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Original Article

A comparative study for the utility of antenatal corticosteroid therapy for the reduction of neonatal respiratory morbidity and mortality from preterm delivery

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Abstract

Background: *Antenatal corticosteroids have proven to be beneficial to the newborn but no effectiveness has been seen in mothers. Death due to preterm birth is not uncommon, but antenatal steroids are not routinely used in developing countries. We assessed the effectiveness of antenatal corticosteroids in late preterm period.*

Methods: *This is a retrospective analysis of prospectively collected data of mothers with singleton pregnancies at risk of prematurity. A course of antenatal corticosteroid therapy (dexamethasone, minimum one dose) was administered within 7 days of delivery; perinatal morbidity and mortality was studied and compared to those who did not receive corticosteroids (control).*

Results: *A total of eighty patients (forty in each group) were included. Baseline characteristics in the two groups were comparable. There was a lower incidence of requirement of invasive ventilation (30% vs. 85%, $p < 0.001$), development of neonatal necrotizing enterocolitis (0% vs. 12.5%, $p = 0.021$), need for surfactant (25% vs. 80%, $p < 0.001$), neonatal mortality (0% vs. 27.5%, $p < 0.001$) and higher incidence of discharge to home (100% vs. 72.5%, $p < 0.001$) in those that received steroids compared to the control group. Perinatal morbidity, including respiratory distress syndrome, intraventricular hemorrhage and bronchopulmonary dysplasia between the two groups was not significant.*

Conclusions: *Timely administration of antenatal corticosteroids appears safe and significantly reduces perinatal morbidity/mortality in preterm birth. The benefits may outweigh risks but long-term outcomes remain to be studied.*

Keywords: *Preterm birth, low birth weight, antenatal steroids, respiratory distress syndrome, neonatal mortality.*

Introduction

Preterm birth is a serious public health problem and is a leading cause of perinatal death and disability.[1]Late preterm birth includes those deliveries that occur between 34 and 36 weeks 6 days.[2] This subgroup constitutes 75% of total preterm births (24–36 weeks 6 days).[3] Timely obstetric and new born care is necessary to reduce morbidity. This has economic and health consequences deserving adequate preventive and management strategies. Care given to mother during antenatal period has a significant bearing on the new born survival. Antenatal corticosteroids (ACS) are usedfor accelerating fetal lung maturation for women at risk of pre-term birth which results in decrease of neonatal morbidity and mortality.[4] Antenatal corticosteroids are effective in reducing respiratory distress syndrome (RDS) and other complications of premature delivery.[5] Randomized trials have shown that a course of ACS therapy administered to women at risk for preterm delivery reduced the incidence and severity of RDS and mortality in offspring.[6] Survival rates of very-low- birth weight preterms are increasing. Despite survival rates increasing to approximately 70%, intraventricular hemorrhage (IVH) contributes to mortality and morbidity.[7] Subsequent trials have shown that ACS also improves circulatory stability in preterm neonates, resulting in lower rates of IVH and necrotizing enterocolitis compared with unexposed preterm neonates.[8] So, this study was aimed to compare the true benefit of ACS in late preterm period.

Methods

We conducted a retrospective analysis of prospectively collected data of mothers with singleton pregnancies at risk of prematurity among 24 and 34 weeks of gestation at a tertiary care teaching hospital in India. Ethical clearance was obtained from the Institutional Ethics Committee of hospital and waiver of consent was also obtained. New-borns whose mothers were exposed to antenatal corticosteroid therapy, in accordance with the individual decision of the obstetrician with gestational age between 24-34 weeks in the past one year were included. Presence of major congenital malformations, corticosteroids used for other than fetal maturation, ACS use occurring more than seven days before the delivery, incomplete patient details and missing information were excluded. Missing data was dealt with available case analysis. Some of them had received steroids, while others did not due to various reasons. The steroid included a course of dexamethasone being administered within 7 days of delivery which is four doses of dexamethasone 6 mg intramuscularly 12 hours apart.

