ORIGINAL ARTICLE

Surfactant Therapy In Respiratory Distress Syndrome - The First Local Experience

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Summary

An open prospective descriptive pilot study was undertaken to assess the effectiveness and experience in the use of Exosurf Neonatal, a synthetic surfactant, on preterm infants with respiratory distress syndrome in the neonatal intensive care unit of the Paediatric Institute. Of 10 infants treated, seven (70%) survived with no major handicap on discharge. The mean duration of ventilation for these survivors was 6.4 days, mean duration of oxygen therapy 9.1 days and mean length of hospital stay 38.3 days. A comparison was made with a retrospective analysis of 15 neonates who were admitted during an eight month period prior to the pilot study. These infants were mechanically ventilated for respiratory distress syndrome but not given surfactant therapy. Of these, nine (60%) survived ($P>0.1$ compared to Exosurf treated infants), but two developed post haemorrhagic hydrocephalus requiring shunting. For these nine survivors, the mean duration of ventilator therapy was 12.6 days, the mean duration of oxygen therapy 20.7 days and the mean length of hospital stay 70.8 days. This difference was statistically significant ($P<0.05$). Of the three Exosurf Neonatal treated infants who died, two were extremely premature. Both developed grade IV periventricular haemorrhage while the third infant was admitted in shock and hypothermia and died from intraventricular haemorrhage and pulmonary interstitial emphysema.

Except for the very sick and extremely premature infants, surfactant therapy is useful in reducing the mortality and morbidity of premature infants with respiratory distress syndrome in our neonatal intensive unit.

Key words: Synthetic surfactant, Respiratory distress syndrome.

Introduction

The use of exogenous surfactant to prevent or ameliorate the severity of respiratory distress syndrome (RDS) has been widely investigated in many parts of the world[1-6] and the prophylactic and rescue strategies have both shown substantial benefits.

From June to September 1992, an open prospective pilot study was conducted on 10 premature neonates with respiratory distress syndrome. This was a rescue trial and is believed to be the first trial of exogenous surfactant therapy in Malaysia. The objectives were to assess the effectiveness of Exosurf Neonatal therapy on the clinical course and survival of infants with respiratory distress

syndrome and to allow clinicians an opportunity to gain personal experience in the use of surfactant therapy.

Methods

Surfactant preparation

The surfactant used in this study (Exosurf Neonatal as Intratracheal Suspension, The Wellcome Foundation Ltd) is a totally synthetic material developed by Clements. The Exosurf surfactant is composed of dipalmitoyl phosphatidylcholine (DPPC), hexadecanol and tyloxapol in a 13.5:1.5:1 ratio and has been formulated as a sterile lyophilised powder that is stored under vacuum. Each 10ml vial contains 108mg DPPC, 12mg hexadecanol, 8mg tyloxapol, and 46.75mg sodium chloride. Hexadecanol serves as the spreading agent. When constituted with 8ml sterile water immediately before administration, the surfactant suspension contains 13.5mg/ml DPPC, 1.5mg/ml hexadecanol, and 1mg/ml tyloxapol in 0.1N sodium chloride[7]. The reconstituted suspension reduces static surface tension to less than 10mN on the Wilhemny balance[8,9]. On repetitive compression in a bubble tensiometer modified from Enhorning the reconstituted suspension reduces surface tension to 0 to 3mN. With a recently developed captive bubble technique[10], dynamic surface tensions of less than 2mN are found on repetitive compression of the reconstituted suspension.

Clinial trial design

This was an open trial involving the use of 5ml/kg doses of Exosurf, given 12 hours apart to 10 premature infants weighing at least 700gm with established RDS who required mechanical ventilation, and had an arterial/alveolar partial pressure of oxygen (a/A PO_2) ratio less than 0.22. The diagnosis of RDS was based on the history and clinical picture and confirmed by a chest X-ray. Initial dosing occurred between the two and 24 hours of age, the second dose was given 12 hours later to all infants who remained on the ventilator. Informed consent was obtained from the parents in every patient.

