The incidence and outcome of respiratory distress syndrome in preterm babies in relation to administration of antenatal corticosteroids

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ABSTRACT

Background: Premature infants have a higher incidence of respiratory distress syndrome (RDS), which is one of the main causes of early neonatal mortality. Objectives: The objective is to study the incidence and outcome of RDS in preterm babies <34 weeks of gestation born to mothers who had received antenatal corticosteroids (ACS). Methodology: A prospective observational study was conducted among preterm babies from January 2015 to December 2015 in a tertiary care hospital of South India. Details of the mothers with a period of gestation 34 weeks or less who had received ACS were recorded. Results: The study population included 749 preterm babies (<34 weeks) delivered in our hospital. Among them, 698 (93.2%) mothers received two doses of ACS and 51 (6.8%) received only a single dose of ACS. Neonates whose mothers received two doses of ACS had a significantly lower incidence of RDS (27.6% vs. 100%, p<0.001), lower rate of mechanical ventilation (45% vs. 72.5%, p<0.001), and higher survival rate (87% vs. 68.6%, p=0.001) than neonates whose mothers received a single dose of ACS. The occurrence of RDS is highest in 26–28 weeks babies (60%) and least in 28–32 weeks babies (32%). Conclusion: A single complete course of ACS (two doses 24 h apart) is efficacious than one dose of ACS with respect to prevention of RDS, neonatal mortality, and need for mechanical ventilation.

Key words: Antenatal corticosteroid, Preterm, Respiratory distress syndrome, Surfactant

The morbidity and mortality rates of premature infants are much higher than those of full-term babies. Premature infants have a higher incidence of respiratory distress syndrome (RDS), which is one of the main causes of early neonatal mortality. Corticosteroid consumption in pregnancy can stimulate the maturation of alveolar type 2 cells to produce surfactant and elicit architectural maturation of the fetal lung. Therefore, antenatal corticosteroid (ACS) can reduce the incidence of RDS, perinatal and neonatal death, and severe morbidity in premature infants below 34 weeks gestation. Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. The National Institute of Health recommended the use of ACS among mothers with gestational age between 24 and 34 weeks to improve the outcome of preterm infants and in particular will reduce the incidence and severity of RDS. Recommendation of ACS treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 h apart or four doses of 6 mg of dexamethasone given intramuscularly 12 h apart. Several studies regarding repeated courses or weekly courses of ACS for preterm infants to enhance their lung maturation were reported. A Cochrane Database review published in 2006 summarized 21 studies including 3885 mothers and 4269 infants and confirmed significant reductions in the risks of mortality, RDS, and intraventricular haemorrhage among preterm infants by 31%, 44%, and 46%, respectively, after a single course of steroids. Although the effects of ACS on lung maturation appear to be dose dependent, the biological effects and optimal dosage regimen of antenatal glucocorticoids remain under investigation. Although our hospital policy is to give two doses of betamethasone 24 h apart, some of the mothers delivered within 24 h of the first dose of steroid. The babies of mothers who received a single dose of corticosteroid were included in the study as a separate group. It is a well-known fact that a single course (two doses) of ACS for the pregnant woman at risk of preterm delivery is the standard of care. There are many studies that compare the outcome between a single course and multiple courses of ACS. A single course of ACS is two doses of ACS 24 h apart for mothers with imminent preterm birth. However, there are no studies that compare the outcome of preterm babies whose mothers received a single dose and those with two doses of betamethasone in a single course of antenatal steroid therapy. Hence, the present study was conducted with an aim to measure the incidence of RDS and its outcome in preterm babies of <34 weeks of gestation born to mothers who had received ACS and to compare the outcome between a single-dose ACS and double-dose ACS groups.
**METHODOLOGY**

We undertook a prospective observational study in a tertiary care teaching hospital in Kerala, South India. The study was approved by the institutional ethical committee. Informed written consent was obtained from parents of all subjects before enrolment in the study.

All preterm babies of <34 weeks gestational age born to mothers who had received ACS (single dose or two doses) in our hospital during the period January 2015–December 2015 were included in the study. The babies with major structural anomalies, chromosomal abnormalities, and steroid use for other indications were excluded from the study. Based on the past 12 months admission rate in our hospital, with requisite inclusion and exclusion criteria, a convenient sample size of 749 consecutive preterm newborns and their mothers were included in the study.

Details of the mothers with a period of gestation 34 weeks or less who had received ACS were collected from the place of delivery (labor room or operation theater). Those who received two doses of ACS and those who delivered within 24 h of the first dose were followed up, and their newborns were monitored for the probable occurrence of RDS. Infants were divided into one-dose ACS group and two-dose ACS group to evaluate the different outcome between these two groups. The outcome was measured as the proportion of babies who developed RDS. RDS was defined as onset of respiratory distress within 6 hours of birth in a preterm baby (<34 weeks) with chest X-ray showing poor expansion, air bronchogram, or reticulogranular pattern.

