ROLE OF EARLY POSTNATAL DEXAMETHASONE IN RESPIRATORY DISTRESS SYNDROME

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Objective: *To study the effect of early postnatal dexamethasone therapy on severity of hyaline membrane disease.* ***Design:*** *Prospective, randomized, controlled, unblinded study. Setting: Neonatal Intensive Care Unit.* ***Methods:*** *19 babies who had hyaline membrane disease were included in this study. The inclusion criteria were clinical and radiographic diagnosis of RDS, requiring mechanical ventilation and FiO_2 >0.3. Ten babies received injection dexamethasone 0.5 mg/kg/dose 12 hourly for 3 days starting within 6 hours of birth. The control group did not receive any drug. Babies with active infection, bleeding tendency and congenital malformation were excluded. None of the babies received surfactant. The duration of ventilation and $AaDO_2$ and FiO_2 requirements from day one to five were calculated.* ***Results:*** *The initial $AaDO_2$ were similar in both the groups but on day 3, 4, 5 $AaDO_2$ were low in study group (201, 85, 70) compared to control group (236, 209, 162). The initial FiO_2 were 0.66 and 0.63 in dexamethasone and control groups, respectively and remained high till day 2 and came down in study group on days 3, 4 and 5 (0.41, 0.27, 0.27) compared to control group (0.53, 0.34, 0.42). The mean duration of ventilation was shorter in dexamethasone group (87 hours) vs control group (120 hours).* ***Conclusion:*** *Early use of postnatal dexamethasone reduces the disease severity and oxygen requirement in RDS and hence would be useful in the Indian context.*

Key words: *Alveolar arterial oxygen gradient, C-reactive protein, Fraction of inspired oxygen, Respiratory distress syndrome.*

MORTALITY and morbidity related to hyaline membrane disease (HMD) is high in our country. Surfactant is the well established modality of therapy in HMD in West. However, the cost is a prohibitive factor for routine use in our country. On the other hand many mothers may report too late in labor making antenatal steroid ineffective or may have a contraindication to postpone the delivery, *e.g.,* antepartum hemorrhage, eclampsia, *etc.* Glucocorticoids administered postnatally have been shown to improve short term lung function(l,2). We report a prospective, randomized, controlled trial of early postnatal dexamethasone treatment in preterm babies with HMD.

Subjects and Methods

This study was conducted in the Neonatal Intensive Care Unit at PGIMER, Chandigarh over 6 months period (from February 1996 to July 1996). Infants of less than 34 weeks and less than 2000 grams

who could be provided ventilation were included in the study. The inclusion criteria were: clinical (retraction, grunt, poor air entry) and radiographic (bilateral reticulo-granular or whiteout appearance) evidence of respiratory distress syndrome (RDS), requiring mechanical ventilation and $FiO_2 > 0.3$. Babies with evidence of infection, *e.g.,* history of chorioamnionitis in mother and any two positive rapid diagnostic tests (micro-ESR, CRP, absolute neutrophil count and gastric aspirate for polymorphs) in the baby were excluded. Presence of bleeding in the baby and congenital malformations were also taken as exclusion criteria.

After initial stabilization, the babies were randomly assigned to either dexamethasone or control group. The study group received injection dexamthasone starting within 6 hours of birth in a dose of 0.5 mg/kg/dose 12 hourly for 3 days. The control group did not receive any drug. No baby received surfactant. All babies received intermittent mandatory ventilation (IMV). Ventilatory and other managements of these babies were done as per the unit protocol by the treating physician.

Data collection included baseline patient characteristics (birth weight, gestational age, sex, Apgar score), obstetric data, use of antenatal steroid, severity of initial disease (age at mechanical ventilation, initial $AaDO_2$, initial FiO_2 (fraction of inspired oxygen) maximum $AaDO_2$ (alveolar arterial oxygen gradient) and age at maximum $AaDO_2$), $AaDO_2$ and oxygen requirement from day one to five. $AaDO_2$ and FiO_2 were calculated in the beginning of ventilation and subsequently at the end of 24 hours, 48 hours, 72 hours and at the end of 4th and 5th day. Mortality rate, incidence of sepsis, patent ductus arteriosus (PDA), pneumothoraces and side effects of steroid (hypertension, hyperglycemia, *Gl* bleeding) were also recorded.

