



# Clinical History of Curosurf: From Composition to Comparative Trials

A review of strategic studies

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## INTRODUCTION

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Although the underlying cause of respiratory distress syndrome (RDS) was identified over four decades ago, it was not until the early 1990s that the first surfactants were approved for clinical use. During this time surfactant preparations underwent rigorous clinical testing. Poractant alfa (Curosurf®, Chiesi Farmaceutici), a natural porcine-derived surfactant, is one of the most extensively studied preparations having undergone a wide range of clinical trials. The purpose of the Curosurf Collection is to provide clinicians with reviews of strategic publications – from the first clinical trial to large-scale comparative, international trials – in an easy-to-use, accessible format. The Collection comprises publications spanning the period 1987-2004 and topics discussed include composition of poractant alfa, effects of dosage regimen and timing of administration on clinical outcomes, use of poractant alfa in combination with nasal continuous positive airway pressure as well as comparison studies on the efficacy and safety of natural and synthetic preparations.

These studies, including some of the largest trials performed in neonatology, demonstrate that poractant alfa decreases the severity of RDS, reduces pneumothorax, increases survival without lung disease and decreases mortality in infants with RDS. In the comparison trial by Ainsworth et al., the significantly lower mortality in neonates receiving poractant alfa compared with those on pumactant, resulted in the trial being stopped early. Furthermore, the recently published study by Ramanathan et al. demonstrated that poractant alfa at an initial dose of 200 mg/kg, allowed earlier weaning from supplemental oxygen, permitted less re-dosing and conferred a survival advantage in infants of  $\leq 32$  weeks, compared with beractant at an initial dose of 100 mg/kg.

Before a therapy becomes widely used and acceptable it should be both effective and safe. The publications reviewed in the Curosurf Collection provide testament to the efficacy and safety of poractant alfa and the increased survival rates among preterm infants treated with poractant alfa.

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# Structural and functional characterization of porcine surfactant isolated by liquid-gel chromatography

Robertson B, Curstedt T, Johansson J, et al.

*Progress in Respiration Research* 1990;25:237–246

## Background

Clinical differences observed in comparative trials with surfactants are attributed to the unique composition of natural surfactants. In this paper poractant alfa (Curosurf®, Chiesi Farmaceutici), a natural porcine surfactant with demonstrated safety and efficacy, is characterised.

## Aim

To review the structural and functional characteristics of poractant alfa.

## Composition

Poractant alfa, isolated from minced porcine lungs by a combination of washing, centrifugation, chloroform: methanol extraction and liquid-gel chromatography, contains approximately 99% polar lipids (mainly phospholipids) and 1% hydrophobic proteins (SP-B and SP-C) in molar proportions (1:3). Phosphatidylcholine (PC) is the predominant phospholipid (75%) and dipalmitoylphosphatidylcholine (DPPC) constitutes about 46% of this fraction, with phosphatidylglycerol (PG) making up 4%. The complete amino acid sequences of porcine SP-B (8.7kDa) and SP-C (3.7kDa) show the former consists of 79 residues with 8 half-cysteine residues and a total of 39% branched chain hydrophobic residues (mainly leucine and valine), while the latter consists of 35 amino acid residues (13 valine and leucine) and a middle region made up of branched chain hydrophobic residues.

## Surface properties

At 37°C, using the pulsating bubble technique, there was a critical concentration (range 3–5mg/mL) above which optimal activity was recorded and below which surfactant activity was unsatisfactory. Optimal surface properties were lost at a concentration of 10mg/mL and at temperatures <30°C. When surfactant is administered as prophylaxis to neonates it becomes mixed with fetal lung liquid before (or soon after) the onset of ventilation and there is evidence that the concentration of surfactant in this liquid (volume about 30mL/kg at birth) must exceed the critical level (3–5mg/mL) to ensure proper lung function.

## Physiological properties

When poractant alfa was instilled into the airways of newborn and control rabbits (ventilated using a standardised tidal volume of 10–12mL/kg), at least some immature newborn rabbits with a gestational age of 26.5 days could be ventilated for 60 minutes with adequate PCO<sub>2</sub>. Average values for lung-thorax compliance in poractant alfa-treated and control animals were 0.55 and 0.35mL/cm H<sub>2</sub>O.kg, respectively. Poractant alfa did not cause deterioration of compliance in mature newborn animals. In addition, treatment with an adequate dose of poractant alfa promoted uniform alveolar expansion in the immature neonatal lung.

## Inactivation by serum proteins

In vitro activity of poractant alfa (10mg/mL) was reduced at protein concentrations >0.3mg/mL

while at concentrations  $>1\text{mg/mL}$  minimum surface tension remained  $>20\text{mN/m}$ . Poractant alfa was inhibited by lung oedema fluid from animals subjected to prolonged hyperoxia.

### **Immunogenicity of surfactant-associated proteins**

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Serum antibodies have not been detected in surviving infants treated with poractant alfa in the neonatal period. Circulating surfactant-ant surfactant immune complexes, detected in patients with neonatal RDS, do not seem to cause any harmful effects. Toxicological studies with

poractant alfa did not show any detrimental effects.

### **Lung defence system**

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In vitro studies indicate that poractant alfa may have a bacteriostatic effect at least against *Escherichia coli*. Short-term incubation (30 minutes) with low concentrations of poractant alfa stimulated phagocytosis and enhanced the metabolic burst of blood monocytes (part of the non-specific inflammatory response), but long-term incubation decreased the functional activity of phagocytic cells.

