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Antenatal Corticosteroids and Respiratory Distresses Outcome in Preterm Neonates

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ABSTRACT

Background: The value of antenatal corticosteroid regimen in lessening respiratory distress risk in preterm neonates has been well known, and accordingly, antenatal corticosteroid therapy was recommended for any pregnant woman likely to deliver between 24 and 34 weeks of gestation. Therefore, this study aimed to assess the association between the administration of antenatal corticosteroids within the ideal interval of one week before birth and the outcomes of preterm neonates.

Methods: This prospective cohort study included 80 preterm neonates admitted to the neonatal intensive care unit with gestational age from 32 to 37 complete weeks at Suez Canal University Hospitals, Ismailia, Egypt. The newborns were then divided into groups A (did not receive antenatal corticosteroids; n=40) and B (received antenatal corticosteroids; n=40).

Results: Severe respiratory distress syndrome was significantly less frequent in group B ($P<0.05$) with lower levels of need for oxygen supplementation ($P<0.05$).

Conclusion: Neonates who received antenatal corticosteroids developed less severe respiratory distress, compared to neonates who did not receive this medication. The results favored the use of antenatal corticosteroids to prevent respiratory distress when administrated within the ideal interval of one week before birth.

Keywords: Antenatal, Corticosteroids, Preterm, Respiratory distress syndrome (RDS)

Introduction

Preterm labor is still a significant global problem despite advances in current neonatal medicine. In a study conducted by Blencowe et al., the rate of preterm labor was likely to be more than 11% worldwide and may reach 18% in some African countries. It is dramatic that more than 60% of preterm neonates were born in poor countries in South Asia and Sub-Saharan Africa (1). Respiratory distress syndrome (RDS) in preterm infants occurs due to numerous causes, such as surfactant deficiency and poor maturity of the lung (2).

Antenatal corticosteroids stimulate types 1 and 2 pneumocytes development lessening respiratory distress risk in preterm neonates (3). Furthermore, they have several non-respiratory benefits as reducing the risk of necrotizing enterocolitis, intra-ventricular hemorrhage (IVH), neonatal intensive care unit (NICU) admission, and neonatal mortality (4). Sinclair revealed preterm cases that required treatment with antenatal corticosteroids to prevent RDS (5). Over 20 years in an original randomized trial, a multidisciplinary National Institutes of Health panel concluded in a consensus statement that antenatal corticosteroids for fetal maturation reduced neonatal mortality, RDS, and IVH in preterm infants and should be used for pregnancies likely to deliver between 24 to 34 weeks of gestation (6). The 2016 American Congress of Obstetricians and Gynecologists practice bulletin regarding antenatal corticosteroids recommended a single course of antenatal corticosteroids for pregnant women between 24 and 34 weeks gestation at risk of preterm delivery (7).

However, argumentative issues concerning the use of antenatal corticosteroids remain unsolved to

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know whether the treatment should be extended to neonates beyond 34 weeks, where the risks of RDS and other problems of prematurity are less significant. Regarding the biological credibility that antenatal corticosteroid administration would benefit older fetuses, some obstetricians have given corticosteroids outside this recommended gestational window (7). Therefore, this study aimed to assess the association of antenatal corticosteroid administration within the ideal interval of one week before birth with the outcomes of preterm neonates.

Methods

This prospective cohort study was conducted in the NICU at Suez Canal University Hospital Ismailia, Egypt. The study population was preterm neonates with gestational age from 32 to 37 weeks admitted to the NICU at Suez Canal University Hospitals, Ismailia, Egypt. The preterm neonates were divided into two groups of A (did not receive antenatal corticosteroids; n=40) and B (received antenatal corticosteroids; n=40).

Inclusion criteria

Preterm neonates admitted to the NICU with gestational age from 32 to 37 weeks and complete medical records were included in this study. The neonates were considered exposed to antenatal corticosteroids if their mothers had either received a single course of antenatal cortices-teroids between 24 weeks and 33 weeks of gestation or at 23 weeks of gestation when they were at risk of preterm delivery within 7 days (8).

