Original article

Outcome of preterm neonates born to women of a developing country at risk of preterm birth exposed to varying doses of antenatal corticosteroid: A prospective observational study

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ABSTRACT

Background: Antenatal corticosteroid (ACS) is used in women at risk of preterm births to reduce mortality and morbidity of the neonate born. However its effect may not always be beneficial especially in the women with risk factors for sepsis which is quite high in developing countries.

Methods: Neonates (26–35 weeks gestational age) delivered to mothers who received 2–4 doses of ACS (group 1) or 0–1 dose (group 2) were compared for incidence, severity of Respiratory distress syndrome (RDS) and death. Various morbidities of prematurity were also compared among the two groups.

Results: Less number of neonates developed RDS in group 1 (28.1%) than group 2 (37.8%) ($p = 0.011$). Few babies needed CPAP in group 1 (34.1% vs 53.9%; 0.006), however more babies needed mechanical ventilation (MV) (62.2% vs 41.7%; 0.005) in group 1. Mortality was similar (20.5% vs 20.1%; $p = 0.71$). Group 1 neonates with 2–4 doses of ACS had less Intraventricular hemorrhage (IVH) (0.3% vs 2.6%; $p = 0.04$) but sepsis rates (12% vs 6.2%; 0.02) were increased. Other morbidities of prematurity were comparable.

Conclusion: Similar to the previous literature, decrease in incidence of RDS and IVH was found in neonates with higher (2–4) doses of ACS. However more cases of culture positive sepsis and severe RDS occurred in these neonates.

1. Introduction

Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising. Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born.¹ Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015.² In the lower-income countries, on average, 12% babies are born too early compared with 9% in higher-income countries. Within countries, poorer families are at higher risk. In top 10 countries with the greatest number of preterm births, India with 3,519,100 preterm births ranks first.³ Preterm neonates are prone to a number of complications. RDS is one of the most early and urgent requiring immediate interventions.

Antenatal corticosteroid (ACS) is an effective therapy to reduce respiratory distress and improve neurological morbidity and mortality in the preterm newborn.⁴ This has become a standard care in cases of imminent or anticipated preterm delivery.⁵ However, a general concern exists regarding the administration of ACS in cases of suspected

intrauterine infection.^{6–8} Cochrane database review published in 2006 summarized 21 studies confirmed significant reduction in risk of mortality, Respiratory distress syndrome (RDS) and Intraventricular hemorrhage (IVH).⁵ On the basis of this strong evidence, use of ACS for women at high risk of preterm births is widely recommended by national & international health organizations.^{9,10} Further studies showed multiple courses do not improve preterm-birth outcomes, and are associated with a decreased weight, length, and head circumference at birth.¹¹ Most of the evidence comes from the high income countries with paucity of data from low middle income countries.¹² Eight studies in 2006 systematic review had increase in puerperal sepsis and fever with dexamethasone. The risks and benefits of ACS in poor population could be very different from those in well nourished, wealthy population with access to round the clock newborn care. A trial done in low and middle income countries including India showed that there was no benefit in preterm infants and rather there was higher neonatal mortality in steroid group.¹³ A possibility is that ACS might compromise a neonate's immune system and increase their susceptibility to infection.¹³ Therefore it is the need of the hour to study the interaction of

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neonatal sepsis with ACS especially in developing countries, hence this study was done.

2. Methods

2.1. Study population

This study was conducted on consecutively enrolled preterm babies delivered to women at risk of preterm birth. Women delivering preterm babies (between 26 and 35 weeks of gestation) were enrolled and status of ACS coverage was assessed. The preterm infants whose mothers had received 2 or more doses of ACS constituted group 1 and whose mothers either received single dose or not received ACS formed group 2. Neonates with major congenital malformations and suspected congenital heart disease were excluded. Gestational age (GA) was determined based on last menstrual period (LMP) and/or antenatal ultrasonography. Preterm labor diagnosis was based on persistent uterine contraction accompanied by dilatation and or effacement of the cervix.