Clinical data was extracted relevant to mothers age, pre-existing clinical and obstetric diseases in the present pregnancy, presence of premature delivery labour; need for tocolytics, presence of prolonged rupture of membranes (>24 hours)and chorioamnionitis. Variables in new born included resuscitation in the delivery room, the Apgar score, birth weight and gestational age. Outcome included respiratory distress syndrome within 6 hours of life and the presence of typical radiological finding, need for mechanical ventilation and duration of ventilation, Use of surfactant among the patients whose diagnosis was respiratory distress syndrome and intrahospital death were studied. RDS was diagnosed by clinicians through observing the presence of respiratory rate (RR) > 60/minute, subcostal or intercostal recessions, expiratory grunt or groaning, presence of nasal flaring, suprasternal retractions, decreased air entry on auscultation of the chest, gasping, choking and presence of cyanosis.[9] Gestational age determination was done by considering ultrasound measurement of the embryo in the first trimester, fundal height and details of last menstruation. Ballard's score assessed by clinicians was used to confirm the neonate's gestation age within 24 h of birth.

Maternal blood and amniotic fluids (if needed) were collected prior to treatment with antibiotics,

steroids and tocolysis. Maternal blood had been obtained via venipuncture of the cubital vein at admission. PROM was confirmed clinically by per speculum examination. Patients were followed till delivery and managed as per appropriate guidelines. Prenatal morbidity and neonatal mortality were studied. This study was conducted in accordance with Good Clinical Practice and in a manner to conform to the Helsinki Declaration of 1975, as revised in 2013 concerning human rights.

Statistical Analysis

Statistical analysis was carried out with the help of Statistical Package for the Social Sciences (SPSS) Statistics for Windows [version 24.0, Professional] (IBM Corp., Armonk, N.Y., USA). The description of the data was done in the form of arithmetic mean ± SD for quantitative data, and frequency (%) for qualitative (categorical) data. For quantitative data, unpaired Student's t-test was used. For comparison of categorical variables, chi-square test was used if the number of elements in each cell were 5 or higher and Fisher's exact test, otherwise. Results are graphically represented as 3d stacked bar graphs and pie chart as deemed necessary. A p-value of< 0.05 was considered statistically significant.

Results

Eighty patients met the inclusion criteria; 40 received steroids, while the other 40 did not. The baseline characteristics in the two groups were comparable (Table 1) viz. maternal age, pregnancy-induced hypertension, diabetes mellitus, use of tocolytics, PROM >18 hrs, chorioamnionitis, cesarean section and vaginal delivery. No significant difference was seen between the two groups in other parameters which includes birth weight, gestational age, Apgar Score 1 and 5 min, need for resuscitation and small for gestational age (Table 2).

The mean gestational age at delivery was 31.2 weeks among those who received ACS and30.75 weeks among controls (p =0.320). A one-minute Apgar score of < 7 was assigned to 97.5% of cases compared to 92.5% of controls ($p > 0.05$). The mean birth weight was 1.41±0.29kg among those who received ACS and 1.42±0.37 kg among controls (p=0.916). Compared with women who received antenatal corticosteroids those unexposed appeared more likely to have neonates who required ventilatory support (85% vs. 30% $p < 0.001$) (Figure 1), development of neonatal necrotizing enterocolitis (12.5% vs. 0%, $p = 0.021$), need for surfactant (80%vs.25%, $p < 0.001$) (Figure 2), neonatal mortality (27.5%vs.0%, $p < 0.001$) and lower incidence of discharge to home (72.5% vs. 100%, $p < 0.001$) (Figure 3). The beneficial effect of ACS on preventing surfactant use was evident. There were no significant differences among the groups regarding all of the above perinatal morbidity, including respiratory distress syndrome, intraventricular hemorrhage and bronchopulmonary dysplasia. The highest mortality rate was observed in neonates diagnosed with RDS. No deaths occurred in neonates without RDS. The mean birth weight was 1.2 kg among those who died, had a mean gestational age of 29.3 weeks, eight were born by cesarean section and 3 with normal vaginal delivery and their Apgar 0 and 1 min score was <7.