## Key points

- Poractant alfa, a natural surfactant isolated from pig lungs, is the only surfactant to undergo additional liquid-gel chromatography purification.
- Poractant alfa contains the hydrophobic proteins SP-B and SP-C, essential for the uniform spreading of the surfactant monolayer throughout the lung and in preventing the alveoli from collapsing at end-expiration.
- Bacteriological safety and the absence of immunological response have been demonstrated in vivo and in vitro.



# Severe neonatal respiratory distress syndrome treated with the isolated phospholipid fraction of natural surfactant

Noack G, Berggren P, Curstedt T, et al.

*Acta Paediatrica Scandinavica* 1987;76:697–705

## Background

The beneficial effects of surfactant replacement in patients with respiratory distress syndrome (RDS), first reported in 1980, resulted in the development of many new surfactant preparations. Poractant alfa (Curosurf®, Chiesi Farmaceutici), derived from porcine lungs, contains only polar lipids and the essential hydrophobic proteins (SP-B and SP-C). A pilot trial was conducted to determine the effects of poractant alfa in neonates with RDS.

## Aim

To investigate the effects of poractant alfa in newborn infants with severe RDS.

## Methods

In a non-randomised, pilot trial, 10 newborn infants (795–1680g) with severe RDS were treated with the isolated phospholipid fraction of bovine (n=7) or porcine surfactant (n=3).

Before receiving surfactants (dose 200mg/kg) all infants were on artificial ventilation (FiO<sub>2</sub> 0.60-1.00). Treatment with surfactant at a median age of 10.5 hours was in all cases an emergency procedure.

## Results

The arterial to alveolar oxygen tension ratio (a/APO<sub>2</sub>) increased from 0.10 to 0.35 within 2 hours of surfactant administration. There was a concomitant improvement in lung aeration on chest roentgenograms and a significant reduction in right-to-left shunt. Four infants died of cerebral haemorrhage; two of them also had a patent ductus arteriosus. One surviving infant developed bronchopulmonary dysplasia and another died of sudden infant death syndrome (SIDS) at eight months of age. No antibodies to surfactant were detected in survivors.

## Key points

- This pilot trial shows that neonatal RDS can be effectively treated with poractant alfa.
- The improvements in lung function and the lack of immunological complications provided the rationale for large-scale clinical trials with poractant alfa.

# Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial

Collaborative European Multicenter Study Group  
*Pediatrics* 1988;82:683–691

## Background

By the late 1980s there was good evidence that the incidence and severity of respiratory distress syndrome (RDS) could be reduced by prophylactic treatment with surfactant preparations. In addition, randomised trials in infants with established RDS indicated that surfactant treatment might be effective. These trials, however, enrolled small numbers of infants. This large, randomised multicentre trial was designed to investigate the efficacy of poractant alfa (Curosurf®, Chiesi Farmaceutici) in neonates with severe RDS.

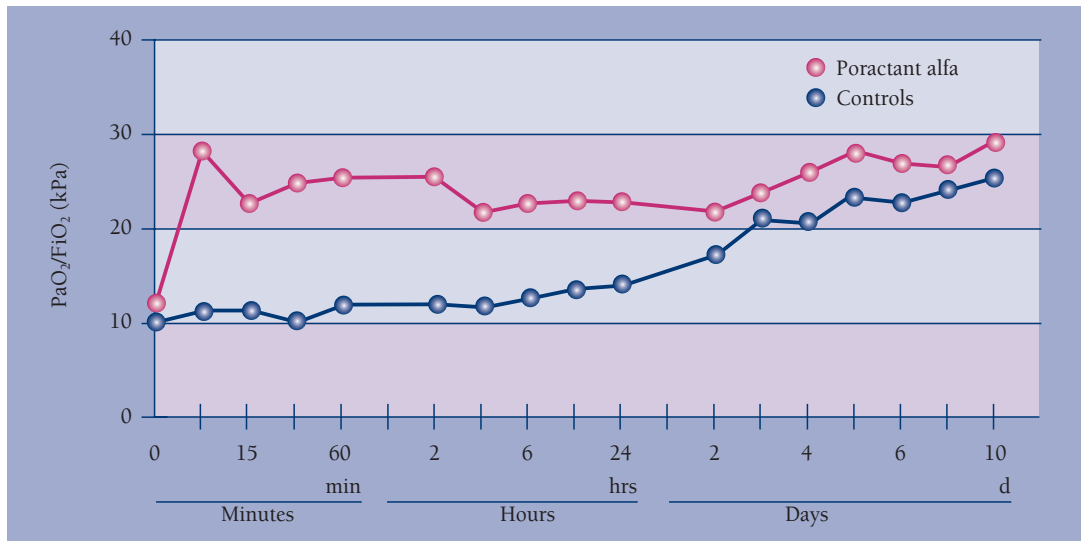
## Aim

To determine the effects of replacement therapy with poractant alfa in neonates with severe RDS.

## Methods

In a multicentre trial, neonates (birth weight 700–2000g) with clinical and radiological findings indicative of RDS who required artificial ventilation (fraction of inspired oxygen [FiO<sub>2</sub>] ≥0.60) and had no complicating disease were enrolled from eight European intensive care units. Infants were randomised to receive either a single large dose of poractant alfa (200mg/kg) at a median age of 9 hours (range 2–15) or

**Figure 1.** Alveolar oxygenation (PaO<sub>2</sub>/FiO<sub>2</sub> ratio) in poractant alfa and control infants at various intervals after randomisation



Time scale not linear and values generated from a population that became increasingly selected with time.