2.2. Data collection

The policy of using ACS included injection dexamethasone, 6 mg, intramuscular and repeated 12 h to maximum of 4 doses. Preterm babies were resuscitated with T piece resuscitator when required. Preterm babies developing signs of RDS such as presence of at least 2 of the following criteria (NNPD report_2002-03)¹⁴: respiratory rate > 60/minute subcostal/intercostal recessions, expiratory grunt/groaning were first initiated on continuous positive airway pressure (CPAP). The criteria for initiation of mechanical ventilation (MV) included any of the following¹ failure of optimal CPAP (> 8–9 cm of water) or apnea on CPAP (ii) PaO₂ < 50 mmHg or SpO₂ < 89% on FiO₂ 0.8 (iii) PaCO₂ > 60 mmHg with pH < 7.25 (iv) apnea or gasping respiration. The strategy for use of surfactant was early rescue therapy, advised for those who required CPAP with FiO₂ 40% or more or on MV. Patients were followed till their outcome. Maternal details like age, parity, socioeconomic status, residence, antenatal care, medical diseases like diabetes, rheumatic heart disease, thyroid disorder, anemia, tuberculosis, HIV infection, pregnancy related disorders: gestational diabetes (GDM), antepartum hemorrhage, pregnancy induced hypertension (PIH), TORCH infection, ACS: doses, timing (period of gestation) route were noted. Intrapartum details like chorioamnionitis (maternal fever, foul smelling discharge, colour of liquor, uterine tenderness, maternal tachycardia, fetal tachycardia, maternal total leukocyte count), meconium stained amniotic fluid, evidence of fetal distress, prolonged labor, obstructed labor, mode of delivery, resuscitation details were noted. Neonatal details: weight, sex, GA, age at onset of symptoms, type of respiratory support required, complications, duration of hospital stay, outcome.

2.3. Outcomes

The primary outcomes were recorded in form of occurrence of RDS, its severity and death. Secondary outcomes: occurrence of necrotizing enterocolitis (NEC), sepsis, patent ductus arteriosus (PDA), Intraventricular hemorrhage (IVH), chronic lung disease (CLD), periventricular leukomalacia (PVL) and length of hospital stay were measured.^{14,15}

2.4. RDS diagnosis

RDS/HMD (Hyaline membrane disease) was diagnosed by presence of all of the three criteria¹⁴

- Pre-term neonate
- Respiratory distress having onset within 6 h of birth
- Amniotic fluid Lecithin/Sphingomyelin ratio of < 1.5, or negative gastric aspirate shake test or skiagram of chest showing poor expansion with air bronchogram/reticulogranular pattern/ground glass opacity.

Severity of RDS was decided in accordance with requirement of various form of respiratory support and its duration (oxygen alone, CPAP, MV).

2.5. Statistical analysis

Assuming the incidence of RDS in preterm newborn infants with none or single dose of ACS of 30%, to detect a difference in incidence of RDS of 10% in preterm babies exposed to 2–4 doses of ACS and accepting two sided alpha error of 5%, a sample size of 231–293 subjects in each group was needed to give 70–80% power to the study. Analysis was performed using SPSS software, version 21. Descriptive analysis of qualitative and quantitative data presented as frequency table and mean $\pm$ standard deviation or median (inter-quartile range) respectively. Categorical data was analyzed using Chi-square test or Fisher-exact test and continuous data by *t*-test or Mann-Whitney *U* test. A *p*-value of 0.05 was considered to be statistically significant.

Ethical approval

Ethical clearance was obtained from the Institutional ethical committee.

3. Results

Total number of deliveries was 8637 during study period, of which 7860 were live born and 777 were still born. Of 7860 live births, 1273 were preterm births. 677 Neonates were excluded due to congenital malformations, congenital heart defect or refusal to take part in the study. A total of 596 preterms were enrolled and on the basis of maternal exposure to ACS, 292 were grouped in group 1 and 304 in group 2. Among the 292 neonates in group 1, who received 2, 3 and 4 doses of ACS were 17(5.8%), 46(15.8%) and 229(78.4%) respectively. Of 304 neonates in group 2 217(56.2%) received nil dose and 133 (43.8%) received 1 dose. As shown in Table 1, the base line neonatal characteristics were similar among two groups. Antenatal maternal characteristics were also comparable except group 1 had more primipara mothers as compared to group2 (78.1% vs 69.4%; *p* = 0.02).

As shown in Table 2, incidence of RDS in group 1 was 28.1% and 37.8% in group 2, which was statistically significant (*p* = 0.011). Severity of RDS was assessed by the need of different respiratory support as shown in Table 2. More RDS babies in group 1(62.2%) required MV as compared to group 2 (41.7%), and it was statistically significant (*p* = 0.005). Although less number of RDS neonates needed CPAP (34.1% vs 53.9%; 0.006) and oxygen (3.7% vs 4.3%; 0.81). 60(20.5%) babies expired in group 2 as compared to 61(20.1%) in group 1 which was statistically insignificant (*p* = 0.71). However among the 60 expired neonates of group 1, 35/60(58.3%) were culture positive sepsis versus 19/61(31.1%) in group 2 (*p* < 0.001).