These newborns were classified based on their gestational age into three groups as 26–28 weeks, 28–32 weeks, and 32–34 weeks. The incidence of RDS, the requirement of continuous positive airway pressure (CPAP), mechanical ventilation, and need for surfactant were compared between the groups. The neonatal outcome including survival rate, the need for surfactant treatment, requirement of CPAP, and mechanical ventilation was also analyzed and compared between the one-dose and two-dose ACS groups.

Data were analyzed using the Statistical Package for the Social Sciences software version 22.0 (SPSS, IBM Inc., New York). Baseline variables were described by descriptive statistics, and dichotomous variables were compared by Chi-square test. The p<0.05 was considered statistically significant.

**RESULTS**

The study included 749 preterm newborns (<34 weeks) of 9320 deliveries that occurred in the year 2015 in our hospital.

The mothers of all these 749 preterm babies received corticosteroid during their antenatal period. Among 749 mothers, 698 (93.2%) received two doses of antenatal steroid, and of 749 preterm babies, 244 (32.6%) developed RDS. All babies required oxygen support, among which 120 (49.2%) babies received CPAP and 124 (50.8%) required mechanical ventilation. Our unit did not practice rescue surfactant administration. Hence, the surfactant was administered only to babies who have a Downe’s score of more than 4. A total of 72.5% babies with RDS required surfactant, of which 76.8% survived. Among babies who received two doses of antenatal steroids, 137 (70%) required surfactant therapy and 56 (30%) babies improved without surfactant therapy. The survival rate among babies with RDS was 83.2% (203) (Table 1). Gestational age-wise distribution (Table 2) showed that 83.7% of babies were from 28 to 32 weeks group. The incidence of RDS

Table 1: Baseline characteristics of preterm babies and mothers

| Mother and Baby details                              | Total (%) | One dose ACS (%) | Two dose ACS (%) |
|------------------------------------------------------|-----------|------------------|------------------|
| Mothers received ACS and delivered preterm           | 749       | 51 (6.8)         | 698 (93.2)       |
| Preterm babies developed RDS                         | 244 (32.6)| 51 (20.9)        | 193 (79.1)       |
| Babies with RDS needed CPAP support                 | 120 (49.2)| 14 (11.6)        | 106 (88.4)       |
| Babies with RDS needed mechanical ventilation       | 124 (50.8)| 37 (29.8)        | 87 (70.2)        |
| Babies with RDS received surfactant                 | 177 (72.5)| 40 (22.59)       | 137 (77.4)       |
| Babies with RDS not received surfactant             | 67 (27.5) | 11 (16.4)        | 56 (83.58)       |

Details of Babies with RDS

|                         | Total | Died | Survived |
|-------------------------|-------|------|----------|
| Preterm babies developed RDS | 244 (32.6) | 41 (16.8) | 203 (83.2) |
| Preterm babies with RDS received surfactant | 177 (72.5) | 41 (23.16) | 136 (76.83) |

**Table 2: Gestational age-wise distribution of preterm newborns**

| Gestational age | 26–28 weeks n=5 | 28–32 weeks n=627 | 32–34 weeks n=117 | Total |
|-----------------|-----------------|------------------|------------------|-------|
| Received ACS (2)| 3 (0.4)         | 582 (83)         | 113 (16)         | 698   |
| Received ACS (1)| 2 (3.9)         | 45 (88.2)        | 4 (7.8)          | 51    |
| RDS             | 3 (60)          | 201 (32)         | 40 (34)          | 244   |
| Oxygen support  | 3 (100)         | 201 (100)        | 40 (100)         | 244   |
| CPAP            | 0 (0)           | 98 (49)          | 22 (55)          | 120   |
| Mechanical ventilation | 3 (100) | 103 (51)        | 6 (15)           | 124   |
| Surfactant      | 3 (100)         | 163 (81)         | 11 (27.5)        | 177   |

**RDS: Respiratory distress syndrome, ACS: Antenatal corticosteroids, CPAP: Continuous positive airway pressure**
was more in babies <28 weeks (60%) than in the 32–34 weeks group (34%) and 28–32 weeks group (32%). The data showed that 28–32 weeks group was benefitted the most from antenatal steroids.

Among the babies, who developed RDS, the need for CPAP and mechanical ventilation was higher for preterm babies born to mothers who received a single dose of corticosteroids than preterm born to mothers who received two doses of antenatal steroids (Table 3).