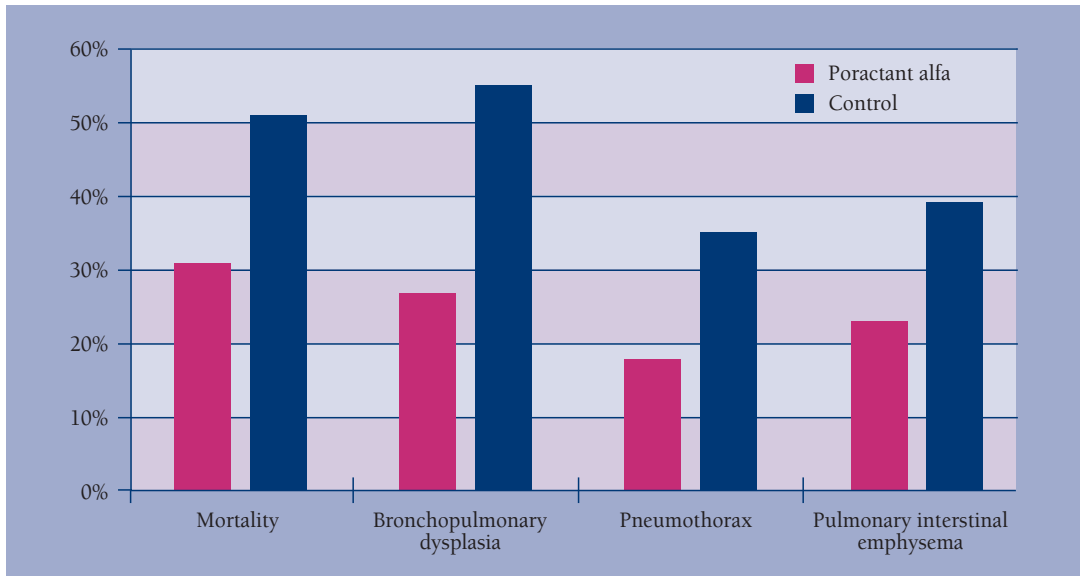
control therapy. Control infants did not receive placebo but were manually ventilated for 2 minutes. Mean FiO<sub>2</sub> before therapy was the same (0.80) in both groups.

## Results

Overall, 146 neonates were eligible for analysis (77 poractant alfa, 69 controls). Infants receiving poractant alfa showed a rapid improvement of oxygenation, as reflected by the increase in mean partial pressure of arterial oxygen (PaO<sub>2</sub>) from 57 to 148mmHg (7.5 to 19.5 kPa) within 5 minutes of treatment and a nearly threefold increase in PaO<sub>2</sub>/ FiO<sub>2</sub> ratio [Figure 1]. Six hours after randomisation, PaO<sub>2</sub>/

FiO<sub>2</sub> ratio still showed a 98% improvement in poractant alfa-treated infants compared with controls (p<0.001), and significant differences in favour of treatment persisted until 48 hours after randomisation. Treatment with poractant alfa significantly decreased neonatal mortality (≤ 28 days) from 51 to 31% compared with controls (p<0.05) [Figure 2]. The incidence of pulmonary interstitial emphysema and pneumothorax was significantly lower in the poractant alfa group (23 vs. 39%; p<0.05 and 18 vs. 35%; p<0.05). The percentages of survivors without bronchopulmonary dysplasia were 55 and 26% (p<0.001) in the poractant alfa and control groups, respectively.

Figure 2. Mortality and complications (%) in poractant alfa and control infants 28 days from birth



## Key points

- Poractant alfa treatment improves lung function and short-term outcome in infants with severe RDS.
- Treatment with a single dose of poractant alfa reduces neonatal mortality by 40% and the incidence of pneumothorax by half.
- This study was the first to show improved survival with surfactant therapy.



# Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf

Speer CP, Robertson B, Curstedt T et al.  
*Pediatrics* 1992;89:13–20

## Background

When this study was carried out the optimal therapeutic regimen remained to be defined. This study was designed to determine if the beneficial effects of poractant alfa (Curosurf®, Chiesi Farmaceutici), in infants with very severe RDS could be enhanced by using additional smaller doses in infants with a suboptimal response or those showing relapse.

## Aim

To compare the effects of single and multiple doses of poractant alfa in neonates with severe RDS.

## Methods

In a randomised, European multicentre trial, neonates (birth weight 700-2000g) with severe RDS requiring mechanical ventilation (fraction of inspired oxygen [ $FiO_2$ ]  $\geq 0.60$ ) were randomised (aged 2–15 hours) to receive either single dose therapy with poractant alfa (200mg/kg) or multiple dose therapy [Table 1]. Single dose poractant alfa was administered immediately after randomisation, while multiple dose therapy (two additional doses of 100mg/kg each) was administered 12 and 24 hours after the initial dose provided patients still needed artificial ventilation with  $FiO_2 > 0.21$ .

## Results

A total of 343/357 infants randomised (176 single dose, 167 multiple) were evaluable for

analysis. In both groups there was a rapid improvement in oxygenation, as reflected by a three-fold increase in arterial to alveolar oxygen tension ratio ( $a/APO_2$ ) within 5 minutes of poractant alfa administration ( $p < 0.001$ ).

