

# DO LARGE PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME BENEFIT FROM EARLY SURFACTANT?

N. Khosravi and P. Mohagheghi\*

Department of Neonatology, Rassoul Akram Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

**Abstract-** Large preterm infants are generally not considered good candidates for surfactant treatment until they have been intubated for progressing respiratory distress. This study has been done to detect the effect of electively providing early single-dose surfactant to large preterm babies with mild to moderate respiratory distress syndrome (RDS). A randomized clinical trial was performed on 45 infants with birth weight > 1250 grams, gestational age < 36 weeks, postnatal age 0-12 hours,  $FiO_2 > 40\%$  and no immediate need for intubation. They were randomly divided into two interventional (n = 22) and control (n = 23) groups. Interventional group infants were intubated and received surfactant in the first 12 hours of life with signs of mild to moderate RDS and were extubated as soon as possible. The control group infants were only intubated and received surfactant when clinically or radiographically indicated. The primary outcome was duration of assisted ventilation. Interventional group infants had a median duration of assisted ventilation of 4.45 hours compared to 1.02 hours in the control group in the first 24 hours of life, since only 8 of 23 infants in the control group (34%) needed intubation and mechanical ventilation. There were no differences in the two groups for need of subsequent retreatment with surfactant and requirement for supplemental oxygen or mechanical ventilation, hospital stay and adverse outcomes. Results of this study indicate that elective intubation for administration of early single-dose surfactant to large preterm infants is not necessary.

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**Key words:** Preterm infants, surfactant, respiratory distress syndrome

## INTRODUCTION

All regimens of surfactant administration for prophylaxis or treatment of neonatal respiratory distress syndrome had shown a major impact in reducing the morbidity and mortality rates from the disease (1). The safety and efficacy of exogenous surfactant have been clearly established (2). Meta analyses demonstrated that, compared to selective

administration, prophylactic administration of natural surfactant to infants less than 30 weeks of gestation resulted in a greater reduction in neonatal mortality and a reduction in the combined outcome of bronchopulmonary dysplasia or death (3).

Since surfactant is administered through an endotracheal tube and intubation has its own complications, large preterm infants are generally not considered good candidates for surfactant treatment until they have been intubated for progressing respiratory distress (2). At what point do the potential benefits of decreased mortality, pneumothorax, and lung injury from prophylactic surfactant exceed the potential risks of endotracheal intubation and the costs of surfactant dosing to infants who would not have required it is not known.

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### Corresponding Author:

Parisa Mohagheghi, MD, NICU Ward, Hazrat Rassoul Akram Hospital, subspecialty in Neonatology, Assistant Professor, Iran University of Medical Sciences, Tehran, Iran  
Tel: +98 21 66525328, 09121324615  
Fax: +98 21 66525328  
E mail: pmohagh@yahoo.com

## Early surfactant for large infants

Although nasal continuous positive pressure (CPAP) and supplemental oxygen often suffice for respiratory distress syndrome (RDS) treatment in larger infants, some may require mechanical ventilation.

Few studies have been done about the reduced need of intubation and ventilator support after single dose of surfactant administration in large infants. Verder *et al.* randomly assigned 73 non-ventilated large preterm infants to surfactant prophylaxis followed by nasal CPAP or CPAP alone and reported a reduction in proportion of infants who were subsequently intubated (43% vs 85%). There was no difference in median length of ventilation or oxygen therapy (1). Based on the only differences reported in that study, the early treatment strategy would require intubating 2.4 infants for early surfactant to avoid intubating one infant later on. Systematic early intubation would expose more infants to additional risks of airway complications and there are some concerns of pulmonary air leaks and intracranial hemorrhage (4). So we need more information to justify the routine administration of surfactant to large preterm infants with mild to moderate RDS.

This clinical trial has been performed in two NICUs in Tehran to determine the effect of early surfactant administration in large preterm infants.

## MATERIALS AND METHODS

This was a randomized clinical trial designed to evaluate the efficacy and safety of elective brief intubation for early single-dose surfactant administration in large preterm infants with mild to moderate RDS. The study was approved by Ethics Committee of Iran University of Medical Sciences and written informed consent was obtained from parents of all subjects.

Eligibility criteria included birth weight > 1250 grams, gestational age < 36 weeks, postnatal age 0-12 hours,  $FiO_2 > 40\%$ , clinical presentation or chest radiograph consistent with RDS, no requirement for mechanical ventilation (by the written protocols of the ward), no known congenital anomalies of the cardiac or respiratory system.

Forty-five infants were randomly divided into two groups; interventional (n = 22) and control (n =

23). Interventional group infants were intubated and received surfactant (4 mL/kg Survanta) in the first 12 hours of birth and they were extubated as soon as possible unless their  $FiO_2$  remained greater than before intubation. In these cases mechanical ventilation was provided according to ward protocols. Control group infants were given surfactant when they met the usual criteria of the ward for intubation.