The antenatal dose should consist of either two 12-mg doses of intramuscular (IM) betame-thasone 24 h apart or four 6-mg doses of IM dexamethasone twice daily (8). Neonates with major congenital anomalies (defined as life-threatening, disabling, or requiring major surgery), including chromosomal trisomy were excluded from the study. Non-probability comprehensive sampling method was conducted, and the sample size was calculated using the following formula (9):

$$n = \left[\frac{Z_{\alpha/2}}{E}\right]^2 * P(1-P)$$

Where n signifies the sample size, and $Z_{\alpha/2}$=1.96 (the critical value that divides the central 95% of the Z distribution from the 5% in the tail). Moreover, E denotes the margin of error/width of confidence interval=5%, and P indicates the prevalence/proportion in the study group=5%. Accordingly, the sample size was estimated at 80 cases who were divided into two equal groups of 40 neonates per group.

The data were collected from the previously mentioned study population through a previously designed interview-based questionnaire. This questionnaire included three main categories to seek antenatal, natal, and neonatal information. The data were collected, coded, and entered into the computer via Microsoft Excel 2013 program. Following that, the obtained data were analyzed in SPSS software (version 20.0) (SPSS, Chicago, IL, USA) and presented as numbers and percentages using tables and graphs with a confidence interval of 95%. Furthermore, Kruskal-Wallis, Mann-Whitney U test, and Spearman's correlation tests were used for non-parametric data. On the other hand, parametric data were analyzed utilizing t-test, chi-square, and ANOVA. A p-value less than 0.05 was considered statistically significant.

The study protocol was approved by the Research Ethics Committee of Faculty of Medicine at Suez Canal University, Ismailia, Egypt, in February 2019. Moreover, written informed consent was taken from all the legally authorized representatives of the participants before taking any data or conducting any investigations.

Results

In total, 80 preterm infants with RDS were included in this study to assess the corticosteroid effect on the respiratory outcome. The study population was divided into two groups of preterm who did not receive (group A; n=40) and those who received antenatal corticosteroids (group B; n=40). There was no statistical difference between the two groups in terms of maternal characteristics. The mean ages of the control (A) and study groups (B) were determined at 24.8±3.9 and 25.1±3.2 weeks, respectively, which showed no significant difference between the two groups in this regard.

Regarding maternal disease, the majority of the neonates in groups A (92.5%) and B (92.5%) had no diseases. Totally, 12 (30%) and 15 (37.5%) mothers in groups A and B had a normal delivery, respectively. Furthermore, 2 (5%) and 1 (2.5%) mothers suffered from diabetes mellitus in groups A and B, respectively.

Regarding the medical condition, 1 (2.5%) and 2 (5%) mothers had hypertension (HTN) in groups A and B, respectively. The majority of mothers in groups A (95%) and B (92.5%) did not take any medication. Only 1 (2.5%) mother was

Table 1. Respiratory distress characteristics of the study population

Characteristics		Control Group (n=40)	Study Group (n=40)	P-value
Grade	I	11 (27.5%)	30 (75%)	<0.05
	II	13 (32.5%)	10 (25%)	
	III	10 (25%)	0 (0%)	
	IV	6 (15%)	0 (0%)	
Mode of oxygen delivery	Nasal	23 (57.5%)	29 (72.5%)	<0.05
	CPAP	9 (22.5%)	7 (17.5%)	
	MV	8 (20%)	4 (10%)	

Grade I: Tachypnea
Grade II: Tachypnea and subcostal retraction
Grade III: Tachypnea, subcostal retraction and grunting
Grade IV: Tachypnea, subcostal retraction, grunting and cyanosis

Table 2. Respiratory distress characteristics of the two groups regarding the type of corticosteroid

