Brief Reports

Single Dose Surfactant Rescue Therapy in Neonatal Respiratory Distress Syndrome

K.P. Sanghvi
R.H. Merchant

Neonatal mortality due to Respiratory Distress Syndrome (RDS) has significantly declined after the advent of surfactant therapy(l). Surfactant has been evaluated in many large multicenter, randomized controlled trials which indicate that both prophylactic and therapeutic administration of surfactant in RDS decreases morbidity and mortality(2-7). Surfactant use is still not widely prevalent in our country(8). Lack of trained personnel, high cost and relative non-availability are the major deterrents to the widespread use of surfactant. This study presents our experience with surfactant use in newborn infants with RDS.

Subjects and Methods

Inborn infants with RDS were mechanically ventilated if they were unable to maintain a PaO_2 ≥50 mm Hg and/or a $PaCO_2$ ≤ 50 mm Hg on a CPAP of 6-8 cm of H_2O and an FiO_2 of ≤ 0.6. Single dose rescue sufactant therapy was administered to these infants from 1st January 1995 to 31st December 1996, if they met the following eligibility criteria: *(a)* Clinical evidence of RDS; *(b)* Radiological evidence of Grades III-IV RDS(9); (c) Need for mechanical ventilation; *(d)* Age less than 24 hours; (e) Arteriolar to alveolar (a/A) PO_2 ratio of < 0.22; and *if)* Availability of parental consent. Infants with RDS were excluded if there was a history of rupture of membranes > 12 hours, meconium stained liquor or chorioamnionitis or the infants had major congenital malformations, an Apgar score < 5 at 5 minutes or congenital sepsis.

Three types of surfactant were used - Exosurf (Burroughs Wellcome Co., USA; dose 5 ml/kg), Survanta (Abbott Laboratories, USA; dose 4 ml/kg), and Alveofact (Boehringer Ingelheim, Germany; dose 1.2 ml/kg). Surfactant was administered over a period of 5-10 minutes by a neonatologist (KPS) through a side port adapter. FiO_2 and ventilator settings were immediately adjusted to maintain adequate blood gases (PaO_2 50-70 mm Hg, PaCO2 40-50 mm Hg and pH > 7.25) with the lowest possible peak inspiratory pressures and FiO_2Routine endotracheal tube suctioning was avoided for the first six hours after surfactant administration. Cerebral ultrasound scans were done on days 4 and 14 and before discharge. In the event of earlier death an immediate post mortem cerebral ultrasound scan was done. Fundus examination was done at 14 and 28 days of postnatal age and on discharge. Cerebral scans and eye examinations were repeated at weekly intervals, if found to be abnormal. Patent ductus arteriosus was diagnosed clinically and confirmed by echocardiography. Meperidine (1 mg/kg/dose) every 4-6 hours intravenously was used as sedative analgesic.

From the Department of Neonatal Medicine, N. Wadia Maternity Hospital, Mumbai 400 012.

Reprint requests: Dr. R.H. Merchant, Director Neonatal Services, N. Wadia Maternity Hospital, Acharya Donde Marg, Parel, Mumbai 400 012.

Manuscript received: July 11,1997;
Initial review completed: September 3,1997;
Revision accepted: January 27,1998.

The variables used to assess response to surfactant therapy were a/A ratios at 0, 1 and 24 hours and FiO_2 at 0 and 24 hours post surfactant therapy. The other outcome measures included were number of babies extubated, mortality while in hospital and the complications seen in these infants.

Results

There were 109 infants born with RDS over the study period, 34 (31.2%) met eligibility criteria for surfactant therapy. Of these nine infants met the exclusion criteria (rupture of membranes > 12 hours in five and Apgar scores < 5 at 5 minutes in four and in three surfactant could not be administered due to non availability of neonatologist (KPS). The mean birth weight of the 22 enrolled infants was 1179.1 g (range 600-1720 g) and the mean gestational age was 29.8 weeks (range 26-33 weeks). None of the babies were small for gestational age. Alveofact was administered to two infants, and Survanta and Exosurf to 10 babies each. The mean age at surfactant therapy was 10.6 ± 6.4 hours and the mean duration of ventilation was 104.4 ± 55 hours.

Mean (SD) a/A ratios increased from 0.13 ± 0.04 pre-surfactant therapy to 0.19 + 0.05, at one hour post-therapy and 0.37 + 0.1, at 24 hours post therapy. Similarly the mean FiO_2 decreased from 0.85 ± 0.12 before therapy to 0.41 ± 0.2, 24 hours post therapy. Of the 22 infants administered surfactant 16 (72.7%) were extubated. Out of six infants who could not be extubated, four died of undiagnosed endotracheal tube clock, electricity failure, lack of oxygen supply and intraventricular hemorrhage, and two died of pulmonary hemorrhage. Of the seven babies who died post extubation, six died of sepsis (three after 28 days of life) and one of necrotising enterocolitis.

Complications seen in these 22 infants included sepsis in ten, patent ductus arteriosus in five, intraventricular hemorrhage in four (grade IV=1, grade II=2, grade I=1), retinopathy of prematurity in two, and chronic lung disease, necrotising enterocolitis, and periventricular leukomalacia in one each. There were no differences between survivors and non survivors except for the ventilation duration *(Table 1)*.

Discussion

Natural and synthetic surfactants were both effective in increasing the a/A ratio and decreasing the FiO_2 in the present study. Other studies(2-8,10,ll) have shown that both natural and artificial surfactants lead to prompt and sustained improvement in oxygenation and decreased need for ventilatory support. No attempt was made to compare the relative efficacy of the various types of surfactants used and the outcome in relation to antenatal use of steroids as the study was not prospectively designed for hypothesis testing.