Two neonatal units are operational in the neonatal intensive care unit in the Paediatric Institute. The study was initially intended only for infants admitted to the Ministry of Health unit. However, one infant who had very severe lung disease admitted to the University unit was also given the surfactant and included in the study.

Exosurf was injected during mechanical ventilation via a special endotracheal tube adaptor fitted with a right angle Luer-Lock side port (Respiratory Support Products Inc, Santa Ana, California).

Each dose was divided into 2.5ml/kg aliquots; both of which were administered with the patients supine and without interrupting mechanical ventilation. Each aliquot was injected slowly for a minimum of one to two minutes. The rate of injection was further slowed in infants who reacted with decreases in oxygenation or heart rate. After each aliquot the infants were rotated 45 degrees (first to the left, then to the right) for 30 seconds in an attempt to achieve better pulmonary distribution. Thereafter infants were returned to the midline position. Suctioning was withheld for two hours after dosing unless clinical necessity dictated otherwise. Monitoring of oxygenation status via a pulse oximeter and blood gas analyses was done on each case and the objective was to maintain partial pressure of arterial oxygen (PaO_2) in the region of 50 to 70mm Hg and partial pressure of arterial carbon dioxide ($PaCO_2$) in the region of 40 to 50mm Hg.

Data collection

Information was recorded for each mother's demographic profile, medical and obstetric history and index pregnancy, labour and delivery. Infants' ventilator and oxygen requirements were recorded daily. Chest radiography was obtained on Day 1 before the first dose of Exosurf and whenever indicated clinically. These X-rays were evaluated by attending clinicians. The infants were assessed daily for patent ductus arteriosus (PDA) by clinical examination. Cardiac echocardiography was done for confirmation when necessary. Diagnosis of PDA was made if any one of the following was observed[11]:

1. a continuous murmur at any time
2. a systolic murmur while the infant was receiving intermittent mandatory ventilation (IMV)
3. an active precordium during IMV
4. a pulse pressure more than 30mm Hg during IMV
5. hepatomegaly during IMV (hepatic edge more than 3cm below the right costal margin)
6. cardiomegaly or pulmonary plethora on chest radiograph
7. ductal patency as shown by two-dimensional echocardiography. The presence or absence of PDA was recorded each day till discharge.

Cranial ultrasound was done for all infants by attending clinicians at least once before administering the first dose of Exosurf and subsequently, repeat scans were done as indicated.
The results were classified as indicating:

- subependymal haemorrhage (Grade 1)
- intraventricular haemorrhage without ventricular dilatation (Grade 2)
- intraventricular haemorrhage with ventricular dilatation (Grade 3) or
- periventricular echodensities (PVED) (Grade 4).

The diagnosis of bronchopulmonary dysplasia eight days after enrolment was made on the basis of a combination of clinical[12] and radiographic[13] criteria.

Three criteria had to be met: the presence of tachypnoea and retractions, the need for supplemental oxygen to maintain the pulse oximeter reading above 85 per cent saturation and abnormalities on the chest radiography with a score of four or more on the Edwards Scale. None of the infants underwent an autopsy. For infants who died between 10 and 28 days of age, bronchopulmonary dysplasia was diagnosed if, at the time of death they required more than 60 per cent oxygen and a mean airway pressure of 7cm H_2O, had persistent abnormalities in the chest films, and if there was no other explanation for respiratory failure.

The occurrence of air leaks, necrotising enterocolitis (NEC) and pulmory haemorrhage was also recorded. Diagnoses of air leaks and necrotising enterocolitis were made clinically and radiologically.

Data analysis

The primary outcome measure to be affected by Exosurf administration was prospectively designated as survival on discharge. Other main study end points were mean duration of ventilation, oxygen therapy and hospital stay. Any adverse reactions associated with the use of Exosurf were also recorded. For a comparative analysis, the above end points were also determined on 15 premature infants with respiratory distress syndrome who required mechanical ventilation and were hospitalised from October 1991 to May 1992.