The primary outcome measures were: *(i)* Duration of ventilation; *(ii)* Disease severity as measured by: *(a)* $AaDO_2 = \{FiO_2 \times (760\text{-}47)\text{-}PACO_2\text{-}PaO_2\}$ and *(b)* Oxygen requirement. Statistical analysis was done by using Student's "t" test for comparison of means of continuous variables.

Results

Forty three babies developed HMD during the study period who were less than 34 weeks and 2000 grams but only 28 could be provided ventilation. Eight babies were excluded subsequently due to nonavailability of blood gases due to technical fault and 1 baby who had complete congenital heart block was also excluded. So a total of 19 babies were studied of whom 10 babies received injection dexamethasone and 9 babies did not receive any steroid. *Table I* shows the baseline characteristics of two groups. No significant difference was found except that the control group had more males. The mean Apgar score at 5 minutes and per cent of babies receiving antenatal steroid were similar. The initial severity of disease is shown in *Table II.* There was no significant difference between two groups.

The initial $AaDO_2$ were similar and remained so till 48 hours but on days 3, 4 and 5, $AaDO_2$ were low in the study group; the values on the consecutive days being 201, 85, 70 and 236, 209, 162 in the dexa and control groups, respectively *(Fig. 1)*. However, the differences were statistically not significant ($p>0.05$). The initial FiO_2 were 0.66 and 0.63 in dexamethasone and control groups, respectively and remained high in both the groups till day 2 and FiO_2 requirement came down in study group on days 3, 4 and 5 (0.41, 0.27, 0.27) compared to control group (0.53, 0.34, 0.42) (Fig. 2)

TABLE I–*Baseline Characteristics*

Characteristic	Study Group (n=10)	Control Group (n=9)
Birth weight	1444±213	1453±340
Gestation (wks)	30 9±2 23	31±2 69
Small for gestational age (n)	1	2
Sex (M/F)	6/4	8/1
5 min Apgar score	7 8±1 3	7 2±1 7
Antenatal steroid (n)	4	4

TABLE II–*Disease Characteristics*

Characteristic	Study Group (n=10)	Control Group (n=9)
Age at starting ventilation (h)	3 6±1 98	5 6±4
Initial $AaDO_2$	314±150	332±127
Max $AaDO_2$	383±196	405±197
Max $AaDO_2$ (h)	20 9±15 8	29 8±25
Initial FiO_2	0 63±0 26	0 66±0 26

though the differences were statistically not significant ($p>0.05$). FiO_2 and AaDCX, at the points of study were the lowest values achieved on that day.

Mean duration of ventilation was shorter in dexamethasone group (87±42 hours) vs control group (120±46 hours). One baby in dexamethasone group needed reventilation at 32 hours of life who was initially extubated at 22 hours of life. Only 1 had culture positive sepsis in dexamethasone group and 2 in control group. Dexamethasone did not produce any significant side effect. Three babies in dexamethasone group and 1 baby in control group had PDA. None of the babies had bronchopulmonary dysplasia (BPD).

Four babies had pneumothorax in dexamethasone group and 3 in control group. Pneumothorax developed at a significantly lower pressure in dexamethasone group compared to the control group. There was no significant difference of pressure in the dexamethasone group who had pneumothorax compared to those who did not have pneumothorax *(Table III)*. In the control group, pneumothorax occurred only when babies received significantly higher pressure.

