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Surfactant treatment and incidence of intraventricular haemorrhage in severe respiratory distress syndrome

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SUMMARY As part of a multicentre study of porcine surfactant administration in respiratory distress syndrome, 29 babies weighing 2000 g or less were studied in the neonatal intensive care unit of the Royal Maternity Hospital, Belfast. Fourteen babies of a mean gestational age of 28·1 weeks were randomly allocated to the treatment group (200 mg/kg phospholipid given intratracheally) and 15 babies of a mean gestational age of 28·7 weeks formed the control group. All babies had severe respiratory distress syndrome (oxygen requirement over 60%, mechanical ventilation, and age 15 hours or less). Almost immediate improvement in oxygenation was seen in the treated group so that oxygen concentrations could be reduced and remained significantly lower than those of control babies for the first seven days of life. Alveolar-arterial oxygen gradients were also significantly different for the first five days after treatment. More babies in the treatment group survived (79% *v* 40%) but the difference was not significant. The incidence of pneumothorax and of intraventricular haemorrhage, however, was significantly lower in treated babies compared with controls. For babies weighing less than 1200 g the risk of developing or extending intraventricular haemorrhage after entry to the study was also reduced in the treatment group (29% *v* 100%).

Surfactant replacement has been shown to be an effective treatment for neonatal respiratory distress syndrome in a number of non-randomised[1-3] and randomised controlled trials.[4-11] The latter trials were designed to prevent respiratory distress syndrome[5-9] or to treat established disease (intervention studies).[4 10 11] Three studies showed reduced mortality in treated babies.[5 8 9] and one showed a decreased incidence of intraventricular haemorrhage after prophylaxis with surfactant at birth.[5]

We report the results of a randomised intervenion study of surfactant replacement in neonatal respiratory distress syndrome, which for the first time shows a decreased incidence of intraventricular haemorrhage in treated babies.

Surfactant

The surfactant was prepared from minced porcine lungs by chloroform-methanol extraction and liquid gel chromatography,[12] and it contains roughly 99% of polar lipids, mainly phospholipids, and 1% of hydrophobic proteins (molecular weight <15 000). After chromatography the material was dissolved in chloroform and passed through a 0·2 μm filter. The subsequent steps of the preparation procedure, including evaporation of the chloroform and suspension in saline, were carried out under sterile conditions. Repeated bacterial cultures from the original batch and from the individual phials after the instillation procedure gave negative results. The physiological activity of our surfactant has been documented in experiments on preterm newborn rabbits receiving artificial ventilation.[12 13]

Patients and methods

Twenty nine preterm infants with birth weights of 700–2000 g were entered in the study. All infants had clinical and radiological findings of severe respiratory distress syndrome[14] between two and 15 hours from birth and required mechanical ventilation with oxygen concentrations of 60% or more.

These babies were all severely ill and had a median age at the start of mechanical ventilation of less than 30 minutes. Only 10% of babies having mechanical ventilation for respiratory distress syndrome were ill enough to fulfil the study entry criteria. Babies were excluded if they had severe birth asphyxia (Apgar score of <5 at five minutes), streptococcal pneumonia, major congenital anomalies, or intraventricular haemorrhage (grade III-IV on ultrasound scan[15]) before entry into the study. Informed consent was obtained from the parents of each baby and the study protocol was approved by the research ethical committee of the Queen's University of Belfast.

After enrolment babies were randomly allocated into control and treatment groups by a consultant neonatologist. Randomisation was stratified by birth weight of <1200 g and ≥1200 g, to ensure equal numbers of smaller babies in each group. Treated babies were disconnected from the ventilator and 1·25 ml/kg (phospholipid concentration 80 mg/ml) of surfactant was instilled into each main bronchus via a 5 French gauge feeding tube. Between and after instillations the baby was ventilated by manual bagging for one minute. In control babies manual ventilation for two minutes was performed but no surfactant was instilled. The babies were then reconnected to the ventilator at the same oxygen concentration and ventilator settings. Clinical care of the babies after enrolment was by consultants and junior doctors who were unaware of the randomisation procedure. Babies in both groups were assessed by serial chest radiographs, arterial blood gases, ventilator settings, echocardiography, and calculated alveolar-arterial oxygen gradients (A-aDO_2) using a modified equation, where FiO_2 is the fraction of inspired oxygen concentration[5]:

$$\text{A-a}DO_2 = FiO_2 \times 713 - \frac{PaCO_2}{0{\cdot}8} - PaO_2$$

Complications such as pneumothorax[16] and bronchopulmonary dysplasia[17] were diagnosed radiologically, patent ductus arteriosus by echocardiography,[18] and intraventricular haemorrhage by ultrasound scan.[15 19] Echocardiography and cerebral ultrasound scans were performed before entry and thereafter at intervals of 15 minutes, one, four, six, and 24 hours, and daily until 10 days. Babies were studied until death or discharge from hospital. Outpatient follow up of survivors at intervals of three months continued but is not the subject of this report.