Results

The neonatal intensive care unit in the Paediatric Institute is predominantly a nursery for cases born outside the hospital and referred for neonatal care when indicated. Occasionally babies from the Maternity Hospital Kuala Lumpur (MHKL) are transferred to this nursery when an intensive care bed is not available there.

Of the 10 infants in the pilot study, five were males and five were females. The mean gestational age was 31.1 weeks and the mean birth weight 1408 grams. This compared with eight males and seven females with a mean gestational age of 29.4 weeks and a mean birthweight of 1265 grams in the retrospective non Exosurf study group (Table I). There was no significant difference in these two characteristics between the study groups.

The infants tolerated the administration of Exosurf well. Only one showed a transient bradycardia and desaturation associated with coughing during the procedure.

The survival rate of the 10 infants treated with Exosurf at discharge was 70% (Table II). Clinically they were well on discharge. Of the three Exosurf treated infants who died, one weighed 830 grams with a gestational age of 26 weeks, another 988 grams with gestational age of 28 weeks. Both were very unstable when admitted and despite good improvement in respiratory function, subsequently

Table I
Demographic features of study groups

	Without Exosurf (n=15)	With Exosurf (n=10)
Birth weight (gm)*	1265 ± 299	1408 ± 468
Gestational age (wk)*	29.4 ± 2.6	31.1 ± 3.4
Gender:		
Male	8	5
Female	7	5
Delivery:		
Vaginal	14	8
Caesarean	1	2
Place of delivery:		
Maternity Hospital Kuala Lumpur	3	1
Private Maternity Homes/Hospitals	6	1
District Hospitals (DH)	4	3
Home	2	5
Prenatal Steroids	0	0
Multiple Pregnancy	0	0

**Values are expressed as mean ± SD*

died of Grade IV periventricular haemorrhage. The latter infant also acquired a methicillin-resistant *Staphylococcus aureus* septicaemia. The third infant was delivered at home at 34 weeks gestation weighing 1200 grams and was admitted with a temperature 32.2°C and unrecordable blood pressure. He died of intraventricular haemorrhage and pulmonary interstitial emphysema (Table VI).

Table II
Outcome on discharge

	No. of survivors (%)	No. of deaths (%)
Without Exosurf (n=15)	9* (60)	6 (40)
With Exosurf (n=10)	7 (70)	3 (30)

* *Two infants developed post haemorrhagic hydrocephalus and required ventriculoperitoneal shunting*

Table III
Mean duration of ventilation, oxygen therapy and hospital stay of survivors

	(Mean Duration in Days) Ventilation	Oxygen therapy	Hospital stay
Without Exosurf (n=9)	12.6	20.7	70.8
With Exosurf (n=7)	6.4	9.1	38.3
P value	<0.05	<0.02	0.05

Table IV
Duration of ventilation, oxygen therapy and hospital stay of non survivors

	(Duration in Days) Ventilation	Oxygen therapy	Hospital stay
	Range (Mean)	Range (Mean)	Range (Mean)
Without Exosurf (n=6)	0.3-91 (20.7)	0.3-91 (24)	0.3-91 (24)
With Exosurf (n=3)	0.9-9 (5.7)	0.9-9 (5.8)	0.9-9 (5.8)

Of the 15 infants who were not given surfactant, the survival rate was 60 per cent, of which two developed post haemorrhagic hydrocephalus requiring shunting. Hence only 46.7 per cent were discharged well (i.e. seven out of 15). These survival outcomes between the two groups were not statistically significant however ($0.1<p<0.5$)

The reduction in days on ventilation and O_2 therapy was statistically significant between the two groups ($p<0.05$ and< 0.02 respectively) [Table III]. The mean duration of hospital stay was 32.5 days shorter for the infants given Exosurf and this difference was just statistically significant ($P=0.05$)

Of the non survivors, infants given Exosurf appeared to have a relatively short period of ventilation, oxygen therapy and hospital stay compared to the non survivors of the non Exosurf group (Table IV). However because of the small numbers of cases in both groups and a wide standard deviation, this difference did not reach statistical significance ($0.1<p<0.5$)

None of the infants given Exosurf had patent ductus arteriosus clinically and none developed pneumothorax, pulmonary haemorrhage or bronchopulmonary dysplasia (Table V).

