Is There a Beneficial Effect of Single Dose Antenatal Steroid Therapy on Mortality and Morbidities in Infants <30 Weeks Gestational Age?

Tek Doz Antenatal Steroid Tedavisi Gestasyonel Yaşı <30 Hafta Bebeklerde Mortalite ve Morbidite Üzerine Etkili mi?

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ABSTRACT

Aim: *Our knowledge regarding the impact of single-dose antenatal corticosteroid treatment on neonatal morbidities of VLBW is still scarce. In this study, we aimed to evaluate outcomes of infants born <30 weeks' gestation that received no ACS, partial course of ACS, and complete course of ACS.*

Material and Method: *In this retrospective study, infants <30 weeks in gestation at birth were included and divided into three groups based on exposure to ACS; Group 1, infants born without ACS exposure, Group 2, infants born after exposure to one dose of betamethasone, Group 3, infants born after exposure to complete the course. Our primary outcome was mortality. Secondary outcomes included the following: PDA, NEC, severe IVH, bronchopulmonary dysplasia, and cystic periventricular leukomalacia (PVL).*

Results: *616 infants were included. The incidence of chorioamnionitis was significantly higher in the complete course ACS group (p<0.05). The mortality rate was highest in the no ACS group (16.0%) compared to other groups but not statistically different. There was a trend toward lower morbidity in the partial course ACS group compared to none.*

Conclusion: *We found no statistically significant benefit of incomplete antenatal corticosteroids in infants born <30 weeks' gestation.*

Key words: *antenatal corticosteroids; betamethasone; neonatal outcomes; very low birth weight infants*

ÖZET

Amaç: *Acil nedenlerle çok düşük doğum ağırlıklı (ÇDDA) bebeklerin önemli bir kısmı tam doz antenatal kortikosteroid tedavisi tamamlanamadan doğsa da, kısmi doz antenatal kortikosteroid (AKS) tedavisinin ÇDDA'lı hastaların neonatal mortalite ve morbiditeleri üzerine etkisine ilişkin bilgilerimiz hala kısıtlıdır. Bu çalışmada, <30 hafta doğan; AKS uygulanmayan, kısmi doz AKS ve tam doz AKS uygulanan bebeklerin sonuçlarını değerlendirmeyi amaçladık.*

Materyal ve Metot: *Bu retrospektif çalışmaya doğum haftası <30 hafta olan bebekler dahil edildi ve AKS uygulanma durumuna göre üç gruba ayrıldı; Grup 1, AKS uygulanmadan doğan bebekler, Grup 2, tek doz betametazon uygulanan bebekler, Grup 3, tam doz AKS uygulanan bebekler. Birincil sonucumuz mortalite idi. İkincil sonuçlar: PDA, NEK, şiddetli IVK, bronkopulmoner displazi ve kistik periventriküler lökomalazi (PVL) olarak belirlendi.*

Bulgular: *616 bebek çalışmaya dahil edildi. Koryoamniyonit sıklığı tam doz AKS grubunda anlamlı olarak daha yüksekti (p<0,05). Mortalite oranı AKS uygulanmayan grupta diğer gruplara kıyasla en yüksek olarak bulunda (%16,0) ancak istatistiksel farklılık bulunmadı. Kısmi doz AKS grubunda, AKS uygulanmayan gruba kıyasla neonatal morbidite sıklığı düşme eğiliminde idi.*

Sonuç: *Sonuç olarak, <30 hafta doğan bebeklerde eksik doz antenatal kortikosteroid tedavisinin anlamlı faydası saptanmadı.*

Anahtar kelimeler: *antenatal kortikosteroid; betametazon; çok düşük doğum ağırlıklı bebek*

Introduction

Despite significant improvements in perinatal care, preterm birth is still one of the leading causes of neonatal morbidity and mortality. Since Liggins's study in 1972[1] demonstrated antenatal corticosteroids (ACS) effect on reducing respiratory distress syndrome (RDS) and mortality in premature births before 34 gestational weeks, ACS has become a mainstay component in the management of cases of premature delivery.

Several studies showed that antenatal administration of corticosteroids accelerates lung maturation and increases surfactant production in the fetal lungs[2,3]. Moreover, Schwab also demonstrated that in addition to preventing RDS, ACS has vasoconstrictive effects on fetal cerebral blood flow and protects the fetus against intraventricular hemorrhage (IVH)[4]. A recent Cochrane systemic review in 2021, including 30 randomized controlled studies, confirmed that after a single course of ACS, the risk of moderate to severe RDS, IVH, and neonatal death in preterm infants significantly reduced by 43.14, and 26%, respectively[5].

