Role of prophylactic surfactant in preterm infants

Gp Capt Daljit Singh*, Brig KS Rana*, Surg Capt Sheila Mathai#

ABSTRACT

BACKGROUND

Respiratory distress syndrome (RDS) in preterm neonates is caused by a deficiency or dysfunction of pulmonary surfactant. The physiological function of surfactant includes the ability to lower surface tension, as well as the ability to rapidly adsorb and spread. A wide variety of surfactant products have been formulated and studied in clinical trials. The present study was designed to find out whether prophylactic administration of surfactant leads to a significant decrease in the risk of neonatal mortality and neonatal morbidity.

METHODS

This was an experimental study in which a total of 125 preterm newborns less than 34 weeks gestation were studied. One hundred preterm newborns (controls) less than 34 weeks gestation were managed in the conventional manner as per the existing protocols in the neonatal intensive care unit. Twenty-five consecutively delivered preterm newborns less than 34 weeks gestation were administered surfactant. Data regarding clinical outcomes including mortality and morbidity profile was collected and analysed.

RESULTS

The mean duration of ventilation in the ventilated babies in the control group and the surfactant group was 129.8 ± 43 hours and 85.7 ± 46 hours, respectively; the difference being statistically significant. In the surfactant group, four babies (16%) died and in the control group, 27 babies (27%) died. The difference was not statistically significant. The number of babies developing retinopathy of prematurity and needing laser treatment for retinopathy of prematurity was greater in the surfactant group.

CONCLUSION

Prophylactic administration of surfactant in preterm newborns of gestational age < 34 weeks is associated with a significant decrease in mean duration of ventilation and an increase in the incidence of retinopathy of prematurity.

MJAFI 2011;67:138–141

Key Words: neonates; preterm; surfactant

INTRODUCTION

Respiratory distress syndrome (RDS) in preterm neonates is caused by a deficiency or dysfunction of pulmonary surfactant. Surfactant lines the alveolar surface and prevents atelectasis at end expiration. Pulmonary surfactant is predominantly dipalmitoylphosphatidylcholine with lesser amounts of other phospholipids including phosphatidylglycerol, phosphatidylethanolamine, and phosphatidylinositol. Pulmonary surfactant also contains neutral lipids and distinct surfactant proteins. The physiologic function of surfactant includes the ability to lower surface tension, as well as the ability to rapidly adsorb and spread, associated with the respiratory cycle. The first attempts to utilise synthetic surfactants occurred in the 1960s. The first successful animal model of surfactant replacement therapy was conducted by Enhörning and coworkers in 1972. Enhörning administered a crude natural surfactant extract obtained from lavage of the lungs of mature rabbits¹ directly into the trachea of immature rabbits. Improvement in lung compliance and alveolar expansion was noted. Success in animal models led to widespread clinical trials of surfactant therapy in the human newborns. A systematic review of the seven randomised controlled trials that compare the prophylactic administration of synthetic surfactant to control treatment in preterm infants at risk of developing RDS suggests that prophylactic administration of synthetic surfactant leads to a significant decrease in the risk of pneumothorax, pulmonary interstitial emphysema, and neonatal mortality.^{2–4} So far, no trials of prophylactic surfactant in preterm neonates were carried out in our country because of the prohibitive cost of the imported drug. During the last decade, preparations of exogenous surfactant have been marketed in our country. This has made it possible to evaluate the prophylactic role of surfactant in preventing respiratory distress syndrome and its associated morbidities in preterm neonates. The present study was designed to find out whether prophylactic administration of surfactant leads to a significant decrease in the risk of neonatal mortality and neonatal morbidity.

MATERIALS AND METHODS

This was an experimental study in which a total of 125 preterm newborns less than 34 weeks gestation were studied. The study was carried out in two phases from December 2003 to November 2006. The inclusion criteria were designed to include newborn babies who were less than 34 weeks gestational age at the time of birth. The gestational age assessment was

*Senior Advisor (Paediatrics), CH (SC) Pune – 40, *Consultant (Paediatrics), CH (SC) Pune – 40, #Senior Advisor (Paediatrics), INHS Asvini Mumbai – 05.