Characteristics		Dexamethasone Group (n=20)	Betamethasone Group (n=20)	P-value
Grade	I	10 (50%)	8 (40%)	0.15
	II	5 (25%)	5 (25%)	
	III	3 (15%)	5 (25%)	
	IV	2 (10%)	2 (10%)	
Mode of oxygen delivery	Nasal	17 (85%)	12 (60%)	0.06
	CPAP	2 (10%)	5 (25%)	
	MV	1 (5%)	3 (15%)	

given insulin in each group; moreover, 1 (2.5%) mother in group A was given Aldomet, compared to 2 (5%) mothers in group B. There was no statistically significant difference between the two groups (P>0.05) regarding the neonates' characteristics, except for Apgar score, which showed higher statistical difference (P<0.05) in group B.

According to the results in Table 1, the RDS grade 1 occurred more in group B, compared to group A, which showed a statistically significant difference between the two groups in this regard (P< 0.05). However, the RDS grades 2,3, and 4 occurred more in group A, compared to B. Regarding the mode of oxygen (O2) delivery, the use of nasal oxygen was more in group B, compared to group A, and the difference was statistically significant (P<0.05). on the other hand, the use of continuous positive airway pressure (CPAP) and mechanical ventilation (MV) was more in group A than that in group B, and the difference was statistically significant (P<0.05). Furthermore, there was an insignificant difference (P>0.05) between the two groups regarding the grade of RDS and the mode of O2 delivery (Table 2). Furthermore, there was no significant difference (P>0.05) regarding the gestational age of the corticosteroid injection in developing respiratory complications in the neonates in group B.

Considering the fetal complications in the current study, group B had a significantly lower rate of sepsis (7.5%), compared to group A (12.5%) (P=0.031). In addition, group B had a significantly lower rate of feeding difficulties (10%) and hypoglycemia (7.5%), compared to group A (feeding difficulties [17.5%] and hypoglycemia [15%]) (P=0.049 and P=0.02, respectively). On the other hand, group B had significantly higher frequencies of sepsis (odds ratio 4.22; 95% CI: 0.85-7.02; P=0.031); however, feeding difficulties (odds ratio 1.1; 95% CI: 0.12-3.69; P=0.049) and hypoglycemia (odds ratio 2.11; 95% CI: 0.81-9.92; P=0.02) showed significantly higher frequencies in group A.

The results in this study also showed no significant difference between the groups regarding the gestational age of the corticosteroid injection in developing seizure, intracerebral hemorrhage (ICH), feeding difficulties, and hypoglycemia complication.

Discussion

The use of antenatal corticosteroids protects the lives of numerous premature neonates. The present study aimed to determine the clinical neonatal outcomes of mothers who received corticosteroids. According to the results, there was no statistically significant difference between the two groups in terms of maternal characteristics, and the groups were matched in this regard. The results also revealed that group B had nearly half neonates (45%) with grade I RDS, whereas group A included the majority of neonates with advanced grades of RDS, which

showed a statistically significant difference between the two groups.

In 1972, Liggins and Howie (10) were the first to demonstrate the effectiveness of a single course of antenatal corticosteroids in reducing the incidence of RDS in the preterm infants enrolled in their randomized control trial. In the same line, a number of systematic reviews have been conducted and demonstrated the advantages associated with the administration of single (4) and repeated therapy (11) of antenatal corticosteroids in women at risk of preterm birth; however, the evidence on the administration of corticosteroids after 35 weeks is more debatable.

Similarly, a meta-analysis was conducted that included four trials comparing prophylactic administration of betamethasone or dexamethasone versus placebo or usual treatment without steroids in term elective cesarean section. The pregnant females were randomized to two treatment groups received either two doses of IM betamethasone 48 h before delivery, or IM dexamethasone (two or four doses) before delivery. They were then compared with a control group who received a saline placebo.