Statistical assessment was by Fisher's exact test, independent *t* test, and Mann-Whitney U test where appropriate. All p values quoted are two tailed.

Results

The clinical characteristics of the two groups of babies are shown in table 1. There were no significant differences between the groups for any of these variables. After surfactant instillation there was an immediate reduction in oxygen requirement (FiO_2) (fig 1). This was seen at 15 minutes (not shown) and remained lower in treated babies for up to seven days. Similarly, A-aDO_2 was significantly lower in treated babies up to five days of age (fig 2). Not all babies showed sustained response so that the standard deviations were quite large for both FiO_2

Table 1 *Clinical characteristics of treated and control groups*

	Treated group (n=14)	*Control group (n=15)*	*p Value*
Birth weight (g) (mean SD)	1316 (303)	1329 (347)	0·91
Gestation (weeks) (mean SD)	28·1 (1·4)	28·7 (2·2)	0·46
Weight <1200 g (No %)	7 (50)	5 (33)	0·59
Males (No %)	8 (57)	10 (67)	0·88
Inborn (No %)	11 (79)	10 (67)	0·77
Given antenatal steroids (No %)	1 (7)	1 (7)	1·0
Antepartum haemorrhage (No %)	8 (57)	4 (27)	0·20
Pre-eclampsia (No %)	2 (14)	3 (20)	1·0
Prolonged rupture of membranes (No %)	5 (36)	3 (20)	0·60
Twin pregnancy (No %)	1 (7)	1 (7)	1·0
Caesarean section (No %)	11 (79)	6 (40)	0·08
Breech delivery (No %)	—	4 (27)	0·11
Apgar scores (median range)			
1 minute	3 (2–5)	3 (2–7)	0·70
5 minutes	7 (5–9)	7 (5–9)	0·47
Intubated at birth (No %)	10 (71)	10 (67)	1·0
Age at entry (hours) (median range)	5 (2–13)	7 (2–15)	0·16
FiO_2 at entry (mean SD)	0·79 (0·12)	0·76 (0·10)	0·42

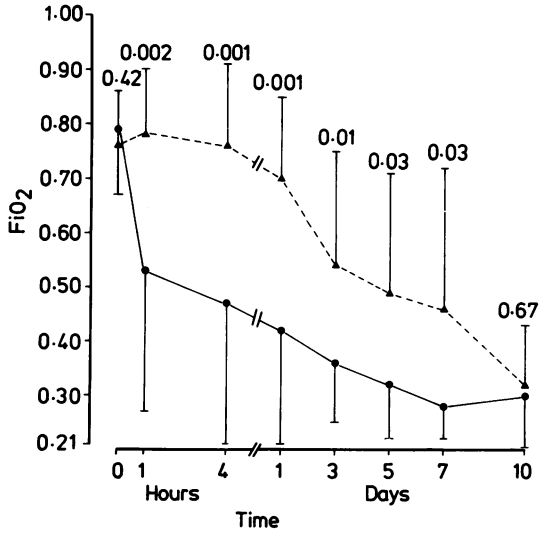

Fig. 1 *Comparison of oxygen requirement (FiO_2) in treated ●——● and control ▲ - - - ▲ groups before entry into the study (time=0) and at one hour, four hours, and one, three, five, seven, and 10 days afterwards. Mean (SD) are shown with p values derived from two tailed independent t tests.*

