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Early surfactant therapy and nasal continuous positive airways pressure for mild respiratory distress syndrome – a pilot study

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Objectives. To determine if the administration of porcine surfactant 100 mg/kg within 24 hours after birth, to infants with respiratory distress syndrome (RDS) receiving nasal continuous positive airways pressure (NCPAP) and inspired oxygen (FiO_2) 0.3 - 0.4, decreased the need for mechanical ventilation (MV) during the first week of life compared with infants in whom the required FiO_2 was allowed to rise above 0.4 before surfactant was administered.

Design and subjects. A study of 102 infants was planned, but terminated early due to slow recruitment, and is presented as pilot data. Twenty-seven preterm infants were randomised into either a low- or a high-threshold group. The low-threshold group received surfactant immediately and the high-threshold group received surfactant if their FiO_2 rose above 0.4. Infants who received surfactant were returned to NCPAP if respiratory effort was adequate.

Setting. The Neonatal Intensive Care Unit, Groote Schuur Hospital, Cape Town.

Results. The mean gestational age for the entire cohort was 31±2 weeks. There were no significant differences between the groups with regard to the need for MV in the first week of life. However, the duration of any form of assisted ventilation (NCPAP and MV) was less in the low-threshold group (p=0.042), and this group had a lower mean $PaCO_2$ at 24 hours (p=0.015).

Conclusions. In this pilot study, the administration of 100 mg/kg porcine surfactant to preterm infants with RDS requiring NCPAP at a threshold FiO_2 of 0.3 - 0.4 improved alveolar ventilation and reduced the duration of any form of assisted ventilation compared with waiting until the FiO_2 was >0.4. There was no significant reduction in the need for MV.

The use of nasal continuous positive airways pressure (NCPAP) in preterm infants with respiratory distress syndrome (RDS) reduces the need for mechanical ventilation (MV)[1] and decreases mortality.[2] MV in preterm infants is further reduced by early administration of porcine surfactant (Curosurf) followed by immediate extubation to NCPAP.[3] Verder *et al.* administered high-dose porcine surfactant (200 mg/kg) to infants of less than 30 weeks' gestation requiring NCPAP and showed that, if administered within the first 72 hours of life, when FiO_2 was between 0.37 and 0.55, the need for subsequent MV during the first 7 days decreased from 63% to 21%.[3]

We use the standard dose of 100 mg/kg porcine surfactant in our unit. Our anecdotal experience suggests that this dose is effective if administered at lower FiO_2 thresholds than those suggested by Verder *et al.*[3] This study was designed to determine if infants with RDS respond better to standard doses of surfactant if administered earlier in the disease process. We hypothesised that if porcine surfactant 100 mg/kg is administered within 24 hours after birth, the need for MV and the duration of any form of assisted ventilation (NCPAP and MV) during the first week of life will be lower if surfactant is administered at a threshold FiO_2 of 0.3 - 0.4 compared with allowing the FiO_2 to rise above 0.4 before the surfactant is administered.

Patients and methods

The study was performed at the Neonatal Intensive Care Unit, Groote Schuur Hospital, from January to November 2006.

Preterm infants (age 0.5 - 24 hours, gestation 28 - 35 weeks, birth weight ≥900 g) with a diagnosis of RDS, requiring NCPAP ≥5 cm of water and FiO_2 of 0.3 - 0.4, were recruited. The FiO_2 was adjusted to maintain oxygen saturation (SaO_2) at 88 - 94%. The diagnosis of RDS was based on the combination of respiratory distress, typical X-ray findings and absence of sepsis at birth.

Infants presenting with any of the following were excluded: signs of significant fetal hypoxia (Apgar score <3 at 5 minutes) or umbilical arterial base deficit ≥16; prolonged rupture of membranes (>3 weeks); congenital sepsis; pneumothorax before recruitment; pre-existing grade 3 or 4 periventricular leucomalacia;[4] or grade 3 or 4 intraventricular haemorrhage.[5] Infants who had received surfactant before the time of

randomisation were also excluded.

Infants were randomised into either a low- or high-threshold treatment group by blindly drawing cards out of an envelope. The low-threshold group received porcine surfactant 100 mg/kg immediately after randomisation, and the high-threshold group only received porcine surfactant 100 mg/kg if their FiO_2 requirement rose above 0.4. The surfactant was administered intra-tracheally and the infants were subsequently extubated and again received NCPAP if respiratory effort was adequate within 10 minutes.

