Comparison of single and double courses of antenatal corticosteroid administration on neonatal mortality and morbidity

Neonatal mortalite ve morbidite üzerine tek doz ve çift doz antenatal kortikosteroid uygulamasının etkisi

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Abstract

Objective: We aimed to evaluate the effects of single and double courses of antenatal corticosteroid administration on neonatal mortality and morbidity.

Materials and Methods: 232 preterm babies delivered between 01. April 2007 and 31. March 2008 with gestational ages of 26- 34 weeks were evaluated prospectively. Infants were divided into three groups. The first group did not receive any antenatal betamethasone therapy. The second group received single (two doses of 12 mg betamethasone administered at 24 hour intervals) and the third group received double (repeated course after one week) courses of betamethasone therapy.

Results: 156 (67.2%) infants received at least one dose of corticosteroid treatment whereas 76 (37.8%) did not. Of 156 infants who had received antenatal betamethasone, 36 (23.1%) developed respiratory distress syndrome (RDS), while the incidence of RDS was 35.5% in 76 preterms who received no antenatal betamethasone (27/76) ($p<0.05$). When single and double courses of bethamethasone administration were compared, 20 (24.7%) infants with single course and 16 (21.3%) infants with two course developed RDS ($p>0.05$).

Conclusion: When single and two courses of antenatal steroid therapy were compared, there was no statistically significant difference between groups regarding the incidence of RDS and mechanical ventilator treatment. (J Turkish-German Gynecol Assoc 2010; 11: 38-43)

Key words: Antenatal betamethasone therapy, respiratory distress syndrome, preterm delivery

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Özet

Amaç: Tek ve çift doz antenatal kortikosteroid uygulamasının neonatal mortalite ve morbiditesi üzerine olan etkisini incelemeyi amaçladık.

Gereç ve Yöntemler: 1 Nisan 2007 ve 31 Mart 2008 tarihleri arasında gestasyonel yaşları 26-34 hafta arasında olup doğurtulan 232 preterm bebek prospektif olarak değerlendirildi. İnfantlar üç gruba ayrıldı. Birinci grup antenatal betametazon tedavisi almadı. İkinci grup yirmidört saat arayla iki doz 12 mg betametazon alırken üçüncü grup bir hafta arayla ikinci betametazon tedavisi aldı.

Bulgular: 156 (%67.2) infant en az tek doz kortikosteroid tedavisi alırken 76'sı (%37.8) kortikosteroid almadı. Antenatal betametazon alan 156 infanttan 36'sında (%23.1) respiaratuar distres sendromu (RDS) gelişirken antenatal betametazon almayan 76 pretermden 27'sinde (%35.5) RDS gelişti ($p<0.05$). Tek ve çift doz betametazon uygulaması karşılaştırıldığında, tek doz betametazon alan 20 (%24.7) infantta, çift doz betametazon alan 16 (%21.3) infantta RDS gelişti ($p>0.05$).

Sonuç: Tek kür ve iki kür betametazon uygulaması karşılaştırıldığında, RDS insidansı ve mekanik ventilasyon ihtiyacı yönünden iki grup arasında istatistiksel olarak anlamlı bir fark saptanmadı ($p>0.05$).

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Anahtar kelimeler: Antenatal betametazon tedavisi, respiratuar distres sendromu, prematüre bebek

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Introduction

Preterm birth and associated complications are one of the leading causes of neonatal mortality and morbidity (1). Antenatal corticosteroids have been used for the prevention of RDS and other complications of prematurity for nearly thirty years. Yet, the debate still exists on the timing and frequency of antenatal steroid administration. It is still unclear whether a single or double course of antenatal steroid is more effective. It has been shown that a single course of antenatal steroid administered to women at risk for preterm delivery reduces neonatal mortality and morbidity (2). The effects of repeated doses are uncertain. They might improve pulmonary complications, but there is concern about the

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reduction of birth weight and adverse neurological outcome. The results of two studies on the long term effects of repeated doses of antenatal steroids are also controversial (3, 4).

In this study we aimed to evaluate the effects of single and two courses of antenatal betamethasone treatment on neonatal mortality and morbidity and to compare these groups with preterm babies who did not receive any antenatal corticosteroids.