Despite comparable with weights and gestational ages of the study infants, the mortality of 59% in the present analysis is high as compared to 3-16% reported by other studies(2-7), but a combined death and CLD incidence of 64% in this study is comparable to 56% reported by others(7). In the present study surfactant was used only in grades III-IV RDS whereas in other reports(2,4-7) it has been used irrespective of the severity of disease. Single dose rescue therapy and stringent inclusion criteria were used to remain within the context of limited financial and physical resources available to us. Experience of earlier trials(10) comparing single to multiple dose therapy suggest that multiple doses are more effective in improving oxygenation and ventilation, and decreasing pneumothoraces and mortality. In one study(11) multiple doses were required in 79% of the

TABLE I—*Clinical Characteristics of Surviving and Non-Surviving Infants Administered Surfactant*

Characteristics		Survivors (n = 9)	Non-survivors (n = 13)
Male sex		6	8
Birth weight (g) Mean (SD)		1335.6 ± 281	1055.4 ± 260
Gestation (weeks) Mean (SD)		28.9 ± 1.5	31.1 ± 2.7
Duration of ventilation (h)* Mean (SD)		125.3 ±81.5	89.9 ± 57.9
Age at surfactant administration (h) Mean (SD)		10.7 ±5.9	10.3 + 6.1
a/A ratio Mean (SD)	0 h	0.13 ±0.04	0.13+0.05
	24 h	0.36 ±0.16	0.30 + 0.13
FiO_2at Mean (SD)	0 h	0.83 ±0.08	0.87±0.14
	24 h	0.28 ±0.18	0.41 ± 0.22
Antenatal steroids (2 doses)		4 (44.4%)	3 (23.1%)
Sepsis		4 (44.4%)	6 (46.2%)

* $p < 0.05$ (by Student 't' test)

infants treated with surfactant. Also expertise with ventilation is relatively recent to our unit and was started one year prior to surfactant therapy.

Sepsis was responsible for 54% of the mortality and six of the seven post extubation deaths. Sepsis is reported to occur in 4-31% of infants given surfactant(2-6) which is lower than 45.6% reported in our study. In India 5-67% of ventilated neonates develop sepsis(12). The present analysis has reported death while in hospital whereas many studies(2-6) have reported survival at 28 days. There were no pneumothoraces and only one case of chronic lung disease. Airleaks have been reported to be 12%-39%(2,4-7) in surfactant treated babies. The incidence of airleaks in the unit was 1.3% of all the ventilated babies during the study period.

There were three preventable deaths (endotracheal tube block, electricity failure and lack of oxygen supply in one each). These reflect the relative inexperience of the medical and nursing staff and the financial constraints of a public hospital in the country. It also underscores the fact that hospitals providing for intensive care of newborns should ensure provision of adequate facilities. Surfactant therapy though expensive had made its advent in the country with more and more centers using surfactant in the treatment of RDS. Results are bound to improve with increasing experience which is essential before optimal effects can be obtained. Lack of infrastructure and the cost (Rs. 20,000-25,000 per dose) may preclude the use of surfactant in many centers and deprive the benefit to many newborns in our country.

REFERENCES

1. Wegman ME. Annual summary of vital

statistics - 1990. Pediatrics 1991; 88: 1081-1092.

2. Gitlin JD, Soll RF, Parad RB, Horbar JD, Feldmen HA, Lucey JF, *et al.* Randomized controlled trial of exogenous surfactant for the treatment of hyaline membrane disease. Pediatrics 1987; 79: 31-37.

3. Raju TNK, Vidyasagar D, Bhat R, Sobel D, McCullock KM, Anderson M, *et al.* Double-blind controlled trial of single dose treatment with bovine surfactant in severe hyaline membrane disease. Lancet 1987; 1:651-656.

4. Fujiwara T, Konishi M, Chida S, Okuyama K, Ogawa Y, Takeuchi Y, *et al.* Surfactant replacement therapy with a single psotventilatory dose of a reconstituted bovine surfactant in preterm neonates with respiratory distress syndrome: Final analysis of a multicenter, double-blind, randomized trial and comparison with similar trials. Pediatrics 1990; 86: 753-764.

5. Long W, Corbet A, Robert Cotton MB, Courtney S, McGuiness G, Walter D, *et al. A* controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. N Engl J Med 1991; 325:1696-1703.

6. Speer CP, Gefeller O, Groneck P, Laufkotter E, Roll C, Hanssler L, *et al.* Randomized clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child 1995; 72: F8-F13.

7. Vermont-Oxford Neonatal Network. A multicenter randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory syndrome. Pediatrics 1996; 97:1-6.

8. Nagesh K, Bhat V, Kunikullaya S, Rajesh N. Surfactant therapy in neonatal respiratory distress syndrome. Indian Pediatr 1994; 31: 971-977.

9. Bomsel F. Contribution of I'etude radiologique de la maladie des membranes hyalines: propos de 110 cas. J Radiol Electrol 1970; 51: 259-268.

10. Dunn M, Shennan A, Possmayer F. Single versus multiple dose surfactant replacement therapy in neonates 30 to 36 weeks with respiratory distress syndrome. Pediatrics 1990; 86: 564-571.

11. Liechty EA, Donovan E, Purohit D, Gihooly J, Feldman B, Noguchi A, *et al.* Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight infants with respiratory distress syndrome. Pediatrics 1991; 88:19-28.

12. Bhakoo ON. Assisted ventilation in neonates: The Indian perspective. Indian Pediatr 1995; 32:1261-1264.