Median duration of assisted ventilation, oxygen therapy, need for retreatment with surfactant and hospital stay were compared in the two groups.

## RESULTS

Forty-five infants were enrolled from September 2004 to August 2005. Their demographic data are shown in Table 1. There were no significant differences between two groups.

Duration of mechanical ventilation was 4.45 hours (range 2-8 h) in interventional group as compared to 1.02 hours in the control group ( $P = 0.005$ ) in the first 24 hours. The other parameters between the two groups were not statistically different (Table 2). Of 22 infants in the interventional group, 8 (36.3%) required subsequent mechanical ventilation for worsening respiratory distress and in the control group 8 infants needed mechanical ventilation as well (34.7%), ( $P = 0.93$ ). Two infants in each group needed additional dose of surfactant in the second day of life due to their high ventilator needs. There was no significant difference in adverse outcomes (air leak, pulmonary hemorrhage, and PDA). There were 2 deaths in each group due to severe sepsis and DIC.

**Table 1.** Baseline characteristics\*

Characteristics	Control (n=23)	Intervention (n=22)
Birth weight (g)†	1642.1 ± 226	1695.9 ± 222
Birth weight (g)		
1250-1500	6	4
1500-1750	10	8
>1750	7	10
Gestational age (wk) †	31.8 ± 2	31.3 ± 1.9
Sex (male/female)	14:9	12:10
Antenatal steroid	7	8
Route of delivery (V/CS)	9:14	7:15

Abbreviations: V, vaginal; CS, Cesarean section.

\*Data are given as number unless specified otherwise.

†Mean ± SD.

Table 2. Outcome data\*

Outcome	Control (n = 23)	Intervention (n = 22)	P value
Duration of assisted ventilation (h) in the first 24 hours†	1.02 ± 0.8 (0-3)	4.45 ± 1.7 (2-8)	0.005
Duration of oxygen therapy (d)	5.17 ± 2.28 (4.3-7.5)	6.1 ± 3(3.8-8)	0.38
Length of hospital stay (d)	20 (13-32)	19 (11-33)	0.95
Air leak	4/23	3/22	1.33(0.26-6.78)
Pulmonary hemorrhage	1/23	1/22	0.95 (0.56-16.2)
Treated PDA	3/23	2/22	1.5 (0.2-9.9)
IVH grade II-IV	2/23	3/22	0.6 (0.9-4)
Death	2/23	2/22	0.95 (0.17-5.3)
Mechanical ventilation	8/23	8/22	0.93 (0.27-3.1)

Abbreviations: PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage.

\*Data are given as number unless specified otherwise.

† Median ± SD (25<sup>th</sup>, 75<sup>th</sup> percentiles).

## DISCUSSION

The first successful surfactant therapy in humans was reported by Fujiwara and colleagues in 1980. Natural and synthetic surfactant has been successfully administered into the lungs of premature infants for treatment of RDS as prophylactic or rescue therapies (5, 6). All regimens of surfactant therapy appear to decrease the incidence of air leaks, and improve oxygenation of ventilated infants. More strikingly mortality from RDS and even overall mortality of ventilated preterm infants is significantly reduced.

Early rescue surfactant administration (within 2 hours of birth) given to infants with RDS requiring mechanical ventilation leads to decreased risk of pneumothorax and pulmonary interstitial emphysema and chronic lung disease (7). Furthermore this strategy seems to reduce the need for subsequent retreatment and mechanical ventilation.

In larger preterm babies, the course of disease may not be evident from the first hour of life and usually surfactant is administered to them when RDS is clinically or radiographically proven (8). Does earlier surfactant administration to these large preterm infants with mild to moderate RDS show to be beneficial? Victorian *et al.* performed a pilot study in Kuwait to determine if a single dose of surfactant would be useful in a situation in which mechanical ventilation was not universally available (2). There was a beneficial acute response in 12 of 14 treated patients, but no longer-term outcomes were reported and there was no control group.

As already noted, Verder *et al.* randomly assigned 73 neonates with moderate to severe RDS to a dose of surfactant followed by NCPAP (1). The need for subsequent mechanical ventilation was reduced, but there was no difference in total duration of mechanical ventilation or use of oxygen.

In our study there was no difference between two groups (intervention or control) for need of subsequent retreatment with surfactant and requirement for supplemental oxygen and mechanical ventilation, hospital stay and adverse outcomes.

In summary, the results of our study do not support the routine use of intubation solely to administer surfactant in large preterm infants with mild to moderate RDS.

### Conflict of interests

The authors declare that they have no competing interests.

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## Early surfactant for large infants

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