Table 1 Comparison of Baseline characteristics in the two groups

Variable	Antenatal steroids Received (n=40)	Antenatal steroids Not Received (n=40)	P value
Maternal age, Mean (±SD), years	24.9±3.6	24.2±3.3	0.368
Pregnancy-induced hypertension			
Yes	16	12	0.348
No	24	28	
Diabetes Mellitus			
Yes	6	8	0.556
No	34	32	
Use of Tocolytics			
Yes	8	7	0.775
No	32	33	
PROM >18 HRS			
Yes	12	8	0.302
No	28	32	
Chorioamnionitis			
Yes	0	3	0.077
No	40	37	
Cesarean section			
Yes	36	31	0.130
No	4	9	
Vaginal delivery			
Yes	4	9	0.130
No	36	31	

The baseline characteristics were comparable between the two groups.

Table 2 Comparison of outcome variables in the two groups

Variable	Antenatal steroids Received (n=40)	Antenatal steroids Not Received (n=40)	P value
Birth weight, Mean (±SD), kg	1.41±0.29	1.42±0.37	0.916
Gestational age, Mean (±SD), weeks	31.2±1.8	30.75±2.2	0.320
Apgar Score 0 min, Mean (±SD)	4.9±1.1	5.4±1	**0.034**
Apgar Score 1 min, Mean (±SD)	6.9±1.2	7±1	0.610
Apgar Score 5 min, Mean (±SD)	8.2±0.7	10.1±11.1	0.294
Resuscitation required			
Yes	8	3	0.105
No	32	37	
Small for gestational age			
Yes	10	4	0.077
No	30	36	
Appropriate for gestational age			
Yes	30	36	0.077
No	10	4	
Respiratory distress syndrome			
Present	40	38	0.152
Absent	0	2	
Need for mechanical ventilation			
Yes	12	34	**<0.001**
No	28	6	
Need for surfactant			
Yes	10	32	**<0.001**
No	30	8	
Bronchopulmonary dysplasia			
Present	2	2	1.000
Absent	38	38	
Necrotizing enterocolitis			
Present	0	5	**0.021**
Absent	40	35	
Neonatal mortality			
Yes	0	11	**<0.001**
No	40	29	
Discharged to home			
Yes	40	29	**<0.001**
No	0	11	

Figure 1 Comparison of requirement of Invasive ventilation between the two groups