**Table 1.** Patient characteristics on entry and outcome at 28 days of age

	Single dose (n = 176)	Multiple doses (n = 167)
<b>Characteristics</b>		
Gestation age (weeks)	29.2±2.5	28.3±2.5
Birth weight (g)	1218±327	1189±321
Males (%)	99 (56.3)	91 (54.4)
Age of treatment (hours)	6.00	6.70
$FiO_2$ at randomisation	0.83	0.90
<b>Complications</b>		
Mortality	37 (21%)	22 (13%)*
Pulmonary Interstitial emphysema	48 (27%)	38 (23%)
Pneumothorax	32 (18%)	15 (9%)*
Bronchopulmonary dysplasia	21 (12%)	22 (13%)
Intraventricular haemorrhage		
Total	75 (43%)	71 (43%)
Grade I-II	41 (23%)	33 (20%)
Grade III-IV	34 (20%)	38 (23%)
Patent ductus arteriosus	91 (52%)	93 (57%)

\*  $p < 0.05$  \*\*  $p < 0.01$  (multiple logistic regression)

As a consequence the  $FiO_2$  could be lowered within 15 minutes from 0.85 to 0.35 in the single dose group and from 0.90 to 0.40 in the multiple dose group. Between 24 hours and 3 days neonates treated with multiple dose needed

less oxygen compared with those in the single dose group ( $p < 0.001$  at 24 and 48 hours;  $p < 0.05$  at day 3). Of the 167 patients in the multiple dose group, 58 (35%) required one additional dose, 42 (25%) required two and 67 (40%) needed three doses. In the single dose group, 120/176 (68%) would have qualified for additional doses. Short-term (0–28 days) outcome data showed a reduction in the incidence of pneumothorax in the multiple dose

group (9% vs. 18%  $p < 0.01$ ) [Table 1]. The combined incidence of mortality and bronchopulmonary dysplasia (the primary endpoint) was significantly reduced in neonates receiving multiple compared with single dose therapy (27 vs. 33%,  $p < 0.08$ ). Mortality at 28 days was reduced from 21% in the single dose group to 13% in neonates receiving multiple dose therapy ( $p < 0.05$ ).

### Key points

- Treatment with multiple doses of poractant alfa is more effective than single doses in severe neonatal RDS.
- Multiple doses of poractant alfa further reduced ventilatory requirements, pneumothorax and mortality.
- Multiple-dose administration of poractant alfa may increase the pool size of alveolar surfactant lipids available for recycling during the recovery phase of the disease.



# Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf 4 trial)

Halliday HL, Tarnow-Mordi WO, Corcoran JD, Patterson CC on behalf of the European Collaborative Multicentre Study Group

*Archives of Disease in Childhood* 1993;69:276–280

## Background

Well-designed, randomised trials have shown that surfactant treatment lowers the incidence of pulmonary interstitial emphysema and pneumothorax and increases survival in neonates treated at birth (or later) when signs of respiratory distress syndrome (RDS) have developed. Furthermore, it has been shown that a single dose of poractant alfa (200mg/kg; Curosurf<sup>®</sup>, Chiesi Farmaceutici) reduces mortality and the incidence of pneumothorax, and that multiple doses (2 additional doses of 100mg/kg) further reduce mortality and pneumothorax. This study compared the efficacy of two regimens of multiple doses of poractant alfa in preterm infants with RDS.

## Aim

To determine if a maximal cumulative dose of poractant alfa (300mg/kg) administered in up to three doses over 24 hours is as effective as a total dose of up to 600mg/kg administered in up to five doses over 72 hours.

## Methods

In a randomised trial involving 82 centres in 13 countries, preterm infants aged <72 hours with clinical and radiological diagnosis of RDS and arterial to alveolar oxygen tension ratio ( $a/APO_2$ ) <0.22 were enrolled. Infants were randomised to receive either low dose poractant alfa (100mg/kg initially with two further doses at 12 and 24 hours up to a maximum dose of

300mg/kg) or high dose poractant alfa (200mg/kg initially with up to four further doses of 100mg/kg up to a maximum of 600mg/kg).

## Results

A total of 2168 infants were randomised to receive either low dose (n=1069) or high dose (n=1099) poractant alfa [Table 1]. There were no significant differences between the low and high dosage groups in the three primary outcomes: rates of death or oxygen dependence at 28 days (51.1 vs. 50.8%; difference -0.3%; 95% confidence interval [CI] -4.6–3.9%) death at any time before hospital discharge (25 vs. 23.5%, difference -1.5%; 95% CI -5.1–2.2%) and death or oxygen dependence at the expected date of delivery (32.2 vs. 31.0%, difference -1.2%; 95% CI -5.2–2.7%) [Table 2]. There were 74 (40 in the low and 34 in the high dose group) cases of protocol deviations, and four (1 low, 3 high dose) did not have RDS or could not be traced. Primary outcomes remained unchanged when these infants were excluded. Only 1/14 prespecified secondary outcome measures showed significant differences between the two groups, with 48.4% of infants in the low dosage group requiring >40% oxygen after 3 days compared with 42.6% of those in the high dose group ( $p<0.01$ ). Infants in the low dose group received a mean (SD) of 2.4 (0.8) doses of surfactant (242mg phospholipid/kg) compared with 2.8 (1.5) doses (380mg phospholipid/kg) in the high dose group.