The intubation and extubation procedures were as follows: reversible analgesia 1 - 2 minutes before intubation was provided with intravenous (IV) morphine 0.1 mg/kg, as used in similar studies.[3] This dose was repeated if adequate sedation was not obtained.[6] The additional use of IV suxamethonium 1 - 2 mg/kg and IV atropine 15 µg/kg was left to the discretion of the attending doctor. After surfactant administration and before extubation, IV naloxone 0.04 mg/kg was given to reverse the morphine, followed by intramuscular (IM) naloxone 0.06 mg/kg. An immediate effect is obtained from the IV dose and a prolonged effect is obtained with the IM dose to maintain the reversal for the duration of the half-life of morphine, which can be up to 12 hours in a preterm infant. The total cumulative dose of naloxone was 0.1mg/kg.

After instillation of exogenous surfactant, infants were ventilated with a self-inflating resuscitation bag (Laerdal, Victoria, Australia) until the return of adequate spontaneous respiratory effort, as judged by the attending clinician. If regular respiratory effort was not established within 10 minutes of surfactant instillation, or if the infant subsequently met criteria for MV, extubation did not occur at that time and MV was continued.

The criteria for continuing MV or re-intubating an infant after treatment with surfactant were any one of the following: arterial to alveolar oxygen tension ratio (a/APO_2) <0.22 if an arterial line was available; FiO_2 >0.55 to maintain SaO_2 at 88 - 94%; recurrent apnoea requiring mask ventilation; respiratory acidosis with pH <7.25; or excessive work of breathing judged clinically.

All infants received routine care and NCPAP was provided using an Infant Flow Driver (Electro Medical Equipment Ltd, East Sussex, England).

The study was approved by the University of Cape Town Human Research Ethics Committee. Prior to this study, the specific FiO_2 threshold for surfactant administration in this group of infants varied between specialists – from 0.3 to 0.5. Because both interventions were within the current standard of care and mothers were frequently unavailable for consent soon after delivery, the Ethics Committee approved obtaining retrospective parental consent for the infants to continue in the study and for researchers to use the data.

Surfactant administration resulted in a greater reduction in duration of assisted ventilation if an FiO_2 administration threshold of 0.3 was used rather than 0.4.

Sample size and statistical analysis

The primary outcome was the need for MV, or death, in the first 7 days of life. Verder *et al.*'s data showed MV rates of 21 - 67% when porcine surfactant was administered at FiO_2 thresholds of 0.37 - 0.77 to infants of <30 weeks' gestation.[3] Our clinical experience with infants at 28 - 35 weeks' gestation was an overall MV rate of 25% when porcine surfactant was administered at variable FiO_2 thresholds ranging from 0.3 to 0.6, but MV was generally not required when porcine surfactant was administered within the first day at a threshold FiO_2 of 0.3. We therefore estimated that there would be a reduction in the incidence of death or the need for MV from 35% in the high-threshold group to 10% in the low-threshold group. Assuming a power of 80% and a significance level (type I error) of 5% (two-tailed), sample size calculation tables[7] predicted that 51 infants per group would be needed. However, in light of the uncertainty of actual MV rates, interim analysis was pre-planned after the first 25 patients.

We anticipated that the sample would be recruited within a 12-month period, based on the number of infants who required NCPAP in the previous year in our unit. However, the narrow FiO_2 recruitment criteria and the requirement to recruit within the first 24 hours resulted in slower recruitment than had been anticipated. After 10 months, only 25 infants met the recruitment criteria and, when the sample size was re-calculated using the recorded MV rates in the first 25 infants, the required sample was 134 infants per group. The study was therefore terminated and converted to a pilot study because it would not have been possible to complete recruitment within 12 months. A final analysis was carried out that included 2 more infants who had been recruited in the interim.

The following secondary outcomes were recorded during the first week of life: duration of any assisted ventilation (NCPAP and MV); arterial partial pressure carbon dioxide ($PaCO_2$) at 24 hours (as an indication of alveolar ventilation); and haemodynamically significant patent ductus arteriosus (PDA). The outcomes measured during the entire hospital stay were: severe (grade 3 or worse) intraventricular haemorrhage[5] or periventricular leucomalacia;[4] necrotising enterocolitis (NEC) defined as modified Bell's stage 2a or worse;[8] suspected sepsis (defined as symptoms suggestive of sepsis with a C-reactive protein progressively rising above 10 mg/l or a positive blood culture); oxygen dependency at 28 days; length of hospital stay; and death before discharge from hospital.

Data were analysed using Stata software version 10 (Statacorp, College Station, Texas, USA). Parametric data were analysed with the two-tailed Student's *t*-test or the one-tailed Student's *t*-test if testing for change in one direction, and were expressed as mean ± standard deviation (SD). Non-parametric data were analysed with the Wilcoxon rank sum test and were expressed

as median (range). Categorical data were analysed with Fisher's exact test or the chi-square test, depending on expected values. Statistical significance was assumed at $p<0.05$.

