Antenatal use of Corticosteroids to Prevent Respiratory Insufficiency in Preterm Babies

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ABSTRACT

Preterm birth is a risk factor in atleast 50% of all neonatal deaths. India has the highest number of preterm births as well as neonatal deaths due to prematurity. Antenatal corticosteroid(ANC) treatment for women who are at risk of preterm delivery has emerged as the most effective intervention for the prevention of Respiratory Distress Syndrome(RDS), reducing early neonatal mortality and morbidity. The study population included 70 preterm babies. Among them, 28 belonged to group 0 (no ANC), 25 in group 1 (single dose of ANC) and 17 in group 2 (double dose of ANC). Babies whose mothers received two doses of ANC had a significantly lower incidence of RDS ($P=0.043$) than neonates whose mothers received a single dose of ANC ($P=0.343$). There is also some beneficial effect in babies born after 24 hours of single dose ANC administration. However, in some cases, babies developed RDS as only single dose was received and delivery occurred within 24 hours of ANC administration. A single complete course of ANC (2 doses of betamethasone 12 mg 24hours apart) is efficacious than one dose of ANC in prevention of RDS.

Keywords: Respiratory Distress Syndrome(RDS), Antenatal Corticosteroids(ANC), Preterm, Betamethasone.

INTRODUCTION

Every year, an estimated 15 million babies are born preterm and this number is rising¹. Infants born preterm are at high risk of neonatal lung disease and associated complications. RDS, a consequence of immature lung development, is the primary cause of early neonatal mortality and contributes to significant immediate and longterm morbidity in survivors. ANC treatment for women at risk of very preterm birth before

34 weeks gestation is one of the most effective treatments for the prevention of RDS, reducing neonatal mortality and morbidity. ANC's accelerate development of type 1 and type 2 pneumocytes that lead to structural and biochemical changes that improve both lung mechanics and gas exchange. ANC administration is important for developing countries where resources are scarce and it is often difficult to provide expensive treatments such as neonatal care.

Although evidence of benefit for the use of ANC's has been available for many years, widespread adoption of this treatment into routine clinical practice was significantly delayed and implementation of their use remained suboptimal in developed countries for many years. There is limited information as to how well this practice has been implemented in developing countries².

METHODOLOGY

A prospective study was conducted over a period of 6 months from October 2018 to March 2019. The study was conducted at Gynaecology and Obstetrics, Pediatric department of PKDAS Institute of Medical sciences and Valluvanad hospital, Palakkad. The study was approved by the Institutional Ethics Committee(IEC) of PK DAS hospital and Valluvanad hospital. Babies whose guardians gave written consent were enrolled into the study. All babies born alive before 37 weeks of gestation, in a six-month period were included in the study. Exclusion criteria included intra-uterine foetal death, immediate expiration after delivery, presence of major congenital malformations, presence of a confirmed or suspected genetic or metabolic disorder, babies born after 37weeks of gestation, delivery not at hospital or if maternal data not available.

The selected new born were classified into **3 groups**:-

- **GROUP 0** – Those who had not been exposed to ANC (prenatal administration of one or two doses of 12mg betamethasone)
- **GROUP 1** – Those who had been exposed to single dose of ANC (incomplete course)
- **GROUP 2** – Those who had been exposed to double dose of ANC (complete course)

Statistical analysis: Data were entered into Microsoft Excel 2007 datasheet and was analysed using software SPSS 20 Version. Chi Square test or Fischer's exact test was used as test of significance for qualitative data. Continuous data

was represented as mean and standard deviation. Independent T-test was used as test of significance to identify the mean difference between two quantitative and qualitative variables. In all the tests, the level of significance was set at 0.05.