Table 1. Characteristics of patients on entry

	Low dose poractant alfa (n = 1069)	High dose poractant alfa (n = 1099)
Mean (SD) gestation (weeks)	29.4 (3.1)	29.3 (3.2)
Mean (SD) birth weight (g)	1390 (604)	1358 (606)
Males (%)	619/1069 (57.9)	629/1099 (57.2)
Age at randomisation (hours)		
Median	6	6
No. of infants	1043	1069
FiO <sub>2</sub>		
Mean (SD)	0.77 (0.18)	0.76 (0.19)
No. of infants	1044	1067
PaO <sub>2</sub> (kPa)		
Mean (SD)	7.4 (2.5)	7.4 (2.4)
No. of infants	1041	1060
a/APO <sub>2</sub> (kPa)		
Mean (SD)	0.12 (0.05)	0.12 (0.06)
No. of infants	1037	1054

FiO<sub>2</sub> = fraction of inspired oxygen; PaO<sub>2</sub> = partial pressure of oxygen; a/APO<sub>2</sub> = arterial to alveolar oxygen tension ratio

Table 2. Primary outcome measures in infants receiving low and high dose poractant alfa (values are numbers [%\*])

	Low dose (n = 1069)	High dose (n = 1099)
Status at 28 days		
Alive, no oxygen	517 (48.9)	533 (49.2)
Oxygen dependent	317 (30.0)	332 (30.7)
Dead	224 (21.1)	218 (20.1)
Not known	11	16
Status at discharge		
Alive	797 (75.0)	834 (76.5)
Dead	265 (25.0)	256 (23.5)
Not known	7	9
Status at expected date of delivery		
Alive, no oxygen	710 (67.8)	736 (69.0)
Oxygen dependent	89 (8.5)	87 (8.2)
Dead	248 (23.7)	249 (22.8)
Not known	13	24
>37 weeks	9	9

\*Percentages calculated after excluding >37 weeks' gestation and 'not known' categories

## Key points

- Low dose poractant alfa was as effective as high dose poractant alfa in the treatment of infants with severe RDS.
- For poractant alfa, an average total dose of 242mg/kg was as good as 380mg/kg and was probably enough to replace the total pool of surfactant phospholipids in the neonatal lung.
- The authors suggest that considerable cost savings could result from the use of a low dose poractant alfa regimen.



# Randomized multicentre trial of treatment with porcine natural surfactant for moderately severe neonatal respiratory distress syndrome

Bevilacqua G, Halliday HL, Parmigiani S, Robertson B on behalf of the Collaborative European Multicentre Study Group

*Journal of Perinatal Medicine* 1993;21:329–340

## Background

Despite the efficacy of surfactants in neonates with respiratory distress syndrome (RDS), complications such as intraventricular haemorrhage (IVH) and bronchopulmonary dysplasia (BPD) are not consistently reduced by surfactant therapy. Multiple regression analysis of data from previous trials show that high fraction of inspired oxygen (FiO<sub>2</sub>) and ventilator requirements on entry were associated with a less favourable response, suggesting that rescue should be given before serious clinical deterioration has occurred. This trial was conducted to compare the effects of treatment with poractant alfa (Curosurf®, Chiesi Farmaceutici) in infants with moderately severe RDS ('early treatment') with those of 'late treatment' administered to infants with advanced disease.

## Aim

To compare the effects of poractant alfa in the treatment of moderately severe RDS with those of poractant alfa given at a more advanced stage of the disease.

## Methods

Newborn infants (mean gestational age 29.8

weeks) requiring mechanical ventilation (MV) for RDS and with a fraction of inspired oxygen (FiO<sub>2</sub>) in the range of 0.40–0.59 were randomised to receive either immediate ('early') treatment with poractant alfa (200mg/kg) or to a control group who were eligible to receive a single dose of poractant alfa (200mg/kg) if FiO<sub>2</sub> increased  $\geq 0.60$  within 48 hours ('late' treatment).

## Results

Out of a total of 188 infants randomised, 182 (86 'early' and 96 controls) were evaluable for analysis. According to the protocol 49 (51%) infants in the control group qualified for 'late' surfactant treatment at a FiO<sub>2</sub> requirement of  $\geq 0.60$ . In both groups, poractant alfa administration caused a rapid improvement of oxygenation but the peak value of partial pressure of arterial oxygen and the variability of response tended to be lower in infants in the early treatment group. Infants who received immediate treatment with poractant alfa had a lower incidence of grade III–IV IVH (7 vs. 18%,  $p < 0.05$ ), lower mortality (9 vs. 23%,  $p < 0.05$ ) and a lower incidence of unfavourable outcome, defined as death or BPD (18 vs. 34%,  $p < 0.05$ ) at 28 days. There were also significant reductions in time on oxygen  $> 21\%$  and time on MV.

## Key points

- Poractant alfa treatment when RDS is moderately severe prevented or reversed the natural progression of the disease and lowered the risk of complications.
- Treatment with poractant alfa was associated with reduced mortality and lower incidence of severe IVH.
- Poractant alfa reduced the duration of oxygen therapy and intermittent positive pressure ventilation in early-treated infants who were more likely to survive without BPD.

# Mortality, severe respiratory distress syndrome, and chronic lung disease of the newborn are reduced more after prophylactic than after therapeutic administration of the surfactant Curosurf

Egberts J, Brand R, Walti H et al.

*Pediatrics* 1997;100:e4 (<http://www.pediatrics.aappublications.org/cgi/content/full/100/1/e4>)

## Background

Prophylactic surfactant replacement for preterm neonates at high risk of developing respiratory distress syndrome (RDS) has a number of potential advantages:

- Facilitation of initial lung aeration
- Improved distribution of surfactant at the air–lung interface
- Decreased barotrauma and alveolar-capillary leakage of inhibitory serum proteins.

## Aim

To test the hypothesis that prophylactic treatment with poractant alfa (Curosurf®, Chiesi Farmaceutici) improves survival and respiratory problems more than rescue treatment for preterm infants of gestational age <31 weeks.