Results

The characteristics of the infants studied are shown in Table I. At recruitment, there was a higher $PaCO_2$ ($p=0.055$), but a lower FiO_2 requirement ($p=0.072$) in the high-threshold group. The mean birth weight for the entire cohort was 1 350±306 g and the mean gestational age was 31±2 weeks.

The outcomes during the first week of life are shown in Table II. Twice as many infants required MV in the high-threshold group, but only 6 infants (22%) in the entire cohort needed MV. The individual durations of MV and NCPAP were less in the low-threshold group, but the difference was not significant. However, there was a significant reduction in assisted ventilation (combined duration of NCPAP and MV) during the first week of life in the low-threshold group ($p=0.042$). Fig. 1 shows how the difference between groups varied with time, and by age 7 days the difference was no longer significant ($p=0.069$). The low-threshold group also had a significantly lower $PaCO_2$ at 24 hours ($p=0.015$).

Outcomes during the entire hospital stay are shown in

TABLE I. CHARACTERISTICS OF INFANTS STUDIED

Characteristic	High threshold (*N*=14)	Low threshold (*N*=13)	Statistical test	*p*
Birth weight (g) (SD)	1 270 (233)	1 435 (359)	2TT	0.17
Gestational age (w) (SD)	31 (2)	32 (2)	2TT	0.14
Male gender (%)	8/14 (57)	7/13 (54)	FE	1.00
Apgar score at 5 min (range)	9 (6 - 9)	9 (6 - 9)	WRS	0.51
Maternal GPH (%)	8/14 (57)	9/13 (69)	FE	0.70
Idiopathic preterm labour (%)	4/14 (29)	3/13 (23)	FE	1.00
Pre-labour rupture of membranes (%)	2/14 (14)	0/13 (0)	FE	0.48
Antepartum haemorrhage (%)	2/14 (14)	1/13 (8)	FE	1.00
Caesarean delivery (%)	10/14 (71)	11/13 (85)	FE	0.65
Maternal HIV+ (%)	1/14 (8)	3/13 (23)	FE	0.59
Two doses antenatal steroids (%)	7/14 (50)	9/13 (69)	Chi2	0.31
Age at recruitment (h) (range)	6.5 (1 - 24)	4 (1.5 - 18)	WRS	0.54
$PaCO_2$ at recruitment (range)	7.3 (4.75 - 7.5)	5.86 (3.83 - 8.2)	WRS	0.055
FiO_2 at recruitment (SD)	0.33 (0.03)	0.36 (0.04)	2TT	0.072
FiO_2 before surfactant (SD)	0.45 (0.05)	0.36 (0.04)	2TT	<0.001

FE = Fisher's exact test; GPH = gestational proteinuric hypertension; 2TT = Two-tailed Student's *t*-test; WRS = Wilcoxon rank sum test.

TABLE II. OUTCOMES IN FIRST WEEK OF LIFE

Outcome	High threshold (*N*=14)	Low threshold (*N*=13)	Statistical test	*p*
MV (%)	4/14 (29)	2/13 (15)	FE	0.65
Duration MV (h) (mean, median, range)	16.5; 0; 0 - 89	3.5; 0; 0 - 6	WRS	0.32
Duration of NCPAP (h) (SD)	74.1 (43.3)	53.3 (44.4)	1TT	0.11
Duration of any form of assisted ventilation (h) (SD)	91 (50)	57 (47)	1TT	0.042
$PaCO_2$ in kPa at 24 h (range)	7.31 (4.96 - 7.37)	5.5 (3.68 - 7.35)	2TT	0.015
Pneumothorax after recruitment (%)	1/14 (7)	0/13 (0)	FE	1.00
Significant patent ductus arteriosus (%)	8/14 (57)	5/13 (38)	Chi2	0.33
Number of infants requiring a second dose	1/14 (7)	1/13 (8)	FE	1.00
Number of infants requiring any surfactant	8/14 (57)	13/13 (100)	FE	0.016
Doses surfactant per infant (range)	1 (0 - 2)	1 (1 - 2)	WRS	0.027

FE = Fisher's exact test; 1TT = One-tailed Student's *t*-test; 2TT = Two-tailed Student's *t*-test; WRS = Wilcoxon rank sum test.