The difference between babies of mothers who had received a single dose and two doses of ACS was statistically significant with respect to oxygen support in babies with RDS. There was no significant difference with respect to the need for surfactant administration and ventilator survival rate between babies of mothers who had received a single dose and two doses of ACS. The survival rate, in relation to the outcome of RDS, was significantly higher for babies of mothers who received two doses of antenatal steroids than the babies whose mothers received a single dose of antenatal steroids, whereas the incidence of RDS was significantly higher among preterm babies born to mothers who had received a single dose of ACS than the preterm babies born to mothers who had received two doses of antenatal steroids 24 h apart (Table 4).

**DISCUSSION**

This study conducted at tertiary care teaching hospital in South India mainly investigated the effect of ACS on the occurrence of RDS and its outcome in preterm babies <34 weeks. We also compared neonatal outcomes of one dose versus two doses ACS in preterm infants. Preterm babies who have been exposed to repeated courses of ACS had a lower incidence of RDS than those who have been exposed to one course of ACS in few well-designed randomized controlled studies and in some other studies. However, some studies showed that there was no significant difference between repeated courses and a single course of ACS treatment. As such, there are no reports on the neonatal outcomes of one dose versus double dose of ACS and preterm infants. In this study, we analyzed the outcome between these groups, though the sample size was low in single dose group.

The study showed that there was a significant benefit of two doses of antenatal betamethasone over a single dose in threatened preterm deliveries with respect to RDS, need for mechanical ventilation, and mortality rate. The overall incidence of RDS in our study was 32.57%. This was slightly higher than the study by Lau et al. (17.6%) and Liggins et al. (9%). The 1994 NIH consensus panel concluded that optimal benefit of ACS was seen at 24 h to 7 days of initiation of treatment. A high rate of occurrence of RDS in our study could be due to the short interval between initiation of therapy and preterm delivery. In this study, the requirement of mechanical ventilation in RDS was significantly associated with single dose steroid (72.5%) compared to double dose (12.4%) (p<0.001). A Cochrane review that summarizes the result of 10 randomized controlled trials says that more than one course of ACS reduces the risk of RDS. In a retrospective cohort study by Vermillion and colleagues, rescue corticosteroid administration was significantly associated with a reduction in the frequency of RDS as well as mean days on the ventilator.

Our study showed a significant survival benefit in babies with two doses of ACS. The reduced incidence of neonatal death with use of ACS in preterm was seen in many other studies. However, in the global networks, ACS trial (ACT), which was a multi-country trial to improve appropriate use of

| Variables                        | One dose (%) | Two doses (%) | p (Chi-square value) |
|----------------------------------|--------------|---------------|----------------------|
| Oxygen support in babies with RDS |              |               |                      |
| CPAP                             | 14 (27.5)    | 106 (55)      | *0.001 (12.18)       |
| Mechanical ventilation           | 37 (72.5)    | 87 (45)       |                      |
| Surfactant therapy in babies who had received ACS |          |               |                      |
| Surfactant given                  | 40 (78.4)    | 137 (70.9)    | 0.289 (1.12)         |
| Surfactant not given              | 11 (21.6)    | 56 (29)       |                      |
| Outcome of RDS                   |              |               |                      |
| Survival                         | 35 (68.62)   | 168 (87)      | *0.0017 (9.79)       |
| Death                            | 16 (31.37)   | 25 (12.9)     |                      |
| Outcome of RDS in ventilated babies |          |               |                      |
| Survival                         | 21 (56.8)    | 62 (71.3)     | 0.116 (2.47)         |
| Death                            | 16 (43.2)    | 25 (28.7)     |                      |
| RDS in babies who had received ACS |          |               |                      |
| RDS present                      | 51 (100)     | 193 (27.6)    | *0.001 (113.27)      |
| RDS absent                       | 0            | 505 (72.3)    |                      |

*p<0.05 (significant), RDS: Respiratory distress syndrome, ACS: Antenatal corticosteroids, CPAP: Continuous positive airway pressure
administration and time from administration to delivery were not available. However, the inclusion of infants who received ACS outside the optimal window for administration, from more than 24 h to 7 days, would be expected to skew the results. Furthermore, data were not collected on whether fetal monitoring was undertaken or the length of maternal hospital admission before delivery.[16] The indication for preterm delivery was not available and may differ between groups.

CONCLUSION

Two doses of ACS 24 h apart can decrease the incidence of RDS, the need for mechanical ventilation, and increased survival rate of preterm. The neonatal outcomes were significantly different between one-dose ACS and two-dose ACS. This study emphasizes the need for developing quality improvement efforts to optimize appropriate and timely antenatal corticosteroid administration. To obtain more reliable and objective information, further research including randomized control trials is necessary.

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