## Methods

A meta-analysis of three randomised trials conducted in four countries (Sweden, The Netherlands, Italy and France) was performed. [1-3] The combined trials enrolled infants of gestational age <31 weeks (26–30 weeks in the Dutch-Swedish study, 26–30 in the French study and 24–30 in the Italian study) and compared the effects of poractant alfa prophylaxis (n = 345) with that of rescue treatment (n = 326) [Table 1]. Outcome variables were severe RDS, neonatal mortality and chronic lung disease (CLD). The random-effects logistic model (accounting for the trial-within-country structure) was applied and adjusted for imbalances of covariates.

Table 1. Summary of treatment protocols for the three trials

Trial	Dutch-Swedish <sup>1</sup> (n = 75)	French <sup>2</sup> (n = 134)	Italian <sup>3</sup> (n = 136)
<b>Prophylaxis</b>			
Time after birth	< 10 minutes	< 15 minutes	< 10 minutes
Dose (mg/kg)	200	100	200
Retreatment if	RDS, IPPV and FiO <sub>2</sub> ≥ 0.60	PaO <sub>2</sub> /FiO <sub>2</sub> < 20kPa at MAP = 8 cm H <sub>2</sub> O	RDS and IPPV irrespective of the FiO <sub>2</sub>
Maximal total dose (mg/kg)	400	400	400
<b>Rescue</b>	(n = 72)	(n = 122)	(n = 132)
Intubation at birth	Yes	No	No
Time after birth	6–24 hours and FiO <sub>2</sub> ≥ 0.60	RDS and IPPV at 3–18 hours and PaO <sub>2</sub> / FiO <sub>2</sub> <20 kPa at MAP = 8 cm H <sub>2</sub> O	RDS and IPPV within 24 hours irrespective of the FiO <sub>2</sub>
Dose (mg/kg)	200	100	200
Retreatment	No	6 hours after first dose and thereafter at 12-hour intervals	No
Maximal total dose (mg/kg)	200	400	200

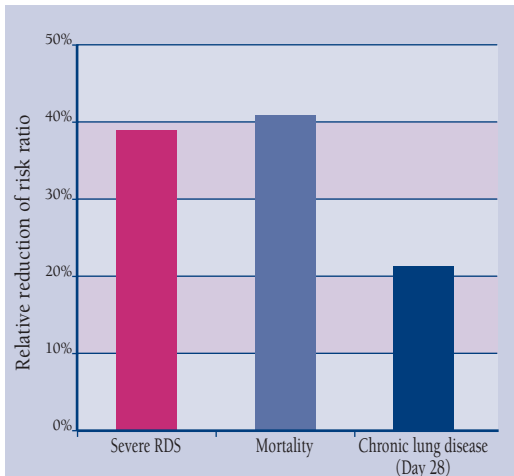
RDS, respiratory distress syndrome; IPPV, intermittent positive pressure ventilation; FiO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of arterial oxygen; MAP, mean arterial pressure

## Results

Mean gestational ages and body weights in the combined trials were 28.3 ( $\pm$  1.7) and 28.0 ( $\pm$  1.7) wk and 1093 ( $\pm$  296) and 1084 ( $\pm$  299) g in the prophylaxis and rescue groups, respectively. The incidence of radiologically and/or clinically diagnosed severe RDS (grade III–IV) at 6 hours after birth was 31.6% in the rescue group and 20% in the prophylaxis group. The relative reduction of risk ratio (RRR) was 37% and odds ratio (OR) was 0.55 (95% confidence interval [CI] 0.38–0.79,  $p=0.001$ ) [Figure 1]. Mortality was reduced in all three trials, resulting in an increased percentage of survivors when comparing prophylaxis (84.9%) with rescue treatment (74.5%). The RRR for

mortality was 41% (OR ie 0.52, 95% CI 0.35–0.76;  $p<0.001$ ). The incidence of CLD at day 28 in the group of prophylactically-treated survivors was lower compared with survivors in the rescue group (24.4 vs. 37%; RRR 23%, OR 0.67 [95% CI 0.45–1.00],  $p<0.05$ ). Gender, birth weight, gestational age and prenatal administration of glucocorticoids were significant confounding variables, with males more likely to develop RDS than females ( $p<0.001$ ). The rate of severe RDS decreased significantly in neonates with higher birth-weight/gestational age. Prenatal administration of glucocorticoids resulted in a lowering of the OR for mortality and RDS but had no effect on the incidence of CLD.

**Figure 1.** Relative reduction of risk ratio (%) of prophylaxis over rescue therapy in mortality, severe respiratory distress syndrome (RDS) and chronic lung disease



## Key points

- Prophylactic administration of poractant alfa has significant advantages over rescue therapy for infants of gestational age < 31 weeks.
- Survival increased and the incidence of severe RDS and CLD decreased at 28 days after birth.

## References

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2. Walti H, Paris-Llado J, Breart G et al. Acta Paediatrica 1995;84:913–921.
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# Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome

Verder H, Robertson B, Greisen G et al. for the Danish-Swedish Multicenter Study Group  
*New England Journal of Medicine* 1994;33:1051–1055

## Background

Early continuous positive airway pressure (CPAP) can delay or arrest the progression of neonatal respiratory distress syndrome (RDS). Following two pilot trials with encouraging results, a multicentre study was designed to investigate whether early nasal CPAP (started at the first signs of respiratory distress) in combination with poractant alfa (Curosurf®, Chiesi Farmaceutici) administered during a short intubation, could halt the progression of RDS, reduce the need for mechanical ventilation (MV) and improve outcomes in newborn infants.

## Aim

To investigate the efficacy of nasal CPAP in combination with poractant alfa in reducing the subsequent need for MV in neonates with moderate-to-severe RDS.