TABLE III. OUTCOMES DURING HOSPITAL STAY

Outcome	High threshold (*N*=14)	Low threshold (*N*=13)	Statistical test	*p*
Death	0	0	-	
Necrotising enterocolitis (%)	1/14 (7)	3/13 (23)	FE	0.33
Sepsis suspected (%)	5/14 (36)	5/13 (38)	FE	1.00
Severe IVH or PVL	0	0	-	
Oxygen-dependent at 28 days	0	0	-	
Hospital stay (d) (SD)	33 (4)	31 (5)	2TT	0.71

FE = Fisher's exact test; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; 2TT = Two-tailed Student's *t*-test.

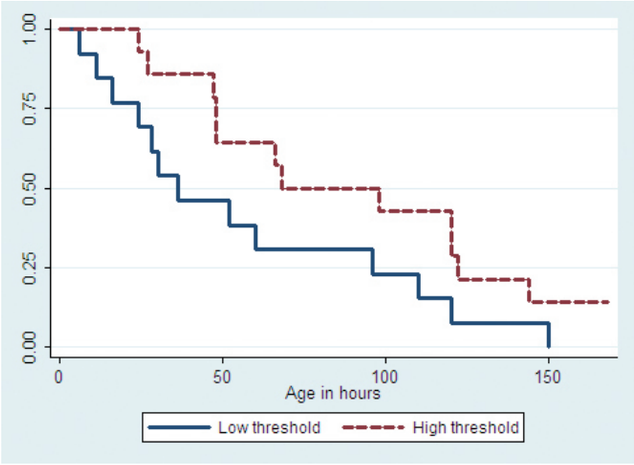

Fig. 1. Proportions of infants requiring any form of assisted ventilation (MV and/or NCPAP) during the first week of life.

Table III. All 13 infants in the low-threshold group received surfactant empirically, but only 8 of the 14 infants in the high-threshold group reached the intervention threshold and received surfactant. One infant from each group required repeat dosing. Fewer infants had a significant PDA in the low-threshold group and there were no pneumothoraces in this group, but these findings were not statistically significant. There were no significant differences in any of the other outcomes. Four infants (16.6%) in the entire study sample developed NEC. However, 3 of the 4 infants only had grade 2a NEC, and only 1 infant had severe disease. Suspected sepsis was diagnosed in 10 infants (37%) in the entire study sample, but blood culture-proven sepsis was diagnosed in only 3 infants. All of the enrolled infants survived and none developed bronchopulmonary dysplasia.

Discussion

The administration of 100 mg/kg porcine surfactant to preterm infants with RDS requiring NCPAP at a threshold FiO_2 of 0.3 - 0.4 reduced the duration of any form of assisted ventilation compared with waiting until the FiO_2 was above 0.4 before administering surfactant. The short duration of assisted ventilation in both groups shows the efficacy of both the low- and high-threshold approach and by age 7 days the difference was no longer significant. The sample size was too small to detect significant differences in the duration of either NCPAP or MV alone. The 22% MV rate in the whole cohort was similar to our previous estimate of 25%, but the differences between the groups were not as large as we had expected. However, the lower $PaCO_2$ at 24 hours in the low-threshold group suggests significantly improved alveolar ventilation after surfactant administration in this group. The higher $PaCO_2$ in the high-threshold group at recruitment may suggest relatively more compromised alveolar ventilation, but the lower FiO_2 at the time is consistent with less severe RDS than is indicated by the $PaCO_2$. It suggests that at recruitment there was no significant difference in severity of RDS between the groups. The low number of infants exposed to complete courses of antenatal steroids reflects the acute nature with which many mothers delivering in our setting present, and the high incidence of maternal gestational proteinuric hypertension is typical for our unit.

Signs of RDS increase significantly when the a/APO_2 ratio decreases below 0.36 (or FiO_2 increases above 0.37).[3,9] However, when Verder *et al.* administered porcine surfactant 200 mg/kg to infants at that threshold, the subsequent requirement for MV was reduced but the duration of NCPAP was not affected significantly.[3] Since those data were collected, evidence has accumulated that supports earlier extubation to NCPAP.[10,11] It shows the increasing preferred use of NCPAP to MV. Because many infants who receive MV may be adequately ventilated on NCPAP, we combined these two categories into one, termed assisted ventilation. The resultant increased hours of assisted ventilation in each group probably explains why we found a greater treatment effect in this combined category compared with MV or NCPAP alone.

