managed in the Second Department Neonatology, Aristotle University of Thessaloniki (the same hospital).

Initially, a total number of 150 pregnant women were included in the study. They presented with threatened preterm labor and were evaluated between the 24th and 34th week of pregnancy. Inclusion criteria were preterm contractions, premature rupture of membranes (PROM), vaginal bleeding and any other condition that required elective preterm delivery. Women with suspected chorio-amnionitis, systemic infection and purpura were excluded from the study.

Women with threatened preterm labor were admitted in the Fetal-Maternal Unit of the aforementioned department. Women remained in the Unit until the resolution of the presenting symptoms or until delivery. Women participating in the study received one of the following three antenatal steroid treatments: Group A (n = 41) received two doses of betamethasone (Celestone Chronodose, Schering-Plough Corp.) 12 mg, intramuscularly, 24 hours apart (standard treatment). Group B (n = 41) received the standard betamethasone treatment plus a third dose of 12 mg after seven days. Group C (n = 40) received the standard betamethasone treatment plus one dose of 12 mg every seven days until delivery. All subjects gave written informed consent.

Quantitative and qualitative parameters involving both neonatal and maternal factors were evaluated. Quantitative parameters included maternal age, gestational age at admission, maternal hematocrit, white blood cell count and C-reactive protein (CRP), duration of maternal hospital stay, gestational age at birth, Apgar scores at the first and fifth minutes after birth, birth weight and duration of neonatal hospital stay. Qualitative parameters included admission diagnosis (contractions, PROM, vaginal bleeding), parity, tocolytic use, antibiotic use, delivery mode, number of fetuses, neonatal gender, admission in neonatal intensive care unit, RDS, surfactant administration, NEC, IVH, neonatal retinopathy, neonatal sepsis and neonatal death.

Table 1. — *Comparison of quantitative and qualitative parameters among the three study groups.*

Parameter	Group A (n = 41)	Group B (n = 41)	Group C (n 40)	*p* value
Quantitative				
Maternal age (years)	29.9 (28.3-31.5)	33.4 (32.4-34.5)	31.6 (30.2-33.0)	0.002
Gestational age at admission (weeks)	28.6 (27.7-29.7)	28.9 (27.8-29.9)	28.21 (27.1-29.3)	0.652
Hct (%)	32.3 (31.3-33.3)	33.0 (32.1-33.9)	32.47 (31.5-33.5)	0.536
WBC (10^3/mm^3)	11.5 (10.5-12.6)	10.8 (10.1-11.5)	11.1 (10.4-11.8)	0.474
CRP (mg/dl)	2.2 (1.1-3.4)	0.7 (0.3-1.1)	0.7 (0.4-0.9)	0.002
Maternal hospitalization (days)	21.5 (17.0-26.1)	24.8 (19.0-29.6)	31.4 (25.3-37.6)	0.026
Gestational age at birth (weeks)	31.3 (30.5-32.2)	31.4 (30.7-32.2)	32.3 (31.5-33.2)	0.151
Apgar score at first minute	7.0 (6.6-7.5)	6.8 (6.3-7.4)	6.9 (6.4-7.4)	0.846
Apgar score at fifth minute	8.4 (8.0-8.8)	8.1 (7.6-8.6)	7.9 (7.4-8.5)	0.368
Neonatal birth weight (gr)	1612 (1429-1795)	1648 (1467-1829)	1684 (1503-1866)	0.853
Neonatal hospitalization (days)	35.6 (24.3-46.9)	24.6 (19.2-30.0)	30.3 (22.3-38.4)	0.196
Qualitative				
Admission diagnosis (contractions/PROM/hemorrhage)	23/14/15	29/2/22	34/7/14	0.008
Parity (I/II/III/IV)	32/5/3/1	28/9/3/1	30/9/2/0	0.667
Tocolytic use (yes/no)	38/3	34/7	37/3	0.128
Antibiotic use (yes/no)	20/21	20/21	19/21	0.338
Delivery mode (caesarean/vaginal)	40/1	39/2	39/1	0.338
Number of fetuses (1/2/3)	31/18/3	29/24/0	29/14/12	0.001
Neonatal gender (male/female)	23/29	29/23	29/26	0.474
Admission at NICU (yes/no)	49/3	43/10	48/7	0.127
RDS (yes/no)	26/26	22/31	29/26	0.127
Surfactant administration (yes/no)	26/26	22/31	29/26	0.480
NEC (yes/no)	1/51	0/53	0/55	0.352
IVH (yes/no)	1/51	1/52	0/55	0.588
Neonatal retinopathy (yes/no)	0/52	0/53	0/55	-
Neonatal sepsis (yes/no)	5/47	5/48	9/46	0.446
Neonatal death (yes/no)	4/48	6/47	3/52	0.532

Data are given as mean (95% confidence interval) or as absolute values. Hct: hematocrit, WBC: white blood count, CRP: C-reactive protein, PROM: premature rupture of membranes, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage.