There is a significant reduction in the occurrence of PDA in infants given Exosurf (5/15 vs 0/10 in non Exosurf group) but there is no significant difference in incidence of the other complications.

Table V
Complications associated with respiratory distress syndrome and prematurity

	Without Exosurf (n=15)	With Exosurf (n=10)
Any IVH	5*	5
Grade III IVH or PVED	5	3
PDA (requiring treatment	5	Nil**
with indomethacin)		
NEC	1	Nil
Air leak:		
Pneumothorax	Nil	Nil
Pulmonary interstitial emphysema	Nil	1
Pulmonary haemorrhage	1	Nil
BPD	2	Nil
Hydrocephalus	2	Nil

* *Only eight out of 15 infants in the non Exosurf group had cranial ultrasound scans done whereas all infants in the Exosurf group had at least one cranial ultrasound scan*

** *$p<0.05$ for the comparison between the groups for PDA*

There is no statistical differences in the other characteristics between the groups

Discussion

Surfactant therapy has been recognised and accepted as a beneficial therapy in the management of *respiratory distress syndrome.* This small study has enabled us to gain some local experience on the use of synthetic surfactant. We were unable to do a controlled study because of cost constraints. Nevertheless, compelling evidence has been obtained from studies[14,15,17,18] all over world with regard to its effectiveness in prophylactic and rescue uses.

For the purpose of comparison a retrospective analysis of a group of historical controls was done. Even though the non Exosurf infants were smaller and more premature (mean of 1265gm and 29.4 weeks vs 1408gm and 31.1 weeks), these differences were not statistically significant. Though the sample sizes were small, there appears to be possible beneficial effects on its use in our neonatal intensive care units. We achieved a reduction in overall mortality on discharge of 25 per cent (40% mortality in non Exosurf vs 30% in Exosurf study group). If only survival with no major handicap was compared, there was an improvement of about 50 per cent (46.7% in non Exosurf and 70% in Exosurf study group). Though these differences are not statistically significant, they are comparable to the reduction in overall mortality from 22 per cent to 61 per cent quoted in other studies[14,15].

The morbidity was also reduced in view of a significantly shorter duration of assisted ventilation, oxygen therapy and hospital stay for the survivors. In many studies, administration of surfactant has been shown to be associated with a slight increase in the incidence of pulmonary haemorrhage[16]. The role of the patent ductus arteriosus has been implicated in this. It is noteworthy that none of the infants in this pilot study had patent ductus arteriosus nor pulmonary haemorrhage clinically. Many studies have also demonstrated the cost effectiveness of Exosurf neonatal therapy[17,18]. We have not done any cost evaluation on our cases but it would seem that with the likelihood of improved survival and lower morbidity, cost savings can be obtained. The three infants who died were the smallest and most premature and unstable when admitted. It appears that for these infants, stabilisation and supportive therapy are probably more crucial than surfactant therapy. Temperature control, homeostasis and prevention and management of intraventricular haemorrhage and infections are of paramount importance. It is probable that the rescue use of a synthetic surfactant improves the morbidity and mortality rates of premature infants with respiratory distress syndrome. If used judiciously in well selected infants, favourable outcomes with overall cost savings can be expected. However, a larger controlled study would be necessary to confirm these findings.

Table VI
Deaths in exosurf treated patients

Case	Gestational (Weeks)	B.W. (GM)	Place of delivery	Factors contributing to death
1	26	830	D.H.	Grade IV IVH
2	28	988	D.H.	Grade IV IVH MRSA Septicaemia
3	34	1200	Home	Hypothermia 32.2°C Hypotension IVH PIE

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