Overall survival was 60% in treated group and 55% in control group. Four babies died in dexamethasone group within 4 days due to pneumothorax. In the control group 2 babies died due to pneumothorax, 1 due to persistent hypoxia and one due to grade 4 intraventricular hemorrhage. Two babies in each group died subsequently after 7 days due to sepsis.

Discussion

Alveolar-arterial oxygen gradient ($AaDO_2$) is used as an indicator of disease severity(3) which quantifies the O_2 gradient between alveoli and blood and indicates the level of gas exchange through the lungs. We used $AaDO_2$ and FiO_2 requirement as clinical indicators of disease severity. Though mean airway pressure (MAP) can be used as a parameter for assessing the severity of disease, $AaDO_2$ and oxygenation index are considered better means of assessing the disease severity(3). In conventional ventilation, higher positive end expiratory pressure (PEEP) is used by some which results in higher mean airway pressure (MAP), but this may not be entirely indicative of disease severity.

Our study shows that dexamethasone administration to preterm babies with RDS decreased the disease severity starting from day 3 till day 5 as compared to untreated group. The treated group required

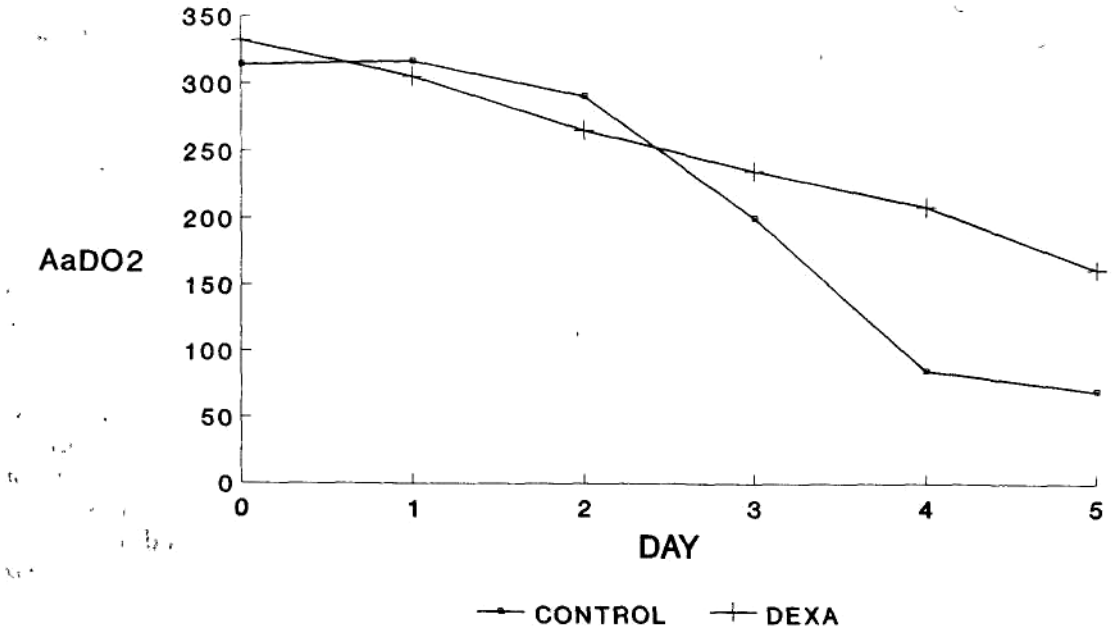

Fig. 1. Trends in $AaDO_2$

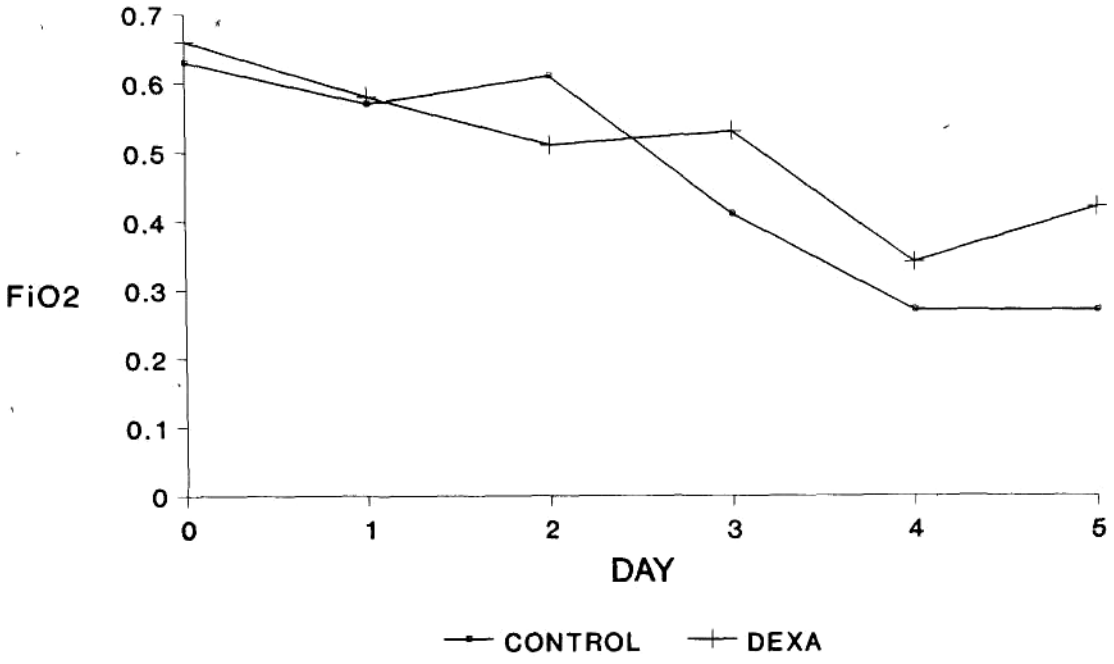

Fig. 2. Trends in FiO_2

TABLE III– *Peak Inspiratory Pressure (PIP) and Pneumothorax*

	Study Group	Control Group	p value
Pneumothorax			
Yes	24.7±4.3	41.6±3.5	< 0.01
No	21.0±3.5	18.6±3.0	> 0.05
p value	> 0.05	p < 0.001	

less oxygen and less hours of ventilation than the control group.