RESULTS AND DISCUSSION

During the period of study, 85 premature infants were born with a gestational age of less than 37 weeks. Of these, it was not possible to recover the records of 15 mothers and so the study was carried out in 70 newborns. Among the 70 newborns, 28 belonged to Group 0, 25 in Group 1 and 17 in Group 2. The mean gestational age at administration was 32 ± 2 . In the study, out of 70 newborns, 42 had been exposed to ANC and 23 developed RDS (49%) whereas in 28 newborns who had not been exposed to ANC, 24 developed RDS (83%). This difference was statistically significant. ($P = 0.009$) (Table 1) In the study population, 25 were exposed to single dose of ANC out of which 15(60%) developed RDS whereas 28 were not exposed and of these, 24(85.71%) developed RDS. This difference was not statistically significant. ($P = 0.060$) (Table 2(a)) Comparison of double dose with no dose of ANC administration was also done. 17 were exposed to double dose of ANC out of which 8 developed RDS (47.1% vs 85.71%) which was statistically significant. ($P = 0.008$) (Table 2(b)) While comparing the general characteristics, obstetric and perinatal history and treatment of preterm babies among the three groups, only mode of delivery showed significance (Table 3). Neonatal complications in preterm babies were compared among the three groups; only RDS ($P=0.015$) and NNHB ($P=0.004$) were found to be significant. (Table 4). The comparison of neonatal complications in case and control groups was done and found that only RDS was significant ($P=0.006$) (Table 5) In the study, 3 newborns died due to severe RDS and cardiac arrest.

Table 1: Association of ANC in prevention of RDS in preterm babies

Corticosteroids used	RDS developed		Total
	YES	NO	
YES	23	19	42
NO	24	4	28
Total	47	23	70

RDS- Respiratory Distress Syndrome, ANC- Antenatal Corticosteroids; $P= 0.009$

Table 2(a): Comparison of Single dose and no steroids

	RDS		TOTAL
	YES	NO	
Single dose	15	10	25
No steroids	24	4	28
Total	39	14	53

P value = 0.060

Table 2(b): Comparison of double dose and no dose of ANC administration.

	RDS		TOTAL
	YES	NO	
Double dose	8	9	17
No dose	24	4	28
Total	32	13	45

P = 0.008

Table 3: General characteristics, obstetric and perinatal history and overall morbidity of preterm infants

Total		Absolute frequency(n=70) n%	Incomplete course (n=25)	Complete course (n=17)	No steroids (n=28)	P value
<u>General characteristics</u>						
Gestational age						
<33weeks		8	2	3	3	0.256
33-34 weeks		20	5	5	10	
34-35weeks		32	14	9	9	
> 35weeks		10	4	0	6	
<u>Gestation</u>						
HTN	YES	2	1	1	0	0.513
	NO	68	24	16	28	
Diabetes	YES	4	3	1	0	0.121
	NO	66	22	16	28	
Oligohydramnios	YES	6	1	3	2	0.367

		NO	64	24	14	26	
Primiparous	YES	6		1	3	2	0.121
	NO	64		24	14	26	
IUGR	YES	1		1	0	0	0.600
	NO	69		24	17	28	
PPROM	YES	10		4	3	3	0.753
	NO	60		21	14	25	
<u>Delivery</u>							
Caesarean		47		20	7	20	0.026
Others		23		5	10	8	
<u>Treatment</u>							
Requiring resuscitation	YES	36		9	9	18	0.132
	NO	34		16	8	10	
Oxygen therapy							
	YES	44		12	10	22	0.641
	NO	26		13	7	6	
CPAP	YES	28		10	5	13	0.55
	NO	42		15	12	15	
Surfactant therapy							
	YES	12		2	2	8	0.15
	NO	58		23	15	20	
Phototherapy	YES	37		13	8	16	0.801
	NO	33		12	9	12	

Table 4: Evaluation of difference in neonatal complications among three groups.

		Incomplete course(n= 25)	Complete course(n=17)	No steroid (n=28)	P value
RDS	YES	15	8	24	0.015
	NO	10	9	4	
NNHB	YES	12	1	14	0.004
	NO	13	16	14	
TTNB	YES	1	4	3	0.153
	NO	24	13	25	
HMD	YES	4	1	5	0.572
	NO	21	16	23	
NEC	YES	2	1	1	0.825
	NO	23	16	27	
Neonatal sepsis					
	YES	2	1	4	0.683
	NO	23	16	24	

Table 5: Evaluation of difference in neonatal complications among two groups

	Betamethasone (n=42)n(%)	Without Betamethasone (n=28) n(%)	P value
RDS	23 (54.76)	24 (85.71)	0.009
NNHB	14(33.3)	13 (46.4)	0.109
TTNB	5 (11.9)	3(10.7)	0.878
HMD	5(11.9)	5 (17.85)	0.486
NEC	3 (7.142)	1(3.57)	0.645
Neonatal sepsis	3 (7.142)	4 (14.28)	0.426