Prophylactic antenatal corticosteroid administration appeared to decrease the risk of RDS (Risk Ratio [RR]: 0.48), transient tachypnea of the neonate (TTN) (RR: 0.43), admission to the NICU for respiratory morbidity (RR: 0.42), and admission to neonatal special care (all levels) for respiratory complications with impaired cortisol precursors (RR: 0.45) (12-14). Kemp et al. performed a study to evaluate the neonates delivered from 32 to <37 gestational weeks. They found a lower rate of RDS in the control (6.9%) and treatment groups (4.7%). Similar risk reduction was also observed with delivery at earlier gestations; however, there was no statistically significant difference among the groups in this regard. A similar trend but significant was again not noted in the control versus treatment groups (4.7% vs. 3.1%, RR: 0.66, 95% CI: 0.38-1.16; P=0.15 (15).

The majority of the neonates (72.5%) in group B required nasal oxygen, whereas half of the neonates in group A needed CPAP and MV, which showed a statistically significant difference between the two groups. In addition, the study group had significantly higher frequencies of severe RDS, compared to those in the control group. This result is consistent with the findings of a study conducted by de la Huerga López et al. (16) on unexposed women. In this study, those who were given antenatal corticosteroids appeared less likely to have neonates with RDS (12.2% vs. 17.1%, P=0.001). The antenatal corticosteroid exposure was also related to the decreased rates of TTN (9.8% vs. 12.9%, P=0.020), decreased need for ventilator support (8.6% v. 11.5%, P=0.022), lower rates of the adverse respiratory composite (22.2% vs. 29.9%, P<0.001), and lower rates of resuscitation in the delivery room (49.7% vs. 55.8%, P=0.007).

A recently conducted systematic review of randomized trials compared antenatal corticosteroid therapy versus placebo/no treatment in women at risk for preterm birth. According to the results, antenatal corticosteroid therapy resulted in a reduction in RDS (Risk Ratio [RR] 0.66, 95% CI: 0.56-0.77; 28 trials, 7764 infants), reduction in moderate to severe RDS (RR 0.59, 95% CI: 0.38-0.91; 6 trials, 1686 infants), and reduction in need for mechanical ventilation (RR 0.68, 95% CI: 0.56-0.84; 9 trials, 1368 infants) (4).

Regarding the fetal complications in the current study, group B had significantly lower rates of sepsis, feeding difficulties, and hypoglycemia, compared to group A. Another study revealed that antenatal corticosteroids in fetuses at risk for preterm birth could also reduce neonatal mortality (RR: 0.69, 95% CI: 0.59-0.81) and severe neonatal morbidity, including sepsis (RR: 0.50, 95% CI: 0.32-0.78), and IVH (RR: 0.55, 95% CI: 0.40-0.76) without increasing maternal and perinatal complications (17). Moreover, there is some evidence, partly derived from non-randomized trials, that steroids in fetuses at risk for preterm birth can also reduce hypoglycemia (17). In another study, dexamethasone appeared to decrease the risk for RDS (RR: 0.50; 95% CI: 0.26-0.94) and admission to NICU for respiratory complications (RR: 0.51; 95% CI: 0.31-0.84; HKSJ CI: 0.11-0.86) (4).

In the current study, there was no significant difference between the groups regarding the gestational age of the corticosteroid injection in developing respiratory complications in the neonates. According to a study, exposure to antenatal corticosteroids during early pregnancy change the proportion of adverse respiratory outcomes in neonates born at 34 0/7-36 6/7 weeks, compared to newborns exposed at late pregnancy; however, this difference was not significant (17).

Biologically, there is no good explanation supporting the cessation of benefit to antenatal corticosteroids after 34 weeks of gestation. Rather, it is more likely that a decrease in the disease burden makes the demonstration of this benefit more difficult. Late preterm neonates are less likely

to have RDS, compared to those born before 34 weeks; however, they are still at risk for respiratory morbidities from other causes. As a pregnancy approaches term, delivery is more likely to result in TTN than RDS. The rate of TTN at 34-36 weeks was higher than that in neonates born beyond 36 weeks (6.2% vs. 0.4%). Escobar et al. evaluated the need for respiratory support among late-preterm neonates, compared to those delivered between 38 and 40 weeks of gestation (18).

