

# THE EFFECTS OF ANTENATAL CORTICOSTEROIDS AND SURFACTANT REPLACEMENT ON NEONATAL RESPIRATORY DISTRESS SYNDROME

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## ABSTRACT

The goal of this study was to determine the effects of antenatal corticosteroids and surfactant replacement on the severity and frequency of Respiratory Distress Syndrome (RDS) in a cohort of premature infants born in Sarajevo, Bosnia and Herzegovina, from 2005 to 2007. The cohort consisted of 172 premature neonates with estimated gestational age between 26 and 34 weeks. Babies with IUGR, babies of diabetic mothers and babies with major congenital defects were excluded. Out of 172 neonates, 80 were treated antenatally with corticosteroids (single course of dexamethasone) and 92/172 were not. There was no statistical difference ( $p>0,5$ ) in average gestational age (31,2 vs. 31,0 GW) and male/female ratio between investigated groups; there were significantly more male patients ( $p<0,05$ ) in both groups. Frequency of RDS was significantly lower in the corticosteroid group (24/80) in relation to the control group (54/92) ( $p<0,001$ ). Severe RDS was significantly ( $p<0,01$ ) more frequent in the control group 34/53 (62,96%) than in the corticosteroid group 6/24 (25,0%). Bovine surfactant (Survanta) was given as a rescue therapy to 78 babies with clinical and radiological signs of RDS who required  $FiO_2>0,40$  and mechanical ventilation. Early surfactant administration within six hours after birth appeared to be effective at reducing mortality then later surfactant administration ( $p<0,005$ ). In the group of babies requiring  $FiO_2\geq 0,6$  at the time of surfactant replacement, the mortality rate was significantly higher ( $p<0,05$ ). In conclusion, we confirm the efficacy of antenatal corticosteroid treatment and early surfactant treatment in a cohort of premature infants born in Sarajevo.

KEY WORDS: RDS, antenatal corticosteroids, surfactant

## INTRODUCTION

The efficacy of antenatal corticosteroid treatments and early postnatal surfactant replacement has been well established. A National Institutes of Health Consensus Development Conference reported a systematic review of all available clinical trial data regarding administration of antenatal corticosteroids to women with premature onset of labor in 1994 (1, 2, 3). As a result, antenatal corticosteroid treatment was recommended for any woman likely to deliver between 24 and 34 weeks gestation. At that time, there was little evidence that such treatment was of benefit to babies of less than 28 weeks gestation. However, subsequent observational data (4) indicate that antenatal steroids are also effective at reducing the incidence of respiratory distress in babies less than 28 weeks. Indeed, it appears that giving antenatal steroids to women at less than 35 weeks gestation shortly before delivery halves the risk of respiratory distress developing after birth, regardless of the gestational age at which delivery occurs (5,6). While betamethasone was the agent used in the first trial of antenatal steroid treatment (7), dexamethasone has been more widely used in many countries. Both drugs (betamethasone and dexamethasone) seem to be of comparable efficacy in most respects, but there are now observational studies suggesting that while antenatal treatment with betamethasone has no effect on, or may actually reduce the risk of subsequent cystic periventricular leukomalacia in the baby, repeated treatment with dexamethasone may increase this risk (8,9,10). Surfactant treatment after birth may augment, but cannot replicate, all the benefits associated with antenatal steroid administration. The efficacy of neonatal surfactant therapy is enhanced by antenatal exposure to corticosteroids (3,11). Although progression of the lung symptoms normally seen in Respiratory Distress Syndrome (RDS) may be modified or halted by ventilatory support, surfactant treatment is still required in about 50% of all premature babies born before 30 weeks gestation. In these cases, timing of surfactant administration is of vital importance to improved outcome. The prophylactic administration of surfactant to preterm neonates at risk has significant advantages over rescue therapy (12-14). Early rescue surfactant replacement, before a complete clinical picture of RDS develops, is preferable to late treatment, although optimal timing of surfactant treatment is not yet clear (14). The aim of this study was to determine the effects of antenatal corticosteroids on the severity and the frequency of RDS and the effects of

timing of surfactant replacement and O<sub>2</sub> requirement on mortality in a cohort of premature infants.

## MATERIAL AND METHODS

One hundred seventy two (172) premature neonates (gestational age 26-34 weeks, aged between 1-72 hours) admitted to the Neonatology Department of the Paediatric Clinic, Clinical University Centre Sarajevo during the two year period from 2005 to 2007 were enrolled in this study. Babies with intra-uterine growth restriction (IUGR), babies of diabetic mothers and babies with major congenital defects were excluded. Comparisons were made between infants treated antenatally with single course of antenatal corticosteroids (four doses of dexamethasone 6 mg, given intramuscularly 12 hours apart) and infants with no antenatal corticosteroid treatment. Bovine surfactant (Survanta, 4 ml/kg) was given to infants with radiological and clinical signs of RDS (tachypnea and cyanosis on room air) who required mechanical ventilation with FiO<sub>2</sub> more than 0.4 following radiological confirmation of correct endotracheal tube placement. Each dose was administered over 30 sec. into each lung quadrant. If oxygen saturation fell below 85% installation was discontinued, and then resumed after the oxygen saturation improved. A second dose of surfactant was given 12 hours later at the discretion of the treating physician. Oxygen requirement was recorded. Severe RDS was defined as O<sub>2</sub> requirement more than 60% (FiO<sub>2</sub>≥0.6). Clinical outcomes were assessed at 28 days. Standard statistical parameters were used: determination of means and standard deviations for normally distributed variables, median and range for variables without a normal distribution, t-test for continuous variables, and  $\chi^2$ -test for categorical and dichotomous variables.