Correspondence: Gp Capt Daljit Singh, Senior Advisor (Paediatrics), Command Hospital (SC) Pune – 40.
E-mail: maapavitra@gmail.com

Received: 16.06.2008; Accepted: 12.02.2011

based on antenatal records and postnatal assessment based on expanded new Ballard scoring system. The babies with congenital malformations and the babies born to mothers with chorioamnionitis were excluded from the study. The first phase of the study related to the time period when exogenous surfactant was not available. One hundred preterm newborns (controls) less than 34 weeks gestation that satisfied the inclusion criteria and were delivered during this time period were managed in the conventional manner as per the existing protocols in the neonatal intensive care unit. The second phase of the study was carried out after the exogenous surfactant became available. A total of 25 consecutively delivered preterm newborns less than 34 weeks gestation who satisfied the inclusion criteria were administered exogenous surfactant by endotracheal route (4 mL/Kg of the surfactant preparation equivalent to 100 mg/Kg of phospholipids) after resuscitation and stabilisation of the neonates shortly after birth. Further management of these babies was guided by their cardiorespiratory status and was as per the existing protocols in the neonatal intensive care unit. In both the groups, follow-up included cranial ultrasound on days three, seven, and at the time of discharge. The babies were evaluated for retinopathy of prematurity at 28 days postnatal age and later, as indicated by the ophthalmologist. Data regarding clinical outcomes including mortality, the incidence of pneumothorax, pulmonary interstitial emphysema, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity were collected and analysed. Continuous normally distributed variables (such as birth weight and gestational age) were analysed using unpaired Student 't' test. Various proportions of neonatal morbidity were analysed using Chi square test or Fisher's exact test when an expected cell value was <5.

RESULTS

Table 1 gives the distribution of baseline parameters in the two groups. Mean birth weight was 1418 ± 311 g (range 625–2110 g) in the control group and 1030 ± 357 g (range 680–2300 g) in the surfactant group. There was a statistically significant difference in the mean birth weights between the two groups ($P < 0.05$). The mean gestational age was 31.42 ± 1.93 weeks

(range 24–34 weeks) in the control group and 28.64 ± 1.86 weeks (range 24–33 weeks) in the surfactant group. There was a statistically significant difference in the mean gestational age between the two groups ($P < 0.05$). Sixty neonates (60%) in the control group and twenty neonates (80%) in the surfactant group were small for gestational age (SGA). Forty neonates (40%) in the control group and five neonates (20%) in the surfactant group were appropriate for gestational age (AGA). Although there was a trend to a greater number of SGA babies in the surfactant group, the difference was not statistically significant ($P = 0.06$). In the control group, forty-two neonates (42%) were females and fifty-eight (58%) were males. In the surfactant group, 10 neonates (40%) were females and 15 (60%) were males. The sex distribution was similar in the two groups. Table 2 shows a comparison of neonatal morbidity between the two groups. There was a statistically significant difference in the number of babies ventilated between the two groups, with a higher percentage being ventilated in the surfactant group. The mean duration of ventilation in the ventilated babies in the control group was 129.8 ± 43 hours. The mean duration of ventilation in the ventilated babies in the surfactant group was 85.7 ± 46 hours. There was a statistically significant difference in the mean duration of ventilation between the two groups. There was no significant difference in the number of babies developing pneumothorax (air leaks), patent ductus arteriosus, pulmonary haemorrhage, chronic lung disease, necrotising enterocolitis, and neonatal sepsis between the two groups. In the control group, four neonates (4%) and in the surfactant group five neonates (20%) were

Table 2 Neonatal morbidity.

Variable	Control group <i>n</i> = 100	Surfactant group <i>n</i> = 25	<i>P</i> value
Ventilated	27 (27%)	23 (92%)	0.001
Duration of ventilation (h) Mean (SD)	129.8 (43)	85.7 (46)	<0.05
Air leaks	4 (4%)	1 (4%)	0.74
Patent ductus arteriosus	4 (4%)	2 (8%)	0.90
Pulmonary haemorrhage	4 (4%)	2 (8%)	0.90
Necrotizing enterocolitis	1 (1%)	1 (4%)	0.32
Intraventricular haemorrhage	3 (3%)	2 (8%)	0.94
Neonatal sepsis	15 (15%)	4 (16%)	0.68
Chronic lung disease	1 (1%)	1 (4%)	0.32
Retinopathy of prematurity (any stage)	4 (4%)	5 (20%)	0.01
Retinopathy of prematurity (needing laser therapy)	2 (2%)	4 (16%)	0.01

Table 1 Baseline characteristics: neonatal.

Variable	Control group <i>n</i> = 100	Surfactant group <i>n</i> = 25	<i>P</i> value
Birth weight (g) Mean (SD)	1418 (311)	1030 (357)	<0.05
Gestation (wk) Mean (SD)	31.42 (1.9)	28.64 (1.86)	<0.05
SGA	60 (60%)	20 (80%)	0.06
Sex			
Female	42 (42%)	10 (40%)	>0.10

Table 3 Neonatal outcome.