On comparing neonatal morbidities (Table 3) were similar in both the groups except IVH, which was less in group 1 (0.3% vs 2.6%; *p* = 0.04) and culture positive sepsis which was on the contrary more in group 1(12% vs 6.2%; *p* = 0.02). Occurrence of NEC (3.8% vs 3.6%; *P* = 0.93), PDA (7.2% vs 9.9%; *P* = 0.25), CLD (2.4%vs 1.6%; *p* = 0.57), PVL (1% vs 0.3%; *P* = 0.31), and length of stay (5 days [3–9.5] vs 5 days [3–10]; *p* = 0.43) were comparable.

4. Discussion

We studied, effect of 2–4 doses of ACS compared to 0–1 dose between 26 and 34 weeks gestation. We used dexamethasone as ACS, which is also recommended by WHO. A Cochrane review (2013) comparing use of different ACS in women at risk of preterm delivery, found no statistical difference between dexamethasone and betamethasone as far as RDS (RR: 1.06, 95% CI 0.88–1.27), neonatal deaths (RR: 1.41, CI 0.54–3.67) were concerned. Although there was a

Table 1
Baseline Maternal & Neonatal demographic variables.

Maternal variables	Group 1 (n = 292)	Group 2 (n = 304)	P value
Age (year) mean $\pm$ SD	25.8 $\pm$ 2.7	26.1 $\pm$ 2.6	0.16
Primipara	228 (78.1%)	211 (69.4%)	0.02
Low Socioeconomic status	89 (30.5%)	80 (26.3%)	0.26
Anemia	51 (17.5%)	60 (19.7%)	0.48
Gestational Diabetes mellitus	10 (3.4%)	8 (2.6%)	0.57
Pregnancy induced hypertension	89 (30.5%)	88 (28.9%)	0.68
Fever < 7 days of delivery	5 (1.7%)	4 (1.3%)	0.75
Premature rupture of membrane	95 (32.5%)	99 (32.6%)	0.99
Prolonged rupture of membrane	52 (17.8%)	59 (19.4%)	0.62
Urinary tract infection	2 (0.7%)	5 (1.6%)	0.45
Tuberculosis	1 (0.3%)	0 (0%)	0.90
Antenatal Checkup $\geq$ 3	150 (51.4%)	141 (46.4%)	0.25
Hypothyroidism	17 (5.8%)	12 (3.9%)	0.29
Rheumatic Heart Disease	5 (1.7%)	9 (3.0%)	0.42
Chorioamnionitis	16 (5.5%)	20 (6.6%)	0.57
Obstructed Labor/Prolonged Labor	6 (2.0%)	7 (2.2%)	0.81
Meconium Stained Amniotic Fluid	6 (2.1%)	15 (4.9%)	0.06
Abnormal Non Stress Test	54 (38.8%)	47 (37.9%)	0.90
Ante Partum Hemorrhage	58 (19.9%)	79 (26%)	0.08
Neonatal variables	Group 1 (n = 292)	Group 2 (n = 304)	P value
Mode of Delivery – Vaginal	147 (49.7%)	174 (57.2%)	0.09
Caesarian Section	145 (49.3%)	130 (42.8%)	
Resuscitation			
Bag & Mask	5 (1.7%)	6 (1.6%)	0.73
Intubation with Intermittent Positive Pressure Ventilation	24 (8.2%)	33 (10.9%)	
Surfactant administration	28 (9.6%)	30 (9.9%)	0.91
Birth weight (gram) mean $\pm$ SD	1617 $\pm$ 434	1628 $\pm$ 386	0.75
Weight Category:			
< 1000 g	27 (9.2%)	15 (4.9%)	
1000–1499 g	101 (34.6%)	109 (35.9%)	0.21
$\geq$ 1500 g	164 (56.2%)	200 (59.2%)	
Gestational age (weeks) mean $\pm$ SD	31.7 $\pm$ 1.8	31.9 $\pm$ 1.6	0.11

SD = Standard Deviation.

Table 2
Incidence and Severity of RDS & Mortality among the two groups.

Parameter	Group 1 (n = 292)	Group 2 (n = 304)	P value
Incidence of RDS	82 (28.1%)	115 (37.8%)	0.011
Severity of RDS			
O ₂ alone	3/82 (3.7%)	5/115 (4.3%)	0.81
CPAP	28/82 (34.1%)	62/115 (53.4%)	0.006
Mechanical ventilation	51/82 (62.2%)	48/115 (41.7%)	0.005
Outcome			
Mortality	60 (20.5%)	61 (20.1%)	0.71
LAMA	3 (1.0%)	6 (2.0%)	

RDS = Respiratory Distress Syndrome, CPAP = Continuous Positive Airway Pressure.