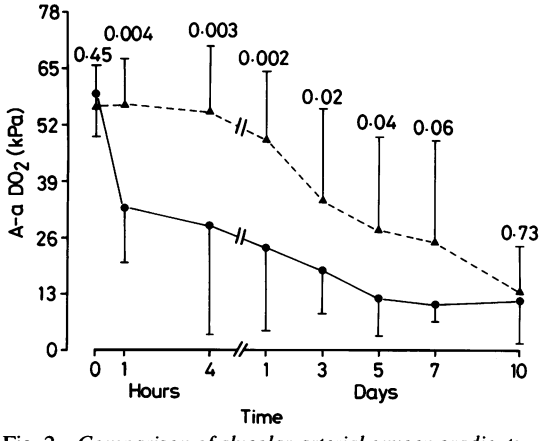

Fig. 2 *Comparison of alveolar-arterial oxygen gradients ($A\text{-}aDO_2$) between treated ●——● and control ▲ - - - ▲ groups.*

and $A\text{-}aDO_2$. To evaluate the significance of differences when the data are not parametrically distributed we also used Mann-Whitney U tests. The p values quoted in the figures are for independent *t* tests but we found no changes after Mann-Whitney U tests except for $A\text{-}aDO_2$ at five days when the difference between the groups was not significant (p=0·07). Table 2 shows the changes in ventilator settings from randomisation up to three days after entry into the study. Oxygen concentrations fell immediately after administration of surfactant; ventilator settings were reduced after a delay of about 24 hours. Peak airway pressure, mean airway pressure, ventilator rate, and inspiratory:expiratory time ratio were all significantly lower in treated infants after 24 hours.

Table 2 *Mean (SD) ventilator settings at randomisation and at four hours, 24 hours, and three days after entry into study*

	Treated group (n=14)	*Control group (n=15)*	*p Value*
	Peak pressure (cm H_2O)		
At randomisation	25 (5)	22 (4)	0·09
After entry			
4 hours	21 (7)	24 (6)	0·29
24 hours	19 (4)	26 (7)	0·005
Three days	15 (9)	26 (8)	0·004
	Mean airway pressure (cm H_2O)		
At randomisation	9 (2)	9 (2)	0·97
After entry			
4 hours	7 (4)	10 (4)	0·12
24 hours	5 (3)	10 (4)	0·001
Three days	4 (3)	10 (4)	0·001
	Rate (breaths/minute)		
At randomisation	47 (9)	44 (9)	0·38
After entry			
4 hours	44 (13)	46 (10)	0·60
24 hours	32 (12)	51 (13)	0·001
Three days	24 (18)	43 (12)	0·005
	Inspiratory:expiratory ratio		
At randomisation	0·8 (0·2)	0·9 (0·3)	0·38
After entry			
4 hours	0·8 (0·4)	1·0 (0·4)	0·40
24 hours	0·6 (0·4)	1·2 (0·9)	0·03
Three days	0·4 (0·3)	0·9 (0·4)	0·001

Table 3 compares the outcome for the two groups. Although survival was greater for treated babies, this did not attain significance using a two tailed Fisher's exact test. For one tailed testing, the mortality was lower for treated babies at the 5% level. Pneumothorax (p=0·005) and bilateral pneumothoraces (p=0·019) occurred more commonly in control babies. Intraventricular haemorrhage was also seen more often in control infants (87% *v* 29%, p=0·004). Five babies had grade I or II intraventricular haemorrhage at entry into the study, three of whom were in the treated group (table 4). Development of new intraventricular haemorrhage or extension occurred significantly more commonly in control babies (p=0·0003), and this was also true for babies weighing <1200 g (p=0·053). (One treated baby had grade II intraventricular haemorrhage that progressed to grade III; one control baby progressed from grade I to

Table 3 *Comparison of outcomes in treated and control groups*

	Treated group (n=14)	*Control group (n=15)*	*p Value*
Survived (No %)	11 (79)	6 (40)	0·08
Survived weighing <1200 g (No %)	5/7 (71)	0/5 —	0·053
Pneumothorax (No %)	3 (21)	12 (80)	0·005
Bilateral	1 (7)	8 (53)	0·019
Muscle relaxants given before pneumothorax (No %)	9 (64)	12 (80)	0·60
Intraventricular haemorrhage (No %)	4 (29)	13 (87)	0·004
Patent ductus arteriosus (No %)	8 (57)	6 (40)	0·58
Indomethacin given (No %)	8 (57)	4 (27)	0·20
Pulmonary interstitial infiltrates on chest radiograph (No %)	9 (64)	3 (20)	0·039
Bronchopulmonary dysplasia in survivors (No %)	3/11 (27)	2/6 (33)	1·0
Duration of IPPV* in survivors (hours) (median range)	194 (47–1510)	239 (141–1472)	0·65
Duration of oxygen treatment in survivors (hours) (median range)	776 (190–3657)	661 (400–2027)	0·74
Age at death (days) (median range)	1 (1–19)	4 (1–29)	0·60

*IPPV=intermittent positive pressure ventilation.