Variable	Surfactant group n=25	Control group n=100	Relative risk (95% confidence intervals)
Deaths	4 (16%)	27 (27%)	0.59 (0.18–1.52)

found to develop retinopathy of prematurity (any stage). In the control group, two babies (2%) and in the surfactant group four babies (16%) needed laser treatment for retinopathy of prematurity. There was a statistically significant difference in the number of babies developing retinopathy of prematurity (any stage) and in the number of babies needing laser treatment for retinopathy of prematurity between the two groups. In surfactant group, four babies (16%) died and in control group, 27 babies (27%) died. The difference was not statistically significant, although a lesser percentage of babies died in the surfactant group (relative risk 0.59, 95% confidence interval (CI) (0.18–1.52)) (Table 3).

DISCUSSION

Respiratory distress syndrome is the most common cause of respiratory difficulty in preterm neonates less than 30 weeks gestation and less than 1200 g in weight. Neonatal RDS affects approximately 1% of all live births. Avery et al⁵ first demonstrated the paucity of alveolar surfactant in the lungs of infants dying of RDS. Surfactant's role is to decrease surface tension in the alveoli preventing collapse at end expiration and loss of lung volume. A series of carefully controlled multicentre clinical trials has made surfactant substitution an exceptionally well-studied form of treatment.^{6,7} Trials of prophylactic administration of surfactant attempted to identify infants at high risk of developing RDS. Randomised controlled trials that compare the prophylactic administration of surfactant to control treatment have been carried out using natural surfactant extracts as well as synthetic surfactant preparations.^{8–24} Although both prophylactic surfactant administration and surfactant treatment of infants with established respiratory distress syndrome are successful treatment strategies, theoretical advantages have been proposed for each strategy. Prophylactic administration offers the theoretical advantage of replacing surfactant before the onset of respiratory insufficiency, decreasing the need for ventilator support and avoiding barotrauma that may result from even short periods of assisted ventilation.²⁵ Surfactant may distribute more homogeneously when given immediately at birth into lungs still filled with fluid, leading to improvement in response and decreasing the risk of lung injury.²⁶

There are few Indian studies on the use of surfactant in newborns.^{27–29} These studies included babies given prophylactic surfactant as well as those given rescue surfactant. In view of the paucity of data in our country on the use of surfactant, we decided to look at the effect of prophylactic surfactant in the preterm babies at the risk of developing RDS. There was

a statistically significant difference in the mean birth weights and mean gestational age between the two groups, both being lesser in the surfactant group. This was related to the fact that in post-surfactant era, smaller and more preterm babies started receiving neonatal intensive care. This was also reflected in a greater percentage of babies receiving ventilation in the surfactant group. Despite the aforementioned, the mean duration of ventilation in the babies in the control group was significantly more than the mean duration of ventilation in the babies in the surfactant group. This clearly shows that among the babies who needed ventilation for RDS; the babies who had been given surfactant needed to be ventilated for a shorter duration. Thus, administering surfactant would reduce the problems related to prolonged ventilation in the ventilated babies.

Among various neonatal morbidities, most of the studies have reported a decrease in the incidence of air leaks with use of prophylactic surfactant.^{8–24} However, in our study, no such decrease in incidence of air leaks was observed. There was a statistically significant difference in the number of babies developing retinopathy of prematurity (any stage) and the number of babies needing laser treatment for retinopathy of prematurity between the two groups ($P=0.01$). The higher percentage of babies developing retinopathy of prematurity (any stage) or needing laser treatment for retinopathy of prematurity in the surfactant group could be related to the greater percentage of babies getting ventilated in the surfactant group. In our study there was a difference in survival between two groups, with a higher percentage of babies surviving in the surfactant group. Similar findings have also been reported by other studies using prophylactic surfactant. A systematic review of the eight randomised controlled trials which compared the prophylactic administration of natural surfactant extract to control treatment has shown that prophylactic administration of natural surfactant extract led to a significant reduction in the risk of neonatal mortality (typical relative risk (RR) 0.60, 95% CI 0.44, 0.83; typical risk difference (RD) -0.07 , 95% CI -0.12 , -0.03).^{8–15} Narang et al²⁹ in an Indian study found that the early neonatal mortality was significantly lower in surfactant (25%) than in the no surfactant group (38.7%). As the number of babies in the surfactant group was small, we could not do a subgroup analysis to decide which babies would benefit the most from this mode of intervention. A larger multicentric prospective randomised controlled trial comparing prophylactic surfactant administration and surfactant treatment of babies with established RDS will help in answering this question. New research on the differences between the allelic variants of the surfactant protein genes is leading to the understanding of individual susceptibility to the development of pulmonary diseases in the neonates.³⁰ Randomised controlled trials to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in preterm infants^{31,32} also need to be done in our country to evaluate and establish the most effective and safest interventions for preterm neonates at risk of developing RDS and associated morbidities.

CONFLICTS OF INTEREST

This study has been funded by research grants from the O/o DGAFMS, New Delhi.