LAMA = Left Against Medical Advice.

statistical reduction in IVH with dexamethasone use, there was no significant difference in severity of IVH and PVL.¹⁶ In an experimental model in lamb, the minimal interval from fetal exposure to corticosteroid till delivery for improved postnatal lung function was found between 8 and 15 h.¹⁷ The maximum interval reported was 24 h to 7 days after dose completion, when the reduction in RDS risk was nearly 50%.¹⁸ In the present study, the patients in group 2 received 0–1 dose of ACS and delivered within 12 h, expecting no benefits from a single dose of ACS. The efficacy of ACS treatment depends on GA. Recent Cochrane database does not support its use in term babies delivered by cesarean.¹⁹ Administration of ACS before 22 weeks of gestation is unlikely to improve lung function, because of very few primitive alveoli at this GA on which drug can exert its effect. A 2016 meta-analysis of RCTs of ACS before 24 weeks of gestation demonstrated a reduction in perinatal mortality at 23 weeks of gestation, however no statistical reduction was observed for RDS, severe IVH or NEC.²⁰ In an

Table 3
Morbidities among the two groups.

	Group 1 (n = 292)	Group 2 (n = 304)	P value
NEC	11 (3.8%)	11 (3.6%)	0.93
PDA	21 (7.2%)	30 (9.9%)	0.25
IVH Grade 3 (at least)	1 (0.3%)	8 (2.6%)	0.04
PVL	3 (1.0%)	1 (0.3%)	0.31
CLD	7 (2.4%)	5 (1.6%)	0.57
Positive Sepsis Screen	61 (20.9%)	83 (27.3%)	0.02
Positive Blood Culture	35 (12.0%)	19 (6.2%)	
Hospital Stay (Days)	5 (3–9.5)	5 (3–10)	0.43
(Median IQR)			

NEC = Necrotizing Enterocolitis, PDA = Patent Ductus Arteriosus, IVH = Intra Ventricular Hemorrhage.

PVL = Peri ventricular Leucomalacia, CLD = Chronic Lung Disease, IQR = Inter Quartile Range.

observational cohort study on extremely premature infants (birth weight, 401–1000 g; GA 22–27 weeks) logistic regression revealed that complete (odds ratio, 0.63; 95% CI, 0.53–0.76), partial (odds ratio, 0.77; 95% CI, 0.63–0.95) ACS courses were associated with lower rates of death or neurodevelopmental impairment compared with no ACS group, mediated by ACS-associated reductions in rates of severe IVH and/or cystic PVL.²¹ We studied women at risk of preterm delivery (26–34 weeks) and preterm babies delivered within the next 7 days. Use of ACS after 34 weeks of gestation is controversial because of inconsistent data about its efficacy, concerns for neonatal hypoglycemia and long term safety. In a triple blinded RCT by Porto et al. no reduction in respiratory disorders of newborns was found.²² However a multicentric randomized controlled trial (RCT) on 1427 late preterm neonates (2016) found significant reduction in neonatal respiratory mortality, morbidity.²³ Authorities like American college of obstetrician and

gynecologist, Royal College of obstetrician and gynecologist have recommended its use beyond 34 weeks of gestation.^{9,10}

In our study, the incidence of RDS was 9.7% lesser in group I babies (2–4 doses of ACS) (28.1% vs 37.8%) compared to group 2 (0–1 dose of ACS) which is statistically significant ($p = 0.011$). The results are similar to cochrane review (2006), which found decreased risk of RDS by 31% (95% CI 27–41%, 4038 infants) in babies who were steroid covered (betamethasone, dexamethasone or hydrocortisone).⁵ A project in four South East Asian countries, (SEA-ORCHID, 2008) found that infants exposed to ACS were less likely to be stillborn (RR 0.06, [95%CI 0.02, 0.25], $p = 0.01$) and were less likely to die prior to hospital discharge (stillbirth and death prior to discharge combined, RR 0.49, [95%CI 0.30, 0.79], $p = 0.01$) compared with infants who were not exposed (31). Roberto et al. from Brazil (2016) found similar incidence of RDS in both the groups, but their baseline maternal and neonatal parameters were not comparable.²⁴

We found severity of RDS was more in group 1 as 62.2% babies required MV compared to 41.7% in group 2. That is although less babies developed RDS but those who developed were more severe than less or unexposed group. Hiroshi Ishikawa (2015) showed that ACS does not affect short- or long-term outcome in SGA infants when birth-weight is less than 1500 g.²⁵ We have equal proportion of SGA babies in the two groups. Besides, there are differences in the genetic makeup, ethnicity, and nutritional status of mothers in our country which might influence the incidence & severity of RDS.