Table 4 *Occurrence of intraventricular haemorrhage and its grade in both groups†*

	Treated group		*Control group*	
	All babies (n=14) (no (%))	*Weight <1200 g (n=7) (no (%))*	*All babies (n=15) (no (%))*	*Weight <1200 g (n=5) (no (%))*
Intraventricular haemorrhage before entry	3 (21)	2 (28)	2 (13)	1 (20)
Grade I	0	0	1	0
Grade II	3	2	1	1
Intraventricular haemorrhage at death or discharge	4 (29)	3 (43)	13 (87)**	5 (100)
Grade I	0	0	2	1
Grade II	2	1	6	2
Grade III	1	1	2	0
Grade IV	1	1	3	2
Intraventricular haemorrhage occurring or extending during study	2 (14)	2 (29)	13 (87)***	5 (100)*
Intraventricular haemorrhage and pneumothorax	1 (17)	1 (14)	12 (80)***	5 (100)*
Intraventricular haemorrhage without pneumothorax	3	2	1	0
Pneumothorax without intraventricular haemorrhage	2	1	0	0
Neither intraventricular haemorrhage or pneumothorax	8 (57)	3 (43)	2 (13)*	0

When compared with treated groups the p values were: *≤0·05, **<0·01, ***<0·001.
†Intraventricular haemorrhage graded according to Papile *et al* (1978).[15]

grade IV; and another control baby from grade II to grade IV.) There were no differences in the incidence of severe intraventricular haemorrhage (grade III or IV) between groups, although the tendency was for the more severe haemorrhages to occur in the control babies. Pneumothorax and intraventricular haemorrhage were associated with each other in controls but not in treated babies (table 4).

Interstitial infiltrates on chest radiography were found more commonly after surfactant instillation (p=0·039), but bacterial cultures from the airways remained sterile for up to seven days.

There were no differences in duration of mechanical ventilation and oxygen treatment in the two groups (table 3). Table 5 shows the causes of death in both groups. Only two babies treated with surfactant died of acute respiratory illness; one after pneumothorax and one with persistent fetal circulation that was unresponsive to tolazoline. This baby was of 26 weeks' gestation and the membranes had been ruptured for five weeks before delivery, making a diagnosis of pulmonary hypoplasia likely, but consent for a postmortem examination was not given. One further treated baby died after the first week from *Pseudomonas* pneumonia and mild

Table 5 *Comparison of babies in each group who died in hospital*

Gestation (weeks)	*Birth weight (g)*	*Age (days)*	*Postmortem examination performed*	*Cause of death*
				Treated group
26	1190	1	+	Hyaline membrane disease, pneumothorax
26	1027	1	−	Pulmonary hypoplasia, persistent fetal circulation
30	1420	19	+	Pneumothorax, pneumonia, pulmonary hypoplasia
				Control group
26	800	1	+	Hyaline membrane disease, pneumothorax, pneumopericardium
27	960	4	+	Hyaline membrane disease, pneumothorax, pneumopericardium, intra-arterial air, intraventricular haemorrhage (IV)
27	1173	8	+	Hyaline membrane disease, pneumothorax, pneumonia
27	875	1	+	Hyaline membrane disease, pneumothorax, intraventricular haemorrhage (IV)
27	1390	7	+	Hyaline membrane disease, pneumothorax, penumonia, intraventricular haemorrhage (IV)
28	845	4	+	Hyaline membrane disease, pneumothorax
28	1556	6	+	Hyaline membrane disease, pneumothorax, pneumonia
29	1395	3	+	Hyaline membrane disease, pneumothorax, pneumopericardium
31	1550	29	+	Pneumothorax, pneumonia, intraventricular haemorrhage (III), bronchopulmonary dysplasia, periventricular leucomalacia

pulmonary hypoplasia. Hyaline membranes were present at necropsy in one of the babies treated with surfactant and in eight of the controls. Acute respiratory failure or complications such as intraventricular haemorrhage or pneumothorax were the causes of death in all control infants, one baby dying at 29 days of bronchopulmonary dysplasia and post-haemorrhagic hydrocephalus with periventricular leucomalacia.