## Methods

This multicentre trial involving 11 neonatal intensive care units in Denmark and Sweden enrolled neonates (gestational age 25–35 weeks, aged 2–72 hours) with clinical and radiological

evidence of RDS, a requirement for nasal CPAP ( $\geq 6$  cm H<sub>2</sub>O) and an arterial to alveolar oxygen tension ratio ( $a/APO_2$ )  $< 0.22$ . Infants were randomised to receive poractant alfa (200 mg/kg) plus nasal CPAP or CPAP alone (controls). Endpoints were the percentage of patients requiring MV (primary endpoint) and the  $a/APO_2$  ratio (secondary endpoint). Indications for MV were an  $a/APO_2$  ratio of  $< 0.15$ , severe apnoeic attacks or both.

## Results

An interim analysis, conducted after 54 infants had been randomised, showed significant benefits for those treated with poractant alfa and CPAP and the trial was stopped. In total 68/73 infants randomised were available for analysis (35 treated with poractant alfa and 33 controls). Six hours after randomisation when the median age of the infants was 18 hours, the mean  $a/APO_2$  was 0.37 in poractant alfa treated infants and 0.25 in controls ( $p < 0.001$ ). The need for subsequent MV was significantly reduced in infants treated with poractant alfa compared with controls (43 vs. 85%,  $p < 0.003$ ) [Table 1].

**Table 1.** Effects of treatment with poractant alfa plus CPAP versus CPAP alone (controls)

	Poractant alfa (n = 35)	Controls (n = 33)	p-value
Need for mechanical ventilation n (%)	15 (43)	28 (85)	0.003
$a/APO_2$ ratio after 6 hours (mean $\pm$ sd)	0.37 $\pm$ 0.15	0.25 $\pm$ 0.10	$< 0.001$

The predominant reasons for use of MV were an  $a/APO_2 < 0.15$  in controls (21/28) and apnoea in poractant alfa-treated infants (10/15) ( $p=0.02$  for the difference). When the 17 infants (8 assigned to poractant alfa and 9 to control therapy) with  $a/APO_2$  ratios  $< 0.15$  at randomisation were excluded from the analysis, the need for subsequent MV was still significantly reduced by surfactant treatment (9/27, 33% in the treated group vs. 20/24, 83% in controls,  $p < 0.001$ ). After 28 days, two of the surfactant-treated infants had died compared with five of the control infants [Table 2]. Multiple regression analysis showed there was a trend towards better outcomes in infants with higher birth weights and infants randomised earlier.

Table 2. Outcomes at 28 days of life

Outcome	Surfactant group (n = 35)	Control group (n = 33)
Death	2 (6)	5 (15)
Intracerebral haemorrhage at day 7		
Grade 1 or 2	5 (14)	3 (9)
Grade 3 or 4	3 (9)	5 (15)
Death or survival with intracerebral hemorrhage grade 3 or 4	4 (11)	9 (27)
Periventricular leukomalacia	0	1 (3)
Pneumothorax	1 (3)	2 (6)
Pulmonary haemorrhage	0	2 (6)
Oxygen required at 28 days	3 (9)	3 (9)
Patent ductus arteriosus*	13 (37)	6 (18)
Necrotizing enterocolitis	0	0
Retinopathy of prematurity**	1 (3)	1 (3)

\* Treated

\*\* Treated with cryotherapy

## Key points

- Treatment with a single dose of poractant alfa in combination with CPAP reduces the need for MV in infants with moderate-to-severe RDS.
- Although the optimal therapeutic regimen has yet to be established, the authors recommend that surfactant is administered when the diagnosis of RDS is made but before serious deterioration has occurred.



# Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation

Verder H, Albertsen P, Ebbesen F et al.

*Pediatrics* 1999;103:e24 (<http://www.pediatrics.aappublications.org/cgi/content/full/103/2/e24>)

## Background

Infants with respiratory distress syndrome (RDS) who require mechanical ventilation (MV) and receive surfactant treatment early in their disease seem to do better than those treated late. There is evidence that poractant alfa (Curosurf®, Chiesi Farmaceutici), in combination with nasal continuous positive airway pressure (CPAP) further reduces the need for MV in neonates with RDS. This study was conducted to determine whether early versus late treatment with poractant alfa reduces the requirement for MV in very preterm infants primarily supported by nasal CPAP.

## Aim

To determine if early poractant alfa plus nasal CPAP reduces the need for MV in newborn infants of <30 weeks' gestation.

## Methods

In a randomised, multicentre controlled trial,

infants of <30 weeks' gestation with RDS and an arterial to alveolar oxygen tension ratio ( $a/APO_2$ ) of <0.35 (when decreased over a period of >30 minutes) were randomised to receive either a single dose of poractant alfa (200mg/kg) immediately after randomisation (early treatment) or when  $a/APO_2$  had decreased further to a level of <0.22 for 30 minutes (late treatment).

## Results

The need for MV (and/or death) within 7 days was reduced from 63% in the late-treated infants to 21% in the early-treated group ( $p=0.0013$ ). Six hours after randomisation mean  $a/APO_2$  rose to 0.48 in early-treated infants compared with 0.36 in late-treated. The need for MV before discharge, was reduced from 68% in the late-treated group to 25% in those receiving early treatment. Increasing numbers of antenatal steroid doses also improved the outcome, especially in the early-treated group.

## Key points

- Early poractant alfa in combination with nasal CPAP significantly improves oxygenation and reduces the subsequent need for MV in infants of <30 weeks' gestational age with RDS.