The baseline characteristics were comparable except caesarean sections were more in group 1 babies (49.3% Vs 42.8%; 0.09). This could have contributed to increased severity of RDS in group I patients. In a study done in middle-low income developing countries by Fernando Althabe it was seen that despite increased use of ACS in low-birth weight infants in the intervention group, neonatal mortality did not decrease in this group and increased in the population overall (27.4/1000 vs 23.9/1000, RR = 1.12, 95% CI 1.02–1.22, p -value = 0.0127). For every 1000 women exposed to this strategy, an excess of 3.5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased.¹³ In a recent study ACS use decreased oxygen dependency at 36 weeks in 11%, advanced resuscitation in delivery room in 24%, severe IVH in 12%, PDA requiring surgery in 3.6% and retinopathy of prematurity in 0.3%, but increased the probability of late-onset sepsis in 2.5%.²⁶ Similar to these two studies, we had more cases of culture positive sepsis occurred in group1.

We found mortality was similar in both the groups (20.5% Vs 20.1%; p value-0.71). Similar results were depicted by Onland & colleagues with no significant reduction in neonatal morbidity and mortality with steroid use.²⁷ A Cochrane review (18 RCT) found ACS was associated with reductions in neonatal mortality in very preterm babies (RR = 0.66; 95% CI 0.59–0.73; 21 studies, 4038 babies).²⁸ Contrary to this there was no effect of ACS on mortality in our study. However all the trials included in the cochrane review were from developed country. Elimian A (2003) like us studied 74 women exposed to ACS & 221 women not exposed to ACS and found no statistically significant difference in the rate of any adverse neonatal morbidity (47.3% vs. 40.7%, $p = 0.32$) or the rate of neonatal morbidity composite (34.4% vs. 37.8% $p = 0.59$) between the two groups.²⁹ A cochrane review (2006) of 21 studies (3885 women and 4269 infants) showed that treatment of women at risk of preterm birth with a single course of ACS reduced the risk of neonatal death by 31% (95% CI 19–42%), RDS by 44% (95% CI 31–57%) and IVH by 46% (95% CI 31%–67%).⁵ ACS use reduced neonatal deaths even when infants were born less than 24 h after the first dose (RR 0.53, 95% CI 0.29–0.96, four studies, 295 infants) till 7 days.⁵ In our study we found reduction in the incidence of IVH (0.3% vs 2.6%; $p = 0.04$) but other morbidities like NEC (3.8% vs 3.6%; $P = 0.93$), PDA (7.2% vs 9.9%; $P = 0.25$), CLD (2.4% vs 1.6%; $p = 0.57$), PVL (1% vs 0.3%; $P = 0.31$), and length of stay (5 days [3–9.5] vs 5 days [3–10]; $p = 0.43$) remained same.

In our study the incidence of maternal infection was similar in 2

groups, assessed by evidence of clinical chorioamnionitis (5.5% vs 6.6%; 0.57), puerperal sepsis (0.4% vs nil; 0.28) and use of antibiotics in the mothers (13.6% vs 15.7%; 0.50). According to cochrane review (2006) there was no increased risk of chorioamnionitis, puerperal sepsis in mother receiving ACS. Similar results were found in a recent cochrane review (2016) showing no significant association between a single course of ACS and chorioamnionitis (RR-0.91, 95% CI, 0.7–1.18, 12 studies, 2485 women) or puerperal sepsis.²⁸ Although a study (F Althabe 2014), from developing country found increased incidence in maternal infections (3% vs 2%, p -value- < 0.0001) with ACS.¹³ This may be because this study was done in developing low income countries verses the earlier studies were from developed world.

4.1. Strengths and limitations of the study

The study was well planned and conducted however the study was single centered and because of the small sample size the power of the study was less than 80% so subgroup analysis was limited by small number of patients.

4.2. Interpretation

The present study demonstrated marginal decrease in the incidence of RDS and IVH in the preterm babies whose mothers received 2–4 doses of ACS compared to those with 0–1 dose. However there was trend to have more cases of severe RDS and higher sepsis among neonates with the higher dose group. Also because of resource poor setting surfactant and CPAP was not available to many of the babies where it was indicated, which would have changed the outcome of these patients.

5. Conclusion

Similar to the previous studies, our study too shows reduction in neonatal RDS and IVH cases by ACS however the substantial increase in the neonatal sepsis rates with more severe RDS in the ACS group, elucidates this issue being sprouted by few earlier studies especially in low middle income country like ours.

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Declaration of competing interest

There is no conflict of interest with respect to research, authorship, and publication of this article.

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