The FiO_2 threshold of 0.3 for surfactant administration has been used in other studies on infants receiving NCPAP.[11,12] Dani *et al.*[11] electively administered porcine surfactant 200 mg/kg to infants <30 weeks' gestation who required FiO_2 ≥0.3 in the first 6 hours of life and randomised the infants to immediate extubation to NCPAP or conventional slow weaning on MV. In Dani *et al.*'s study, the group that was extubated immediately required significantly less MV and NCPAP. Only 2 of the 13 infants in the NCPAP group required MV in the first week. This is lower than the 21% incidence described by Verder *et al.* and is the same proportion as in our low-threshold group, despite the use of a lower surfactant dose of 100 mg/kg. Reininger *et al.*[12] randomised infants of 29 - 35 weeks' gestation to a low-threshold group receiving bovine surfactant (Survanta) 100 mg/kg at FiO_2 ≥0.3, followed by immediate extubation to NCPAP, or a control group who only received surfactant if they required MV for respiratory failure or apnoea. The threshold for surfactant administration in the low-threshold group in that study was subsequently lowered to 0.21 because of very slow recruitment. The incidence of subsequent MV was less in the low-threshold group than in the control group, but was relatively high in both groups at 50% and 70%, respectively.

The early elective administration of bovine surfactant 100 mg/kg to infants receiving NCPAP was also studied by the Texas Neonatal Research Group.[13] Infants with a birth weight ≥1 250 g, ≤36 weeks' gestation and FiO_2 of ≥0.4 were randomised to elective surfactant administration and expedited extubation or expectant management in the control group. The study found no significant advantage to early administration of bovine surfactant and the elective surfactant group had a significantly longer duration of assisted ventilation. However, it is difficult to compare this group with our study group as the mean birth weight in the two groups (2 068 g and 2 040 g, respectively) was significantly higher than that in our group, and 34% of the infants were not receiving oxygen via NCPAP at the time of randomisation.

Although a higher threshold for surfactant administration results in some infants not requiring surfactant at all, it is also associated with a longer duration of any form of assisted ventilation. However, the low rates of MV and reduction in duration of any form of assisted ventilation shown by Dani *et al.*[11] and ourselves probably have more benefit to the neonatal intensive care community of infants than to the individual infant. A reduction in duration of assisted ventilation of only 1 - 2 days per infant may result in a cumulative saving of 1 - 2 months of infant high care (or intensive care) days per year. The reduced time in high care may offset the cost of the additional doses of surfactant and may allow the bed space to be used for other infants. This issue is particularly relevant in a situation with perpetual shortages of beds, as in our own.

A Cochrane review,[14] which included the studies of Dani *et al.* and Reininger *et al.*, found that elective surfactant administration to infants at FiO_2 thresholds of ≤0.45 was

associated with less MV, a lower incidence of bronchopulmonary dysplasia, fewer air-leak syndromes and a lower incidence of PDA than that associated with higher thresholds. In our small sample, we were unable to demonstrate significant reductions in major morbidity, mortality or hospital stay in the low FiO_2 threshold group compared with the higher threshold group. However, the infants in our entire study sample achieved MV rates similar to or lower than those reported in other studies using a higher surfactant dose, and none of those in our study developed bronchopulmonary dysplasia.

The short hospital stays, the lack of oxygen dependence at 28 days, and the absence of severe cerebral morbidity suggest that administration of 100 mg/kg porcine surfactant to preterm infants with RDS receiving NCPAP is safe and beneficial. There was further limited benefit when an administration threshold of FiO_2 >0.3 was used rather than waiting until the FiO_2 rises above 0.4, but a larger study is required to confirm these findings and establish an accurate cost-benefit ratio.

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References

1. Ho JJ, Henderson-Smart DJ, Davis PG. Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2002(2): CD002975.
2. Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2002(2): CD002271.
3. Verder H, Albertsen P, Ebbesen F, *et al*. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics* 1999; 103: E24.
4. De Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992; 49: 1-6.
5. Wezel-Meijer G. *Neonatal Cranial Ultrasonography*. New York: Springer, 2007.
6. Lemyre B, Doucette J, Kalyn A, Gray S, Marrin ML. Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373]. *BMC Pediatr* 2004; 4: 20.
7. Fleiss J. *Statistical Methods for Rates and Proportions*. 2nd ed. Malden, MA USA: Wiley Interscience, 1981.
8. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. *Curr Probl Pediatr* 1987; 17: 213-288.
9. Gilbert R, Keighley JF. The arterial-alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis* 1974; 109: 142-145.
10. Tooley J, Dyke M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. *Acta Paediatr* 2003; 92: 1170-1174.
11. Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics* 2004; 113: e560-563.
12. Reininger A, Khalak R, Kendig JW, *et al*. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. *J Perinatol* 2005; 25: 703-708.
13. Escobedo MB, Gunkel JH, Kennedy KA, *et al*. Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter, randomized trial. *J Pediatr* 2004; 144: 804-808.
14. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007(4): CD003063.