Materials and Methods

This prospective study was conducted in the Ondokuz Mayıs University Faculty of Medicine, Department of Obstetrics and Gynecology between 01. April 2007 and 31. March 2008. Women in preterm labor with a gestational age of 26- 34 weeks were eligible for the study. Women admitted for preterm delivery on odd days received a single course and those admitted on even days of the month received a double course of betamethasone. Women in whom delivery was imminent, without time for the administration of betamethasone ,constituted the control group. Women in the single course group received betamethasone (Celestone®) 12 mg intramuscularly at 24 hour intervals (2x12 mg). The scheduled dose was repeated the next week if the patient still did not deliver and she remained at risk for preterm delivery before 34 weeks of gestation (Double course group). Women who were included in the double course group but delivered before the second dose were included in the single dose group. All women at risk for preterm delivery received ritodrine starting with a dose of 50 μgr/min. When contractions continued, ritodrine infusion was increased by 50 μgr/minute up to 350 μgr/min. The infusion was continued for 24 hours after the cessation of contractions. Babies with major congenital and/or chromosomal abnormalities were excluded from the neonatal outcome data analysis. Recorded maternal clinical parameters were: age, chronic illness (diabetes mellitus, hypertension) and complications of pregnancy (pregnancy induced hypertension, preeclampsia, eclampsia, gestational diabetes), preterm premature rupture of membranes, multiple pregnancy, antenatal corticosteroid administration and courses of antenatal corticosteroids. Recorded neonatal parameters were: method of birth, gestational age, sex, birth weight, 5th minute Apgar score, surfactant administration, requirement for mechanical ventilation (MV) and duration of MV, respiratory distress syndrome (RDS), complications of prematurity [bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leucomalasia (PVL), patent ductus arteriosus (PDA)], length of hospitalization and whether the baby was discharged or died.

During the study period, of 239 babies born before 34 weeks of gestational age, 7 were excluded due to major congenital and/or chromosomal abnormalities and 232 were eligible for the analysis. 156 (66.8%) of these babies were exposed to antenatal corticosteroids 81 (51.9%) received a single course and 75 (49.1%) received double courses of antenatal betamethasone; where 76 (33.2%) babies did not receive antenatal betamethasone.

Respiratory distress syndrome was diagnosed with compatible chest x-ray images and arterial blood gas analysis results in babies with respiratory insufficiency. Surfactant treatment was indicated by the results of arterial blood gas analysis and chest x-ray and a mean alveolar pressure equal to or higher than 7 cmH_2O measured by the attending neonatologist. Survanta® in a dose of 4 ml/kg was used as an early rescue treatment in babies with RDS. Bronchopulmonary dysplasia was defined as oxygen requirement with a duration of 28 days or more in the presence of typical chest x-ray. The diagnosis of PVL and IVH were based on cranial ultrasound examination. Sepsis was diagnosed according to the Töllner score and blood culture results (both clinical and culture proven) (5). Patent ductus arteriosus was diagnosed with echocardiography by a pediatric cardiologist. Necrotising enterocolitis was diagnosed via physical examination, Guiac positive/ bloody stools and abdominal x-ray findings and classified according to Modified Bell's staging criteria (6).

''SPSS for Windows 13.0'' was used for statistical analysis. The data were checked for normal distribution using normality tests. Mann-Whitney U and Chi-square tests were used for group comparisons where data were not normally distributed and the Student-t test was applied for data with normal distribution. A p value <0.05 was considered as significant. The Local Ethics Committee approved the study.

Results

232 preterm babies, with gestational ages of 26- 34 weeks, born in the obstetrics clinic between 01. April 2007- 31. March 2008 constituted the study group. Twenty- six (11.2%) of these were twins. Clinical characteristics of the study group are shown in Table 1.

156 (66.8%) babies had received antenatal corticosteroids: 136 (87.1%) singletons and 20 (12.9%) twins. Of 76 (33.2%) babies who did not receive antenatal betamethasone, 70 (96%) were singletons and 6 (4%) were twins.

Table 1. Clinical characteristics of the study group

	Antenatal steroid (+) (n=156)	Antenatal steroid (-) (n= 76)	p
Birth weight (grams)	1580± 460 (630-2500)	1473± 500 (740-2480)	>0.05
Gestational age (weeks)	30.4± 2.4 (26-34)	29.8± 2.6 (26-34)	>0.05
Male/ Female (%)	49 / 51	47 / 53	>0.05
Vaginal/Caesarean birth (%)	78 / 22	83 / 17	>0.05
Maternal age (years)	27.6± 5.2	27.3± 5.7	>0.05

Values are given as average ± standard deviation (minimum- maximum)

RDS was diagnosed in 36 (23.1%) babies who received antenatal corticosteroids and in 27 (35.5%) who did not (p<0.05). Surfactant use was also statistically different between antenatal steroid administered and non- administered groups (23.1% vs. 35.5%, p<0.05).