For the statistical analysis the SPSS® 15.0 (Statistical Package for the Social Science 15th edition, SPSS Inc, USA) was employed. All tests that were used for the statistical comparison of the various parameters (one-way Anova, Kruskal-Wallis, chi-square, *post hoc* Bonferoni) were two-tailed and significance level was determined at $p < 0.05$. Quantitive results were expressed as mean and 95% confidence interval (CI).

Results

Of the 150 women recruited for the study, only those with complete documentation of all findings were included in the final evaluation: 41 women from Group A, 41 from Group B and 40 from Group C.

The study parameters are presented in Table 1. Maternal age ($p = 0.002$), serum CRP ($p = 0.002$) and duration of hospital stay ($p = 0.026$) were found to be different among the three groups as well as number of fetuses per pregnancy ($p = 0.001$) and admission diagnosis ($p = 0.008$).

When neonates from singleton and multiple pregnancies were compared, no significant difference was found in RDS, although there was a trend towards the latter group ($p = 0.08$). In addition, no significant difference was found among the three groups as far as RDS, NEC, IVH and neonatal death are concerned.

Discussion

It has been clearly demonstrated by numerous clinical trials that the administration of antenatal corticosteroids (betamethasone or dexamethasone) reduces the incidence of neonatal morbidity and mortality [5]. These beneficial effects are maximal when less than a week has elapsed between the initiation of treatment and the time of delivery. Nevertheless, the benefits of antenatal steroids do not completely dissipate a week after the initial treatment [10, 11]. It should be noted that the effects of antenatal steroids depend to a certain extent on the gestational age at birth. When delivery occurs before the 28th week of pregnancy, the neonatal outcome is less favorable, despite corticosteroid administration [12].

The present study did not reveal any detrimental effects of multiple betamethasone courses on maternal health. The neonatal outcome was similar in both standard and repeated steroid treatment protocols, a fact in agreement with recently published papers [13, 14]. Serum CRP and duration of hospital stay were significantly different among the three treatment groups. The difference in CRP could be attributed to the fact that in Group A there were more women who presented with PROM. Of note is the finding that women who presented with PROM and received weekly betamethasone courses (Group C) did not exhibit an increase in the incidence of chorioamnioni-

tis. The duration of hospital stay was longer in Group C. This difference can be explained as women who remained undelivered after the first week of steroid administration were still at risk of preterm labor and, therefore, remained hospitalized for a longer time.

In the present study, no significant difference was found among the three groups as far as neonatal morbidity, mortality, Apgar score, birth weight and surfactant administration are concerned. Thus, multiple steroid courses do not have a more favorable effect on neonatal outcome as compared to standard treatment. However, the practice of administering multiple antenatal corticosteroid courses is very common in many countries [15], despite the fact that repeated doses have been associated with adverse neonatal effects, such as decreased weight, length and head circumference [16].

Of a total number of 160 neonates in the study, 56 were twins and 15 triplets. Although neonates of multiple pregnancies tended to develop RDS more frequently than singletons, this difference was not significant. This is in agreement with other studies, which indicate no benefit from either standard or multiple corticosteroid course administration in twin pregnancies [17]. Of course, the absence of a significant difference in this study can be attributed to lack of study power for this particular endpoint.

Main limitations of this study were the lack of randomization and the relatively small sample, which did not allow for an exhaustive investigation on certain subgroups, such as deliveries before and after the 28th week.

In conclusion, administration of multiple antenatal betamethasone courses to women with threatened preterm labor is not superior to standard treatment with regards to both neonatal and maternal outcomes. This holds true for all neonates regardless of the cause of preterm birth and the number of fetuses per pregnancy (singleton or multiple). In view of the potential adverse effects of multiple steroid courses, there is a need for large randomized controlled trials, which should include long-term follow-up of the exposed neonates in order to determine the optimal antenatal steroid treatment schedule.

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