According to the results, neonates born at 34, 35, and 36 weeks were 19.8-, 9.0-, and 5.2-fold more likely, respectively, to require assisted ventilation, compared to the reference group born at 38-40 weeks of gestation. Other groups have also demonstrated higher respiratory morbidity in late preterm, compared to term neonates (19). These data validate the suggestion that late preterm neonates are at risk for serious respiratory morbidities other than RDS, which affect their early neonatal management. What is currently unknown is whether antenatal corticosteroid administration can decrease these other respiratory morbidities. Therefore, there is necessary that further studies be conducted regarding this issue. The preferred corticosteroids for antenatal therapy are IM betamethasone as two doses of 12 mg each 24 h apart or four doses of 6-mg IM dexamethasone every 12 h.

Compared to cortisol and methylprednisolone, these are devoid of mineralocorticoid activity; accordingly, they are weak in immunosuppressive actions and exhibits a longer duration of actions in the body (20). In the same line, Danesh et al. (21) found that the dexamethasone group had a significantly lower rate of sepsis (2%), compared to the betamethasone group (8%). This is similar to a study performed by Chhatrala and Chawada (22) which revealed significant differences between the two groups in terms of the neonatal mortality rate (4% vs. 4%) and RDS (38% vs. 40%). In addition, the rates of IVH (6% vs. 12%) and lower birth weight (52% vs. 62%) were significantly lower in neonates exposed to dexamethasone, compared to those exposed to betamethasone.

In a study, there was no significant difference between the two groups (betamethasone and dexamethasone) in terms of the rate of developing RDS (P=0.13) and IVH (9.8% vs. 13.8%), which was consistent with the results of this study. However, differences were observed in the reports between betamethasone and dexamethasone. A study showed that although the two agents reduced the risks of RDS and IVH to a comparable extent, betamethasone was more consistently associated with a reduction in neonatal death than dexamethasone (23). Similarly, Lee et al. (24) reported that dexamethasone showed a statistically significant increased risk for neonatal death, compared to betamethasone. Moreover, there were trends for greater risks associated with dexamethasone, compared to betamethasone for IVH. Additionally, one randomized trial reported an increased rate of neonatal hypoglycemia in the infants exposed to betamethasone antenatally, compared to the placebo group (25). Late preterm may have hyper dehydroepiandrosterone in neonates in hypoxic-ischemic encephalopathy (26, 27). Baud O et al. (28) found that betamethasone (not dexamethasone) was associated with a decreased risk of periventricular leukomalacia (a major precursor of cerebral palsy). On the other hand, dexamethasone is substantially cheaper, more readily available, and less likely to decrease fetal breathing movements and heart variability. The results in this study revealed no significant difference between the groups regarding the gestational age of the corticosteroid injection in developing seizure, ICH, feeding difficulties, and hypoglycemia complication in neonates. The administration of the prophylactic corticosteroids for accelerating fetal lung maturation in a subgroup analysis of gestational age at a trial entry showed no evidence that gestational age at trial entry led to different rates of death, RDS, IVH, or birth weight.

Conclusion

This analysis compared women whose gestational age at the trial entry was less than or equal to 35 weeks+0 days or more than 34 weeks and 0 days (4). The significance of this study and its findings is to remind staff of the need to adhere strictly to the protocol, propose a future prospective study comparing the administration or lack of antenatal corticosteroids or different steroid regimens, and use of antenatal administration of corticosteroid therapy to all women at high risk of preterm delivery between 32 and 36 weeks of gestation.

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Conflicts of interest

There is no conflict of interest regarding the publication of this study.

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