DISCUSSION

In consistence with the reviewed literature, the overall rate of birth during the study period was 249. Within this group, 85 of newborns were preterm. These datas are in agreement with those published in most developed countries, where increasing trends have also been reported^{3,4,5}. Some of the underlying causes of preterm delivery are the older age of primiparous mothers, parity, multiple pregnancies, assisted reproductive technologies and an increase in the indication for induced labour and scheduled caesarean delivery.^[6] During the study period, older age primiparous mothers were not seen and assisted reproductive technologies were not used. However, 67.14% of caesarean deliveries, 77.14% parity and 4.28% of multiple pregnancies were observed. These results indicate that all these factors are interrelated. Advanced maternal age is associated with a higher risk of obstetric complications which are often indications for the early termination of pregnancy and is more frequently associated with the need of assisted reproduction technologies, which increases the probability of multiple pregnancy. But this does not comply with this study due to inadequate samples of older primiparous mothers.

In the study, out of 70 preterm infants (PIs), 57(81.43%) required intensive care, giving rise to a considerable number of hospital admission, as this group is the largest among PIs. The general criteria for the admission are having a gestational age of 34 weeks or less, or having a gestational age of more than 34 weeks and birth weight below 2300g or suffering from any disease that requires monitoring and/or treatment. In the past decade, numerous studies have confirmed that these infants, due to their immaturity, have higher morbidity than full-term infants^{7,8,9}.

The evidence shows that the pharmacological induction of foetal lung maturity by means of corticosteroids is the intervention that improves the prognosis of preterm newborns. Consequently, Spanish and American Association of Obstetricians and Gynaecologists recommended antenatal administration of corticosteroids to pregnant women at the risk of preterm delivery between 24-34 weeks of gestation in order to reduce the incidence of acute Respiratory Distress Syndrome, Intraventricular Haemorrhage, Nectrotising Enterocolitis and/or neonatal death¹⁰. In this study, 42(60%) had received ANCs and admission rates were significantly higher in those 28(40%) who had not received them.

Respiratory disorders are among the most frequent morbidities associated with preterm birth. In this study, 47(67.14%) developed RDS and 8(11.42%) developed TTNB. This high

incidence could be due to abnormalities or delays in the clearance of foetal lung fluid after birth. Various studies proposed that sodium transport across the alveolar epithelium is the main mechanism involved in the foetal lung fluid clearance, one which develops as gestational age increases and that becomes particularly important in the last weeks of pregnancy. In preterm infants, the lower number and immaturity of sodium transport mechanism may be involved in the pathogenesis of RDS. The incidence of RDS in the non-steroids groups of PIs was significantly higher than in the steroid exposed group. This is explained in the latest revision of Crowley's metaanalysis¹¹. Similarly, in this study, incidence of RDS is higher in non-exposed group(85.71%) than steroid-exposed group(54.7%) (Table 1). This difference may be explained by the fact that only corticosteroids seem to stimulate the activity of sodium channels in the alveolar epithelium contributing to the reabsorption of lung fluid. There is an evidence that a surge of endogenous steroids and catecholamines accompanies term gestation and spontaneous vaginal delivery, and that these hormonal changes are necessary for foetal maturation and to prepare the foetus to transition successfully to neonatal life. This would account for the higher incidence of RDS in preterm infants who have not been exposed to corticosteroids, especially in those delivered by caesarean section, ie; 83.33% in non-exposed group versus 69.56% in exposed group¹².

This issue is important because RDS is a frequent complication for hospital admission in preterm infants. The rate of morbidity should not be the only factor in deciding which is the gestational age at which administration of ANC's should be recommended. Antenatal treatment could reduce the number of patients admitted to the NICU, resulting in a lower socio-economic burden¹³. Likewise, the Cochrane Review supports the antenatal administration of corticosteroids upto 36^(+6days) weeks of gestation.

In this study, the incidence of Hyaline Membrane Disease(HMD) was very low in both groups and we found less significant difference between them. However, both this condition (17.85% in unexposed and 12% in exposed group)(Table 9) and surfactant administration(28% in unexposed and 9.5% in exposed group) (Table 6) were more frequent in preterm infants who were not exposed to ANC's which could be due to the structural and functional development of foetal lung, which is incomplete in this gestational age group.