## RESULTS

A summary of epidemiologic data for the infants enrolled in the study is presented in Table 1 and Table 2. While there was no statistical significance in average gestational age between the two groups, the infants who developed RDS had approximately one week lower gestational age in both groups. We found no statistical difference in male/female ratio between the two groups, though there were significantly more male than female patients in both groups ( $p < 0.05$ ). Consistent with other published studies, we found a significant decrease in RDS and severe RDS in the infants treated with antenatal corticosteroids (Table 3).

	N°	Average GW	Standard deviation
	n	x	SD
CS group	80	31,21	1,96
RDS	22	29,86	1,89
Control group	92	31,02	2,03
RDS	53	30,06	1,73

TABLE 1. Average gestational age in weeks in Corticosteroid (CS) and Control group

	Male		Female		Total		p
	N°	%	N°	%	N°	%	
CS group	48	60,0	32	40,0	80	100,0	>0,05
Control group	51	55,4	41	44,6	92	100,0	
Total	99	57,6	73	42,4	172	100,0	
p	<0,05						

TABLE 2. Male/female ratio in Corticosteroid (CS) and Control group

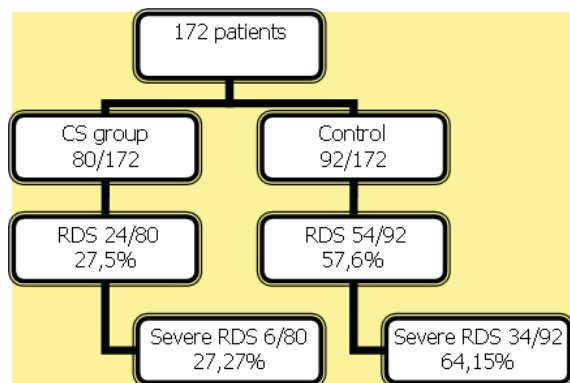


TABLE 3. Frequency and severity of RDS resulting from antenatal corticosteroid (CS) treatment

Mortality data are presented in Table 4 and Table 5. We note significant associations between both late surfactant therapy and higher oxygen requirement and increased mortality.

Hours	Survived	Died	Total (%)	$\chi^2$	p
	N° (%)	N° (%)			
0-6	34 (79)	9 (21)	43 (100)	7,9	0,005
>6	17 (49)	18 (51)	35 (100)		
Total	51	27	78 (100)		

TABLE 4. Outcome of the illness related to the timing of the first surfactant dose

FiO <sub>2</sub>	Survived	Died	Total (%)	$\chi^2$	p
	N° (%)	N° (%)			
<0,6	19 (86)	3 (14)	22 (100)	6,0	0,015
>0,6	32 (57)	24 (43)	56 (100)		
Total	51	27	78 (100)		

TABLE 5. Outcome of the illness in dependency of O<sub>2</sub> requirements

## DISCUSSION

We present a summary of the incidence of RDS and the mortality rates of a cohort of premature infants born in Sarajevo, Bosnia and Herzegovina from 2005 to 2007. Our results are similar to other published data and add to the studies available for inclusion in meta-analyses. We found that infants treated with corticosteroids antenatally were less likely to develop RDS. The target group for the antenatal corticosteroid treatment in our study was the group of preterm babies born before 35 weeks gestation. A Cochrane meta-analysis of 18 randomized trials (15) concluded that antenatal corticosteroid therapy reduces the incidence of RDS, neonatal death and intraventricular haemorrhage. There was evidence of benefit in all major subgroups of preterm babies, regardless of race or gender. Infants born after 34 weeks did not show a statistically significant decrease in RDS although the trend was positive (16). At less than 28 weeks, the numbers of infants studied were small (4, 15, 17, 18). An analysis of 'the number needed to treat' suggests that after 34 weeks, 94 women will need to be treated to prevent one case of RDS, while before 31 weeks one case of RDS is prevented for every five women treated (4). We investigated two predictors of mortality: time of surfactant dose and maximum oxygen requirement. A regression analysis to correct for potential confounders was not possible, however we did find a strong association between later administration of surfactant and increased mortality and between higher oxygen requirement and increased mortality. It is important to give surfactant as soon as the diagnosis of RDS is established, before the complete clinical picture develops. Early treatment when RDS is moderately severe prevents or reverses the natural progression of the disease in at least 50% of the cases and lowers the risk of serious complications (13,14,19). Whether increased oxygen requirement is simply a marker of more severe disease, a marker of delay in surfactant treatment, or a contributing factor to mortality could not be determined with this study design. The prophylactic administration of surfactant in the delivery room is preferable, but should be reserved for the smallest infants with the highest risk of developing RDS and should be given by a person experienced in neonatal resuscitation and surfactant administration.

## CONCLUSION

1. Antenatal corticosteroid administration significantly reduces the incidence and severity of RDS in premature neonates. Every effort should be made to initiate antenatal corticosteroid therapy in women between 24 and 34 weeks of gestation as soon as preterm delivery appears likely,
2. Our study confirms the benefits of early surfactant use in the treatment of RDS in premature infants. Early surfactant use reduces mortality in preterm babies 25-34 weeks gestation with RDS.
3. In neonates who require  $\text{FiO}_2 > 0,4$ , surfactant should be given as soon as possible, before the complete clinical picture of RDS is developed.

### List of Abbreviations

IUGR	-	Intrauterine Growth Restriction
RDS	-	Respiratory Distress Syndrome
MV	-	Mechanical Ventilation
GW	-	Gestational Weeks
CS	-	Corticosteroid Group

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