REFERENCES

- Enhoring G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Paediatrics* 1972;50:58–66.
- Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants (Cochrane Review). In: The Cochrane Library, Oxford, 1999.
- Phibbs RH, Ballard RA, Clements JA, et al. Initial clinical trial of Exosurf, a protein-free synthetic surfactant, for the prophylaxis and early treatment of hyaline membrane disease. *Paediatrics* 1991;88:1–9.
- Corbet A, Bucciarelli R, Goldman S, et al. US Exosurf Paediatric Study Group I. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Paediatric* 1991;118:277–284.
- Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959;97:517–523.
- Halliday HL. Recent clinical trials of surfactant treatment for neonates. *Biol Neonate* 2006;89:323–329.
- Obladen M. History of Surfactant up to 1980. *Biology of the Neonate* 2005;87:308–316.
- Soll RF. Prophylactic administration of natural surfactant extract (Cochrane Review). In: The Cochrane Library, Oxford, 1997.
- Dunn M, Shennan A, Possmayer F. Bovine surfactant prophylaxis in neonates less than 30 weeks' gestation: a randomised controlled trial of prophylaxis versus treatment. *Paediatrics* 1991;87:377–386.
- Enhoring G, Shennan A, Possmayer F, et al. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomised clinical trial. *Paediatrics* 1985;76:145–153.
- Hoekstra RE, Jackson JC, Myers TF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. *Paediatrics* 1991;88:10–18.
- Kendig JW, Notter RH, Cox C, et al. Surfactant replacement therapy at birth: final analysis of a clinical trial and comparisons with similar trials. *Paediatrics* 1988;82:756–762.
- Kwong MS, Egan EA, Notter RH, Shapiro DL. Double-blind clinical trial of calf lung surfactant extract for the prevention of hyaline membrane disease in extremely premature infants. *Paediatrics* 1985;76:585–592.
- Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *N Engl J Med* 1986;315:785–790.
- Shennan A, Dunn M. Surfactant replacement trials—the need to maintain concurrent placebo controls. *Paediatr Res* 1989;25:231A.
- Soll RF, Hoekstra RE, Fangman JJ, et al. Collaborative Surfactant Prevention Study Group. Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. *Paediatrics* 1990;85:1092–1102.
- Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in pre term infants (Cochrane Review). In: The Cochrane Library, Oxford, 1999.
- Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birthweight infants treated with a single dose of a synthetic surfactant. *J Paediatr* 1990;117:947–953.
- Corbet A, Bucciarelli R, Goldman S, et al. US Exosurf Paediatric Study Group I. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Paediatr* 1991;118:277–284.
- Halliday HL, Reid MM, Mehan C, et al. Controlled trial of artificial surfactant to prevent respiratory distress syndrome. *Lancet* 1984;1:476–478.
- Phibbs RH, Ballard RA, Clements JA, et al. Initial clinical trial of Exosurf, a protein-free synthetic surfactant, for the prophylaxis and early treatment of hyaline membrane disease. *Paediatrics* 1991;88:1–9.
- Stevenson D, Walther F, Long W, et al. American Exosurf Neonatal Study Group I. Controlled trial of a single dose of synthetic surfactant at birth in premature infants weighing 500 to 699 grams. *J Paediatric* 1992;120:S3–S12.
- Ten Centre Study Group. Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *Br Med J* 1987;294:991–996.
- Wilkinson AR, Jenkins PA, Jeffrey JA. Two controlled trials of dry artificial surfactant: early effects and later outcome in babies with surfactant deficiency. *Lancet* 1985;2:287–291.
- Nilsson R, Grossman G, Robertson B. Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. *Paediatr Res* 1978;12:249–255.
- Jobe A, Ikegami M, Jacobs H, Jones S. Surfactant and pulmonary blood flow distributions following treatment of premature lambs with natural surfactant. *J Clin Invest* 1984;73:848–856.
- Nagesh K, Bhat V, Kunikullya S, Rajesh N. Surfactant therapy in neonatal respiratory distress syndrome. *Indian Paediatr* 1994;31:971–977.
- Sanghvi KP, Merchant RH. Single dose surfactant rescue therapy in neonatal respiratory distress syndrome. *Indian Paediatr* 1998;35:533–536.
- Narang A, Kumar P, Dutta S, Kumar R. Surfactant Therapy for Hyaline Membrane Disease: the Chandigarh experience. *Indian Paediatr* 2001;38:640–646.
- Lyra PP, Diniz EM. The importance of surfactant on the development of neonatal pulmonary diseases. *Clinics* 2007;62:181–190.
- Kribs A, Pillekamp F, Hünseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age ≤ 27 weeks). *Paediatric Anaesth* 2007;17:364–369.
- Sandri F, Plavka R, Simeoni U, et al. The CURPAP study: an international randomised controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants. *Neonatology* 2008;94:60–62.