There are very few studies on the probable beneficial effect of ANC's administration in preterm infants. To obtain an evidence on this matter, a study was conducted to evaluate the administration of ANC's in women at risk of preterm delivery and concluded that the use of ANC has been shown to be beneficial in women at risk of preterm delivery. This study was found to be similar to study conducted by Maternal Foetal Medicine Units

Network which conducted a prospective multi-center study (Antenatal Late Preterm : Randomised Placebo-Controlled Trial(ALPS))¹⁴.

Respiratory morbidity is not only the primary cause for complications in preterm babies but is accompanied by additional complications such as jaundice, necrotizing enterocolitis, sepsis, ACHD, digestive intolerance which may or may not be associated with the need for respiratory support measures, fluid therapy and parenteral nutrition. These findings are corroborated by the study, as the results showed a significant reduction not only in the risk of developing acute respiratory diseases, but also in the risk of developing jaundice(30.9% in exposed group and 50% in unexposed group) ,necrotizing enterocolitis(7.1% in exposed group and 3.5% in unexposed group) and sepsis(7.1% in exposed and 14.2% in unexposed), and of needing respiratory support (oxygen therapy 52% in exposed group and 78% in unexposed group, nasal CPAP 35% in exposed and 46.4% in unexposed group),fluid therapy and phototherapy(50% in exposed and 57.14% in unexposed group) among PIs exposed to ANC. Thus based on these results, (Table 6) the extension of antenatal corticosteroid administration to PIs would be an effective strategy to reduce the length of hospital stays and the consumption of resources.

In the study, out of 25 babies who were exposed to single dose ANC, 16 who developed RDS were born within 24 hours of ANC administration. There was some beneficial effect in babies born after 24 hours of single dose ANC administration (Table 12). This result complied with study conducted by Gaur et al¹⁵.

The 34-week cut off is still an arbitrary one. While the lung is traditionally considered to have reached structural and biomedical maturity by this gestational age, obtained data are not consistent with this. When analyzing morbidity with gestational age, couldn't find any significance between the reduction in risk with increasing gestational age (Table 3); however, the beneficial effect of ANC treatment was observed throughout the preterm, a finding that was independent of birth weight(Table7b). Furthermore, corticosteroids not only influence the structural and functional maturity of the foetal lung, but also have extrapulmonary effect that contributes to the maturation of different organs and systems^{16,17,18}.

There are studies that do not support the antenatal administration of corticosteroids. The observational multicentre study by Gyamfi-Bannerman et al¹⁸ did not show an association between ANC exposure and a reduction of respiratory morbidity in PIs. A significant

limitation of this study was dose and time of drug administration were unknown, a factor to consider given that the effect of corticosteroids decreases with passage of time.

Another study is a clinical trial in Brazil with a sample of 320 women between 34 – 36 weeks of gestation who were given a course of corticosteroid and placebo. The rate of Acute RDS was very low in both groups, and the rate of TTNB was similar and high in both groups, so the study did not reach sufficient power to detect significant differences¹⁹.

Upto now, no clinical trial has evaluated the long term effects of the administration of antenatal corticosteroids in the preterm period. The effects described most frequently are growth and neurodevelopmental disorders²⁰. A recent study in Sweden suggests that the beneficial effects of ANCs extends beyond 34 weeks and does not seem to increase the risk of adverse neurologic effects²¹.

One of the most feared short term adverse effect is the potential to increase the risk of perinatal infection in PIs, a risk that increases due to the immaturity of their immune systems²². This led to compare and assess the incidence of sepsis, and there was a marked difference between groups 7.1% in exposed group and 14.2% in unexposed group. Thus in this study, the use of antenatal corticosteroids did not increase the risk of infection in PIs.

CONCLUSION

In these settings, the morbidity of preterm infants and respiratory morbidity in particular, is significantly lower in those that had been exposed to complete course of ANCs who did not experience adverse effects in the short-term. If an absence of adverse effect in the long term is confirmed, it may be useful to prolong the administration of ANCs in early weeks of gestation, with the purpose of significantly reducing morbidity and mortality rates, the length of hospital stay, and the need of admission to the NICU. This may help in better utilization of resources and reduce the socio-economic burden associated.

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