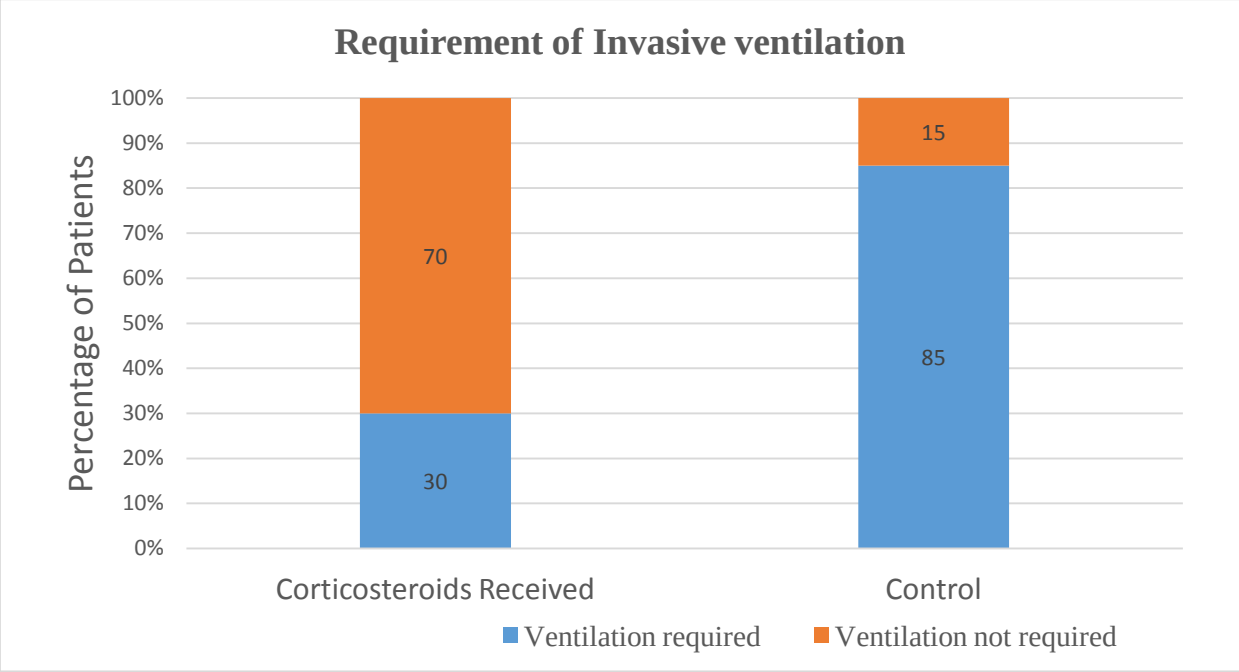


Figure 2 Comparison of requirement of surfactant between