Although the most significant beneficial effects of ACS are shown if ACS is administered between 24 hours and less than seven days before actual delivery[6], a significant population of premature infants would not receive the complete course due to maternal or fetal indications that lead to emergency or imminent delivery. While some studies have demonstrated that a partial course of ACS can reduce morbidity, the literature yielded inconsistent results[7,8]. So far, few studies have primarily focused on assessing the neonatal effects of an incomplete course of ACS on very low birth weight infants (VLBW). Therefore, the literature on the effect of partial course antenatal corticosteroid therapy on VLBW morbidity is still scarce.

In this retrospective cohort study, we aimed to evaluate outcomes of infants born <30 weeks' gestation that received no ACS, partial course of ACS, and complete course of ACS. We sought to demonstrate whether administering a partial course of ACS would benefit mortality or other neonatal outcomes.

Material and Methods

This retrospective cohort study was conducted between January 2014 and October 2017 in a single Level III Intensive Care unit at the Zekai Tahir Burak Women's Health and Children Hospital, Ankara, Türkiye. Hospital Research Ethics Committee approved the study.

Infants <30 weeks in gestation at birth (based on early ultrasound (US) or last menstrual period if the US is not available) who were born in our hospital were considered eligible for inclusion. Infants with congenital or chromosomal anomalies, severe perinatal asphyxia, and whose data were missing were excluded from the study.

Since the current data concerning ACS are insufficient to recommend one steroid over the other, there are considerable differences between countries regarding antenatal corticosteroid choice. At our institution, according to the current recommendation by the American College of Obstetricians and Gynecologists[6], two intramuscular doses of 12 mg of betamethasone are administered 24 hours apart to women who are at risk of premature labor between 24 and 34 weeks gestational age.

Infants were divided into three groups based on exposure to ACS; Group 1, infants born without ACS exposure; Group 2, infants born after exposure to one dose of betamethasone, Group 3, infants born after exposure to complete the course.

The main clinical characteristics such as gestational age, birth weight, gender, delivery mode, 5 minutes Apgar score, requiring delivery room resuscitation (either required endotracheal intubation or other further interventions, such as chest compressions and medications), and the number of twin births, were obtained from medical records. In addition, maternal history of pregnancy-induced hypertension, prolonged rupture of membranes (PROM) (>18 h), and evidence of chorioamnionitis were also recorded. Chorioamnionitis is defined as maternal fever ≥38°C not explained by another source of infection and one or more of the following signs: maternal tachycardia (100 beats per minute (bpm) or more), fetal tachycardia (>160 bpm), white blood cell count of 20000 μL or more, uterine tenderness and foul odor upon delivery of the infant[9].

Our primary outcome was mortality, defined as death before hospital discharge. Secondary outcomes included the following: surfactant administration, patent ductus arteriozus (PDA) requiring either medical or surgical treatment, NEC stage II or more of modified Bell's criteria[10], severe IVH[11], bronchopulmonary dysplasia (BPD), and cystic periventricular leukomalacia (PVL). Two composite outcomes were prespecified: BPD or death and one consisting of intraventricular hemorrhage, cystic PVL, or death. RDS was defined within the first 72 hours to have clinical signs of respiratory distress, including tachypnea, retractions, grunting, or cyanosis with increasing oxygen requirements and diagnostic radiological findings[12]. Jobe classification is used to define BPD, which is defined at the PM 36th week for preterms born before 32 weeks of gestation and on the postnatal 28th day for preterms born at or after 32 weeks of gestation or at the time of discharge, whichever occurs earlier, treatment with oxygen >21% for at least 28 day regardless of the clinical severity of respiratory failure due to RDS or other reasons in the first days of life[13]. Mild BPD cases included breathing room air at 36-week PMA or discharge, whichever comes first excluded. Incidence of pneumothorax, duration of mechanical ventilation and total respiratory support, and length of hospital stay were also recorded.

Statistical Analysis

Infants were classified into three groups according to their ACS exposure. Based on the outcome parameters, these groups were compared. Data were analyzed using SPSS, version 22.0 (SPSS, Chicago, IL). Categorical variables were expressed as percentages and compared

using Pearson's chi-squared and Fisher's exact tests when necessary. Mean, and standard deviation (SD) were used as descriptive variables for continuous variables. These variables were analyzed with the ANOVA test since the parameters are normally distributed. We used a logistic regression model adjusting for the effects of clinical chorioamnionitis to estimate the adjusted odds ratios (ORs) and measure the 95% CI for comparing the three groups regarding the primary and other outcomes. A p-value <0.05 was considered significant.

Results

We assessed 681 infants <30 weeks in gestation at birth during the study period. After excluding 65 infants for missing data, 616 infants were included in the study. There were 274 (44.4%) infants in the complete course, 143 (23.2%) in the partial course, and 199 (32.4%) in the no ACS group.