The incidence of BPD, sepsis, NEC, grade 3 / 4 IVH, PVL and PDA did not differ between babies receiving antenatal corticosteroid treatment and those who did not, as shown in Table 2 (7.7% vs.13.2%, 12.2% vs.17.1%, 4.5% vs.5.3%, 3.8% vs. 6.6%, 9% vs. 13.2%, and 15.4% vs.19.7% respectively; for all p>0.05).

Mechanical ventilation was required in 64 (43%) infants who received antenatal betamethasone and in 42 (57.5%) infants who did not (p<0.05). The average period for MV was 4.1±2.2 days (1-14 days) for babies receiving antenatal steroid therapy and 7.7±6.3 days (1-28 days) for babies not receiving steroids (p<0.05).

The 5th minute Apgar score was above 7 in 120 babies (79.5%) receiving antenatal steroid therapy and in 31 (40.8%) babies having no antenatal steroids (p<0.01).

The length of hospitalization was 11.7±11.4 (1-65) days in infants who received antenatal betamethasone, whereas this was 17.5±16.4 (1-78) days in infants who did not (p<0.01).

Regarding mortality, three (1.9%) babies exposed to antenatal corticosteroids died, whereas eight (10.5%) babies among the ones not receiving antenatal corticosteroids died. The difference was statistically significant (p<0.05) (Table 2). In the group receiving antenatal steroid, death was due to IVH in one and due to RDS in the others. In babies not being exposed to antenatal steroids, the reasons for death were IVH in two, sepsis in one and RDS and related complications in the others.

When the effect of antenatal steroids on RDS according to gestational age was analyzed, it was observed that antenatal steroids significantly reduced the incidence of RDS in babies born between 29-31 weeks and 32-34 weeks (p<0.05). When the incidence of RDS was analyzed in babies born between 26-28 weeks, there was no statistically significant difference between steroid receiving and not receiving groups (p>0.05) (Table 3).

81 (51.9%) babies received a single course and 75 (49.1%) babies received double courses of antenatal betamethasone. The clinical characteristics of single and double course steroid groups are shown in Table 4. Two groups were similar regarding gestational age, birth weight and method of birth (p>0.05).

RDS was observed in 20 (24.7%) babies receiving a single dose and in 16 (21.3%) babies receiving two doses of antenatal corticosteroids and they all received surfactant. The incidence

Table 3. The effect of antenatal corticosteroid treatment on RDS according to gestational age

Gestational age (weeks)	Antenatal steroid (+) (n=156)	Antenatal steroid (-) (n=76)	p
26-28 wk (n=65)			
RDS (+)	18 (45%)	13 (52%)	>0.05
RDS (-)	22 (55%)	12 (48%)	
29-31 wk (n=76)			
RDS (+)	10 (19.6%)	9 (36%)	<0.05*
RDS (-)	41 (80.4%)	16 (64%)	
32-34 wk (n=91)			
RDS (+)	8 (12.3%)	5 (19.2%)	<0.05*
RDS (-)	57 (87.3%)	21 (80.8%)	

RDS: Respiratory distress syndrome , *: p<0.05

Table 2. Neonatal problems in babies with and without antenatal corticosteroid treatment

	Antenatal steroid (+) (n= 156)	Antenatal steroid (-) (n= 76)	P
RDS	36 (23.1%)	27 (35.5%)	<0.05*
Surfactant use	36 (23.1%)	27 (35.5%)	<0.05*
Bronchpulmonary dysplasia	12 (7.7%)	10 (13.2%)	>0.05
Sepsis	19 (12.2%)	13 (17.1%)	>0.05
Necrotising enterocolitis	7 (4.5%)	4 (5.3%)	>0.05
Intraventricular hemorrhage	6 (3.8%)	5 (6.6%)	>0.05
Periventricular leukomalacia	14 (9%)	10 (13.2%)	>0.05
Patent ductus arteriosus	24 (15.4%)	15 (19.7%)	>0.05
MV use	64 (43%)	42 (57.5%)	<0.05*
Days on MV	4.1± 2.2 (1- 14)	7.7± 6.3 (1- 28)	<0.05*
5th minute Apgar score >7	120 (76.9%)	31 (40.8%)	<0.01*
Hospitalization days	11.7± 11.4 (1- 65)	17.5± 16.4 (1- 78)	<0.01*
Mortality	3 (1.9%)	8 (10.5%)	<0.01*

RDS: Respiratory distress syndrome, MV: Mechanical ventilator

Values are given as average ± standard deviation (minimum- maximum) *: p<0.05

for RDS and surfactant use did not differ between the groups (p>0.05). Mechanical ventilation was required in 39 (48.1%) of single course and 31 (41.3%) in double course groups (p>0.05). There was no statistically significant difference regarding days on MV, BPD, sepsis, NEC, IVH, PDA, PVL, 5th minute Apgar scores, length of hospitalization and mortality between single and double course antenatal steroid groups (p>0.05) (Table 4).