The mechanism proposed for the improvement of lung function after dexamethasone therapy are increase in surfactant synthesis and its secretion(4) and decrease in inflammatory changes in ventilated lungs(5). Previous reports of the use of early postnatal steroid treatment have provided mixed results. Baden *et al.(6)* in 1972 used 2 doses of hydrocortisone within 24 hours of life but it failed to show any significant effect on PaO_2, $PaCO_2$, H^+, per cent ambient oxygen needed, $AaDO_2$, need for assisted ventilation or survival. Yeh *et al.{\)* in 1990 used dexamethasone for 12 days and showed improved acute respiratory status. The treated group had significantly higher pulmonary compliance, tidal volume and minute ventilation and required less mean airway pressure for ventilation than babies in the control group.

The higher incidence of pneumothorax in dexamethasone group was possibly due to rapid improvement in compliance and delay in decreasing the pressure. Lack of synchronization could have aggravated the occurrence of pneumothorax in the recovery phase.

Sanders *et al.(2)* used 2 doses of dexamethasone in the first 24-36 hours of life and showed that treated infants had improved survival and shorter duration of hospital stay. In 1996, a multicenter trial(7) used a three day postnatal dexamethasone trial in RDS and showed that there was reduction in requirement of ventilation at 3 days in the treated group. Though none of our babies had BPD, the present study was focussed on the initial one week differences due to dexamethasone therapy.

We conclude that use of steroid had some beneficial effect during the first 5 days of life and in Indian set up when surfactant is still not available to us for routine use, this modality of therapy should be offered. However, our number of patients are too small and hence a multicenter trial with a larger number of patients is required before recommending it for routine use.

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