The demographic characteristics of the infants according to steroid exposure are summarized in Table 1. The three groups did not differ for gestation age, birth weight, gender, 5th minute APGAR score, number of twin gestations, maternal hypertension, and PROM. However, infants who received no ACS were likely to need resuscitation at the delivery room compared to the partial and complete course ACS groups (p<0.05). Also, the incidence of chorioamnionitis was significantly higher in the complete course ACS group compared to the other two groups (p<0.05).

The incidence of surfactant instillation in the complete course group was 48.2%, significantly lower than the partial course and no ACS group (67.2%, 64.3%, respectively) (p<0.05). The mortality rate was higher in the no ACS group (16.0%) compared to the partial and complete course group (14.6% and 12.4%), but it was not statistically different (p>0.05). There were no significant differences between the no ACS and partial ACS groups in terms of mortality, IVH, composite outcome of BPD or death, and IVH/cystic PVL or death, despite lower morbidity rates in the partial ACS group. The incidence of PDA, severe ROP and NEC were similar between groups (Table 2). A logistic regression model was designed to control clinical chorioamnionitis to compare three groups in terms of mortality, IVH and the composite outcome of BPD or death, and IVH/cystic PVL or death. Similar to univariate analysis, no statistical difference was found between groups.

Discussion

In this study, we sought to compare outcomes of infants born <30 gestational weeks exposed to different doses of antenatal corticosteroids to show whether administering an incomplete course of ACS would benefit short-term and long-term morbidities and mortality. Our results demonstrated that among our cohort of preterm infants, there was a significant decrease in the need for surfactant treatment after exposure to a complete course of ACS, in line with previous studies[14]. Additionally, there was a trend towards less morbidity in the partial course ACS group versus none, but the difference was not statistically significant.

If administered a complete dose seven days before delivery in women at risk of preterm birth, the substantial beneficial effects of antenatal steroids are evident. The Latest Cochrane review has suggested that no further randomized clinical trials are needed to demonstrate the effect of the current recommended antenatal corticosteroid regime[5]. Nevertheless, since the current recommended regime of antenatal betamethasone was suggested in 1972 by Liggins and Howie[1], clinical trials testing different dose regimens have never been performed. Schmidt et al. showed that single-dose intramuscular betamethasone significantly improved lung compliance and gas exchange in preterm lambs[15]. Similarly, Ballard et al. demonstrated that one dose of betamethasone benefits early pulmonary function. A single dose of betamethasone 48 hours before delivery increased the maximum lung volume and dynamic compliance of preterm sheep[16]. Also, the latest good practice recommendations of FIGO Working Group for Preterm Birth included administration of antenatal corticosteroids even if preterm birth is expected within 18 hour[17]. However, the literature on the impact of a partial course of ACS on VLBW preterm infants still needs further investigation, as few studies compare the outcomes of infants born following a single betamethasone dose.

Retrospective studies on this subject included different gestational age ranges and yielded inconsistent results so far[8,18]. Although our study found the incidence of delivery room resuscitation decreased among infants exposed to a partial course of ACS, it failed to find a statistically significant reduction in neonatal morbidities following single-dose betamethasone administration compared to the no exposure group. In contrast to our study, Chawla et al. demonstrated that infants exposed to a single dose of ACS had a significantly lower incidence of IVH than those without ACS[18]. However, the overall IVH rate was significantly higher in that study than ours, possibly due to the cohort's lower mean gestational age and birth weight, especially in the no ACS group. Probably higher gestational age of our cohort resulted in lower IVH incidence in all groups and did not enable us to reach statistical significance. Elimian et al. reported a lower need for vasopressors, IVH, and mortality rate in the partial course ACS group[7]. However, the study included neonates born at 23–24

Table 1. Maternal and infant characteristics of study groups

	No ACS (n=199)	Partial (n=143)	Complete (n=274)	p value
Gestational age (weeks) (SD)	28±1.5	28.1±1.2	28.2±1.2	0.67
Gender (male) n (%)	104 (52.3)	68 (47.6)	145 (52.9)	0.56
Birth weight (grams) (SD)	1067±242	1052±230	1058±228	0.2
Apgar, 5. min (<5), n (%)	12 (6)	3 (2.1)	9 (3.3)	0.14
Cesarian section n (%)	166 (83)	118 (82.5)	236 (86.1)	0.56
PIH n (%)	37 (18.5)	30 (20)	52 (18.9)	0.84
Chorioamnionitis n (%)	19 (9.5)	11 (7.7)	50 (18.2)	0.01
Resuscitation in delivery room, n (%)	61 (30)	41 (28)	58 (21.2)	0.047
PROM (>18 h) n (%)	31 (15.5)	20 (13.9)	67 (24.4)	0.07
Twin gestation n (%)	50 (25.1)	34 (23.8)	59 (21.5)	0.64

Partial group includes one dose of betamethasone. Complete group includes two doses of betamethasone. *Plus-minus values are mean ± standard deviation SD: standard deviation, p values <0.05 were considered significant. ACS: antenatal corticosteroid, PROM: prolonged rupture of membranes, PIH: pregnancy induced hypertension.