Discussion

Complications related to preterm labor have a great impact on neonatal morbidity and mortality; with RDS as the leading cause (7). Antenatal corticosteroids have been shown to promote fetal pulmonary maturation and reduce perinatal mortality, pulmonary and cerebral morbidity in preterm babies (8, 9). In the meta-analysis by Crowley et al. (10) antenatal steroids have been shown to reduce the incidence of RDS 50%. In the study by Kari et al (11) and in another study conducted by Brazilian Neonatal Research Network, antenatal steroid treatment reduced both the incidence of RDS and surfactant use and the requirement for MV (12). In the present study, it has also been observed that antenatal corticosteroid administration significantly reduced the incidence of RDS and surfactant use, as well as the need and duration of MV.

Gardner et al. have shown that antenatal corticosteroid treatment improved Apgar scores in babies born <1000 grams (13). In our study, 5th minute Apgar scores were significantly higher in babies receiving antenatal steroids compared to the ones not receiving steroids. There was no difference between single and double course steroid groups regarding 5th minute Apgar scores. The results were in accordance with the data that antenatal steroid administration improves early postnatal adaptation in preterm babies.

Gestational age is one of the main topics of disagreement regarding antenatal corticosteroid administration. Liggins and Howie (14) were the first investigators who, in 1972, showed that antenatal corticosteroid administration reduced the incidence of RDS by 60% in preterm babies with gestational ages between 26-32 weeks. Ballard et al. (15) have stated that antenatal corticosteroid administration to hasten pulmonary maturation may be effective even at >34 weeks of gestational age. The NIH consensus report published in 1994 advised that all fetuses at the risk for preterm birth between 24-34 weeks of gestation are candidates for antenatal corticosteroid treatment (9). In the study by Modarek and Najati (16), including 300 preterms of 29- 34 weeks, it was shown that antenatal corticosteroids prevented RDS. In the present study, we have also shown that antenatal corticosteroid administration reduced the incidence of RDS between 29- 34 weeks.

Although antenatal steroids reduce the incidence of RDS in preterm babies 50%, there is no net reduction in the incidence of BPD. Besides, there are studies showing that

Table 4. The comparison of single and double courses of antenatal corticosteroid treatment groups

	Single course steroid (n=81)	Double course steroid (n=75)	P
Maternal age	28.0± 5.2 (18- 40)	2728± 5.4 (18- 42)	>0.05
Gestational age (weeks)	30.5± 2.4 (26-34)	30.4± 2.4 (26-34)	>0.05
Birth weight (grams)	1567.9± 453 (630-2500)	1593.0± 470 (810-2420)	>0.05
Vaginal/cesarean birth (%)	19.7/80.3	13.5/ 86.5	>0.05
Respiratory distress syndrome	20 (24.7%)	16 (21.3%)	>0.05
Surfactant treatment	20 (24.7%)	16 (21.3%)	>0.05
Mechanical ventilator treatment	39 (48.1%)	31 (41.3%)	>0.05
Days on mechanical ventilator	4.2± 2 (1-10)	3.9± 2.3 (1- 14)	>0.05
Bronchpulmonary dysplasia	7 (8.6%)	5 (6.7%)	>0.05
Sepsis	10 (12.3%)	9 (%12)	>0.05
Necrotising enterocolitis	4 (4.9%)	3 (4%)	>0.05
Intraventricular hemorrhage	4 (4.9%)	2 (2.7%)	>0.05
Patent ductus arteriosus	13 (16%)	11 (14.7%)	>0.05
Periventricular leukomalacia	8 (9.9%)	6 (8%)	>0.05
5th minute Apgar score >7	62 (76.5%)	58 (77.3%)	>0.05
Hospitalization days	12.9± 12.5 (1-50)	10.5± 9.8 (1-65)	>0.05
Mortality	2 (%2.5)	1 (%1.3)	>0.05

Values are given as average ± standard deviation (minimum- maximum)

antenatal exposure to three or more doses of corticosteroids might increase the risk for BPD (17). In the present study, the incidence of BPD was 8.6% in single and 6.7% in double dose groups; without statistical difference. In the ACTORDS study, multiple doses of antenatal steroids have been shown to decrease the risk for BPD in babies < 32 weeks of gestation (20% in the single dose and 12% in the multiple dose group; RR: 0.6). These controversial results might be due to different patient selection criteria in these studies.