Discussion

Respiratory distress syndrome remains the major cause of death and disability in preterm infants. For babies who survive the neonatal period handicaps may result from intraventricular haemorrhage and bronchopulmonary dysplasia. As respiratory distress syndrome is due to surfactant deficiency, replacement treatment should be effective, and it is generally agreed that natural surfactants are more effective than synthetic ones in improving the outlook for babies with this disease.[13 20 21]

Randomised studies of surfactant replacement have been of two types: preventive where the surfactant is given at birth to very immature babies,[5–9] or interventive where surfactant is given only to babies who are very ill with respiratory distress syndrome.[4 10 11] Intervention studies have the advantage that all babies entered have respiratory disease, and smaller study numbers may be needed to show beneficial effects. Interventive studies of natural surfactant replacement have shown a reduced incidence of pneumothorax and death or bronchopulmonary dysplasia in treated infants.[4 10 11] While there was acute improvement in oxygenation, which lasted from three to six days, there was no reduction in the incidence of intraventricular haemorrhage.[4 10 11] Only the largest of the preventive studies showed any reduction in intraventricular haemorrhage after treatment.[5]

We found a similar acute improvement in oxygenation which allowed FiO_2 to be reduced in babies treated with surfactant. The difference between the groups remained significant for one week despite a potential bias in our data collection: five of the most severely ill control babies died between 3 and 7 days of age. After 24 hours ventilator settings could also be reduced and this may have accounted for the decreased incidence of pneumothorax in treated babies, especially those weighing less than 1200 g. The reduction in intraventricular haemorrhage may have been due to a combination of improved oxygenation[22] and decreased occurrence of pneumothorax[23 24] as a result of enhanced lung compliance after surfactant treatment. Changes in cerebral blood flow occur in both pneumothorax and intraventricular haemorrhage and merit further investigation.

Although our study design allowed for random allocation of babies into treatment and control groups, there were more treated babies born by caesarean section for severe placental abruption and more control babies born by breech delivery. These differences were not significant and probably not clinically important as babies in both groups had similar Apgar scores and need for intubation at

birth. We also believe that babies in both groups were at similar risk of developing intraventricular haemorrhage and indeed at time of entry into the study similar numbers had grade I and II haemorrhages.

It has been suggested that grade I (or subependymal) and II haemorrhages have a good prognosis and that only grade III and IV haemorrhages are associated with long term neurological handicaps.[25] Some reports, however, show that up to 50% of infants with grade II haemorrhages will have mild neurological abnormalities.[26] For this reason we believe that our babies treated with surfactant should have an improved long term developmental prognosis when compared with our control infants who were treated with conventional mechanical ventilation. Follow up studies are under way.

Our rates of pneumothorax (80%) and mortality (60%) in the control group were high but they further emphasised the severity of the respiratory distress syndrome in our patients. None of our five control babies of less than 1200 g weight survived. During the study 76 babies weighing <1200 g and without major congenital abnormality had mechanical ventilation for respiratory distress syndrome but only 12 were ill enough to be entered into the trial. Only 11 of the 64 non-study babies died (17%), which compares favourably with the mortality of babies in the treatment group (29%). Our incidence of pneumothorax in a consecutive series of 433 babies treated with mechanical ventilation is 15%.[27] Greenough *et al* have reported an incidence of pneumothorax of 100% in babies making expiratory efforts against the ventilator and suggested that use of muscle relaxants prevented this complication.[28] Twelve (80%) of our control babies, however, were given muscle relaxants or sedation with diazepam before pneumothorax occurred. If muscle relaxants were used they were always started before the age of 48 hours and most of the pneumothoraces occurred after 48 hours. We had no clinical or radiological evidence of pneumothorax before starting muscle relaxants in any baby in the study.

Not all babies showed sustained improvement after surfactant treatment and all continued to need intensive care and mechanical ventilation for some time. In one study infants needed repeated treatments to sustain effects.[8] Prophylaxis may be the best method of further reducing the incidence of intraventricular haemorrhage and other complications. The infiltrates observed radiologically in some patients after surfactant replacement can mimic pneumonia and may be due to a form of interstitial reaction to the exogenous material[29]; we found no evidence of bacterial infection in these babies.

Long term studies on infants treated with surfactant are few[30 31] and before widespread use of this type of treatment occurs further investigations are needed. The data from the present series of patients, however, indicate that surfactant replacement modifies the clinical course in severe respiratory distress syndrome and reduces the incidence of serious complications.

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