the two groups

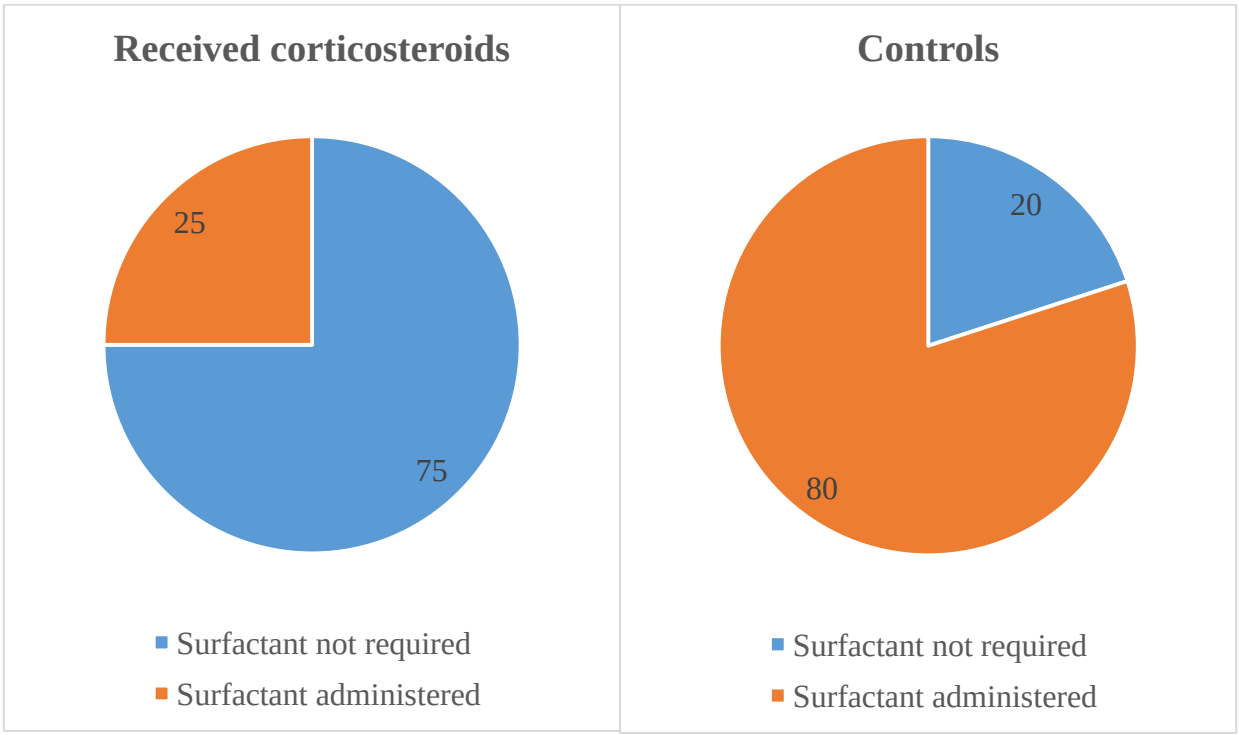
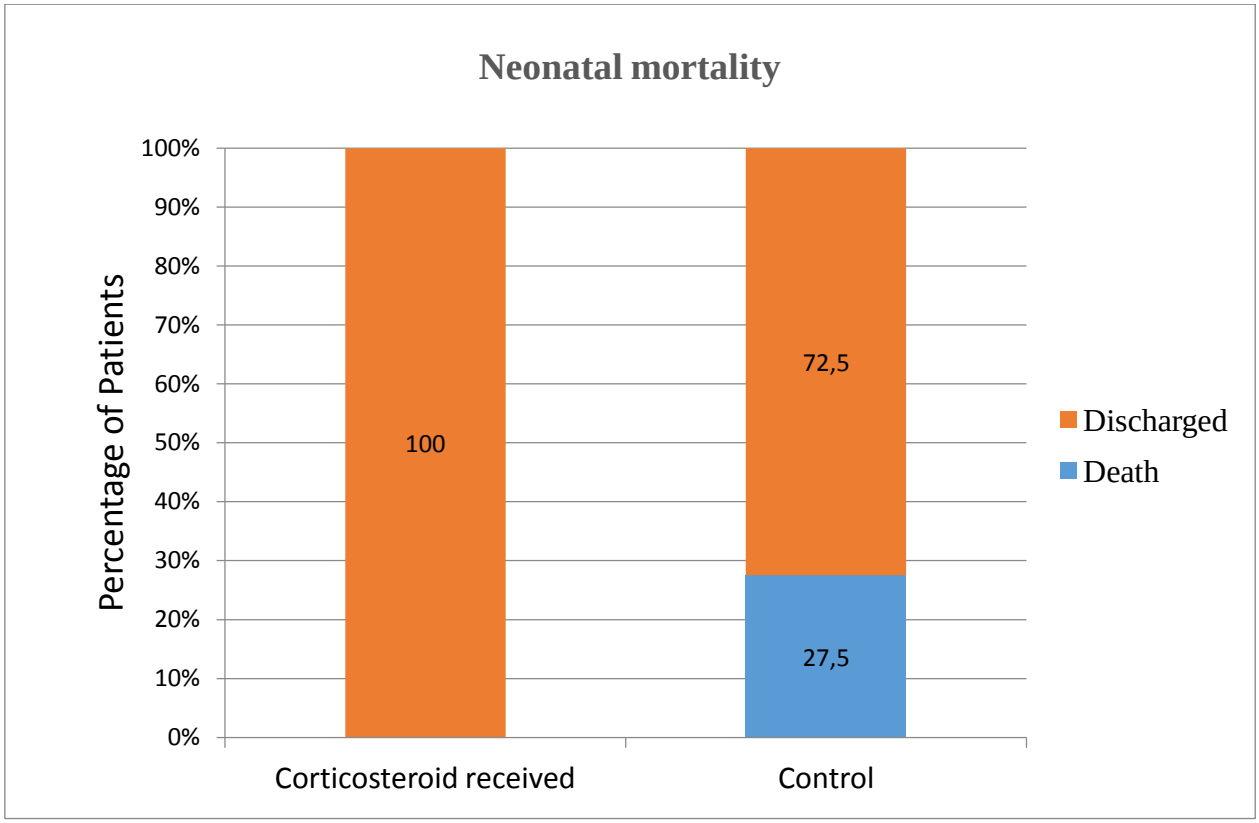