Liggins and Howie reported the reduction in the incidence of IVH after antenatal corticosteroid use (14). Garite et al. (18) have also shown that antenatal steroids reduced the incidence of IVH from 25% to 3% in 24-28 week preterms and they stated that betamethasone had a stabilizing effect on fragile germinal matrix capillaries. In another retrospective study including 514 preterms of 23-34 weeks, there was no difference regarding IVH among babies receiving antenatal steroids and not (12). In the present study, the incidence for IVH was 3.8% in babies receiving antenatal steroids, whereas this was 6.6 % in babies not receiving them. Although the difference was statistically insignificant, this minor difference might be important, since IVH is a major concern for neonatal mortality and long term handicaps.

Halac et al. (19), in a prospective study including 960 newborns, concluded that the incidence of NEC decreased by antenatal betamethasone use. This reduction was also shown by Bauer et al (7.1 % vs 2.0 %) and in the in the meta-analysis by Crowley (reduction by 65%) (20, 21). Conversely, there are studies in the literature showing that they do not influence the incidence of NEC (12,22). In the present study, antenatal corticosteroids did not reduce the incidence of NEC in preterms born between 26- 34 weeks.

Compared to the non-treated group, in babies receiving steroids during the antenatal period, the incidence of RDS, the need for MV and invasive interventions as well as occurrence of other neonatal complications are less frequently observed. As shown in our patient population, shorter hospitalization time in babies of steroid-treated mothers can be considered as an objective parameter supporting this observation.

The present study showed that length of hospitalization decreased significantly in babies receiving antenatal steroids (11.7 vs. 17.5 days). The six day reduction in hospitalization is important both in order to minimize the risk for nosocomial infection and to reduce hospital costs.

Since Liggins and Howie (14) have shown that antenatal steroids were most effective following 48 hours to 7 days of steroid administration and the effect was attenuated after 7 days, some authors have advised weekly courses of antenatal steroid administration to reduce the incidence of RDS and complications of prematurity in women who did not deliver seven days following steroid administration (23).

Ellimian et al. have shown that multiple course steroid treatment reduced the incidence of RDS and surfactant use without affecting growth and without increasing the risk for neonatal sepsis (24). In another study conducted by Pratt et al, when single and multiple course antenatal steroid treatment was compared, multiple course treatment reduced the incidence of RDS, surfactant use and the requirement for MV; although not statistically significant (25). On the contrary, in the present study, we did not show a difference in the incidence of RDS, surfactant use and need for mechanical ventilator among single and double course steroid groups.

The effect of multiple doses of antenatal steroids on birth weight is controversial. In some studies, it has been reported that repeated doses of betamethasone leads to birth weight reduction (5, 17, 26). Conversely, in the study by Guinn et al, no significant difference in birth weight has been observed with multiple courses of steroid therapy (27). In a similarly planned study, a proportional increase of on birth weight in the presence of increasing frequency of betamethasone therapy has been observed (28). We did not observe a difference in birth weight in single and double course antenatal steroid exposed groups; but the number of babies in the present study is too low to reach a conclusion on the reduction of birth weight.

Abbasi et al. (26), French et al. (17) and Crowther et al. (3) have shown that repeated dose steroid treatment not only reduces birth weight, but also leads to a reduction in head circumference. Contrarily, other studies have shown that the weight and head circumference of the babies exposed to repeated doses of antenatal steroids did not differ from the normal population both at discharge (4) and also at the age of three (17).

Belteki and Smith in their review on single and multiple doses of antenatal steroids concluded that, when compared with a single course, weekly repeated doses of antenatal steroids seem to reduce neonatal respiratory morbidity and some of its complications, especially when the delivery was before 32 weeks of gestation (28).

No significant difference has been reported between single and multiple courses of steroid therapy regarding the morbidity and mortality parameters, such as neonatal death, sepsis, IVH, NEC, BPD and PDA (27, 28, 29); similar to the results of the present study.

We conclude that single course antenatal corticosteroid therapy reduces the incidence of RDS, surfactant use, MV requirement, days on MV, duration of hospitalization and mortality; with an improvement of 5th minute Apgar score compared to non antenatal steroid exposed babies. Double course corticosteroid therapy was not superior to single course regarding complications of prematurity.

Conflict of interest

None declared

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