Table 2. Association of ACS dosing and clinical outcomes of the study infants

	No ACS (n,%)	Partial (n,%)	Complete (n,%)	p value
Surfactant administration	123 (67.2)	92 (64.3)	132 (48.2)	0.04
PDA	80 (40.2)	64 (44.7)	92 (33.5)	0.2
Pneumothorax	4 (2)	5 (3.4)	6 (2.1)	0.2
BPD	32 (16)	19 (13.2)	33 (12)	0.32
IVH	25 (12.5)	20 (11.4)	25 (9.1)	0.42
PVL	20 (10.1)	16 (11.1)	20 (7.2)	0.38
NEC	3 (1.5)	5 (3.4)	5 (1.8)	0.62
BPD or death	58 (29.1)	36 (25.1)	63 (23)	0.18
IVH/PVL or death	42 (21.1)	31 (21.6)	50 (18.3)	0.34
Death	32 (16.0)	21 (14.6)	34 (12.4)	0.28
Duration of MV d, (SD)	4.3±7.9	4.5±8.9	3.4±7.7	0.62
Duration of respiratory support, d, (SD)	13.2±12.5	12.9±14.6	12.6±13.4	0.46
Duration of hospital stay d, (SD)	58.7±32.3	58.6±29.9	56.3±30.7	0.53

Partial group included one dose of betamethasone. Complete group included two doses of betamethasone. SD: standart deviation, p values <0.05 were considered as significant. PDA=patent ductus arteriozus, BPD: bronchopulmonary displasia, IVH: intraventricular hemorrhage, PVL: periventrivular leucomalacia, NEC: necrotizing enterocolitis, MV: mechanical ventilation.

gestational weeks with a high mortality rate, which was different from our study population. Like our findings, Costa et al. demonstrated no significant difference in NEC, IVH, and mortality among infants exposed to single-dose betamethasone[8]. Nevertheless, a subgroup analysis showed that one dose of ACS was clinically comparable to the complete dose in the 25–27 weeks subgroup. Salhab et al. included extremely low birth weight infants ≤1000 gr and confirmed that beneficial effects of ACS were dose-dependent as they found no significant differences between the no ACS and partial course ACS group in terms of neonatal outcomes. However, in line with our study, they demonstrated a trend towards less morbidity in the partial course ACS group[19]. Similarly, a multicenter, prospective observational study analyzing the effect of ACS on mortality in preterms 23 to 28 weeks gestational age found only a complete course of ACS administration associated with a reduction in mortality and BPD[20].

A recent study on an animal model suggested that duration of exposure to low-dose ACS rather than total exposure mediates lung maturation[21]. Although it is recommended to start a course of antenatal corticosteroids for all women at high-risk premature delivery, even if only one dose is anticipated[22], a study showed that exposure to ACS at least 24–48 h before delivery reduces the incidence of RDS more significantly[23]. Since our report was designed retrospectively and the data on the timing of ACS before delivery was not noted, we could not analyze the effect of duration of fetal exposure that might have a role in our results. Additionally, it is possible that the underlying cause of emergent premature birth, which resulted in the inability to administer the complete course of ACS, also has a role in neonatal outcomes and increases the risk of morbidities. Perhaps a prospective randomized trial examining whether a single dose is non-inferior to the maximum dose in preventing neonatal complications will adequately address some of these questions[24].

In our study, clinical chorioamnionitis was more common in the complete course ACS group compared to others. A previous study suggests maternal and neonatal infection rates do not increase with antenatal corticosteroid administration[25]. Nonetheless, caution is needed when using ACS in the presence of chorioamnionitis. As antenatal infection is one of precipitating factors of preterm birth, attention must be paid to avoid increasing maternal infection risk while preventing preterm labor. Waterberg et al. found that chorioamnionitis increased neonatal morbidities in VLBW infants[26]. Interestingly, we designed an additional logistic regression model controlling clinical chorioamnionitis among groups in terms of mortality, IVH, and the composite outcome of BPD or death, IVH/cystic PVL or death, and the results did not differ.

There are several limitations of our study. Although our sample size was larger than similar studies[7,8,17,18], it was a single-center study. It was conducted retrospectively, and the underlying cause of preterm delivery and the timing of antenatal corticosteroid administration was not specified.

Conclusion

In conclusion, our study results suggest that although statistically insignificant, there was a trend of less morbidity in the partial course ACS group. As a result, we believe that even a single dose of betamethasone should be administered to every patient at risk of preterm delivery, even if the delivery cannot be delayed until the administration of the second dose. We also think further studies targeting subpopulations of preterms are needed to show the benefit of partial course antenatal corticosteroids for different gestational age subgroups.

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