Figure 3 Comparison of neonatal mortality and discharge between the two groups



Discussion

The present study found that exposure to ACS during pregnancy did not appear to change the proportion of adverse respiratory outcomes in neonates when compared with those of unexposed. Few prospective studies have evaluated respiratory outcomes in late-preterm neonates exposed to steroids.[10] The first randomized controlled trial (RCT) of ACS in 1972 found that exposure to betamethasone decreased the rate of RDS from 25.8% in controls to 9.0% in the treatment group, p=0.003.[11]Among those delivered between 32 to <37 weeks gestation, they found a lower rate of RDS from 6.9% in the control vs. 4.7% in the treatment group; a similar nonsignificant risk reduction to that seen with delivery at earlier gestations. Notably, there were only 4/72 cases of RDS in moderately preterm neonates. A Cochrane systematic review evaluating the rates of RDS in fetuses exposed to steroids that delivered at 34 weeks gestation or beyond found a similar trend but significance was again not reached in control versus treatment groups, 4.7% versus 3.1%.[12] The present study found no association between RDS occurrence and ACS use. Differences in the epidemiology of preterm birth, exposure to infections, pharmacogenetic factors and quality of neonatal care could be the likely reasons for the observed differences. Late-preterm neonates are less likely to have RDS than those born before 34 weeks; however, they at risk for respiratory morbidities from other causes.[10] Porto et al in a RCT found no reduction in the risk of respiratory morbidity with ACS use even after adjustment for subgroups of gestational age. There was no difference in neonatal morbidity or in the duration of stay in hospital between the two groups. Phototherapy for jaundice was required less often in babies whose mothers received ACS.[13] The efficacy of ACS could be affected by ACS completeness and administration-to-delivery.

Lin D et al. performed meta-analysis of 16 observational studies with 36 973 newborns. ACS treatment was associated with a reduction in RDS, IVH and PVL. Subgroup analyses showed ACS completeness, administration-to-delivery interval and multicentre study affected these

associations.[14] ACS accelerates development of type 1 and type 2 pneumocytes, leading to structural and biochemical changes that improve both lung mechanics and gas exchange (eg, surfactant production).[15,16] Other effects include induction of pulmonary beta-receptors, which play a role in surfactant release and absorption of alveolar fluid when stimulated[17]; induction of fetal lung antioxidant enzymes[18]; and upregulation of genes for mediators of pulmonary epithelial sodium and liquid absorption, which are important for postnatal absorption of lung fluid.[19,20] For these changes to occur, however, the lungs need to have reached a stage of development that is biologically responsive to corticosteroids. Given the benefits of ACS, it can be given to pregnant women who are at 23+0 to 33+6 weeks of gestation and at increased risk of preterm birth within the next one to seven days. It is not advisablein patients who rupture membranes or are receiving tocolysis for active preterm labor, or in whom delivery for maternal or fetal indications is anticipated within the next seven days. Antenatal hospitalization does not necessarily mandate a course of ACS. This approach minimizes the need for salvage (rescue, booster) therapy while allowing most patients to receive a course of ACS prior to preterm delivery.

The study does have its strength. This is a comparative study from south Indian region which has showed a benefit towards reducing mortality in neonates at prematurity. The results can act as a reference to future studies. The study does have its limitations. This is a nonrandomized study. Due to the retrospective nature, the results perhaps may have been influenced by selection bias. Only short-term benefit was studied. It is the long-term outcomes that matter among neonates.

To summarize, use of ACS appears safe and significantly reduces perinatal morbidity and mortality in preterm birth. There was no benefit in RDS among neonates who received ACS. The benefits may outweigh risks but long-term outcomes remain to be studied in well-designed prospective randomized controlled trials.

Conflict of Interest: None to disclose.
Financial Disclosure: Nil

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