# A 2-year follow up of babies enrolled in a European multicentre trial of porcine surfactant replacement for severe neonatal respiratory distress syndrome

Robertson B, Curstedt T, Tubman R et al. on behalf of the Collaborative European Multicentre Study Group

*European Journal of Pediatrics* 1992;151:372–376

## Background

Surfactant therapy significantly reduces mortality and the incidence of pulmonary air leaks and increases the number of infants who survive without bronchopulmonary dysplasia (BPD). The long-term effects of treatment are however not known – it is possible that disability might be increased and administration of foreign animal proteins may elicit immunological sequelae. To investigate the long-term effects of surfactant therapy, surviving infants from a multicentre European study<sup>[1]</sup> were prospectively followed-up for 2 years.

## Aim

To determine the long-term effects of poractant alfa (Curosurf®, Chiesi Farmaceutici), in infants enrolled in a European multicentre trial.

## Methods

In the initial trial, neonates (birth weight 700–2000g) aged 2–15 hours with RDS requiring artificial ventilation ( $FiO_2 \geq 0.60$ ), from eight European neonatal intensive care units were randomised to receive a single dose of poractant alfa (200mg/kg) at a median age of 9 hours (range 2–15) or control therapy (did not receive placebo but were manually ventilated for 2 minutes). Surviving infants from this trial were then followed-up at regular intervals according to the normal practice of each unit and infants were also examined in detail at 1 and 2 years corrected age. Histological studies were

conducted on lung sections taken from infants who did not survive the early post-natal period (age 0.5–28 days). Blood samples were taken from surviving infants (treated and controls) at 2 weeks, 3 weeks and 3 months to determine titres of both surfactant-anti-surfactant immune complexes and free serum antibodies to porcine surfactant.

## Results

Of the 146 infants enrolled in the initial trial (77 treated and 69 controls), 24 (31%) treated and 35 (51%) controls died at <28 days ( $p < 0.05$ ). There were 5 late deaths in the first year (4 treated, 1 control) and 4 treated and 2 control infants were unavailable for examination leaving total of 45 treated and 31 control infants seen at a corrected age of 1 year. Forty-four treated and 29 controls were followed to 2 years corrected age. Follow-up rates of survivors were 93% at 1 year and 89% at 2 years. Treated and control infants were similar both at 1 and 2 years in terms of physical growth, the prevalence of persistent respiratory symptoms and the occurrence of major and minor disability [Tables 1 and 2].

**Table 1.** Physical characteristics and respiratory status of infants surviving to corrected ages of 2 years

	Treated (n = 44)	Control (n = 29)
Weight (kg) <sup>a</sup>	11.0 (1.6)	10.8 (1.6)
Length (cm) <sup>a</sup>	84.2 (3.8)	82.6 (8.2)
OFC (cm) <sup>a</sup>	48.0 (1.8)	47.6 (1.8)
Respiratory symptoms (n %)	4 (10)	2 (7)

<sup>a</sup> Mean (sd); OFC= occipitofrontal head circumference.

Serum antibodies recognising poractant alfa and surfactant-anti-surfactant immune complexes were detected in both treated and control infants with no differences in the titres between the two groups. Examination of histological lung sections from 43/59 infants [17/24 treated (71%) and 26/35 (74%) controls] who died revealed a statistically significant difference between groups only for pulmonary interstitial emphysema detected in 9 control infants (aged 1–28 days) but in none of the treated infants ( $p < 0.02$ ).

*Table 2.* Neurodevelopmental outcome of infants surviving to corrected ages of 2 years

	Treated (n = 44)	Control (n = 29)
Disability (n %)		
None	35 (80)	22 (76)
Major	5 (11)	1 (3)
Minor	4 (9)	6 (21)

### Key points

- Poractant alfa treatment for severe RDS reduces neonatal mortality and air leaks and is not associated with an increase in disability 2 years later.
- There were no differences in physical growth, the prevalence of persistent respiratory symptoms or immunological sensitisation to poractant alfa between surfactant treated and control infants at 1 and 2 years after treatment.

### Reference

1. Collaborative European Multicentre Study Group. *Pediatrics* 1998;82:683–691.



# Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome

Speer CP, Gefeller O, Groneck P et al.

*Archives of Disease in Childhood* 1995;72:F8–F13

## Background

Natural surfactant preparations improve oxygenation and lung function more rapidly than synthetic surfactants but there are few comparative data on the effects of different natural surfactants. This pilot trial was designed to compare the effects of two natural surfactants – poractant alfa (Curosurf®, Chiesi Farmaceutici), derived from porcine lungs and beractant, a bovine lung extract.

## Aim

To compare treatment regimens of two widely used natural surfactant (poractant alfa and beractant) preparations in neonates with RDS.

## Methods

In a multicentre pilot study conducted in eight neonatal intensive care units in Germany, preterm infants (birth weight 700–1500g) with clinical and radiological documented RDS and a fraction of inspired oxygen ( $FiO_2$ )  $\geq 0.40$ , were randomised at 1–24 hours of age to receive initial doses of poractant alfa (200mg/kg) or beractant (100mg/kg). Infants who remained dependent on mechanical ventilation (MV) with a  $FiO_2 \geq 0.30$  received up to two additional doses of poractant alfa (each 100mg/kg) after 12 or 24 hours or up to three further doses of beractant (each 100mg/kg) between 6 and 48 hours after the initial dose.

## Results

Of the 75 infants randomised to treatment with

poractant alfa (n=35) or beractant (n=40), two randomised to poractant alfa were excluded for protocol violations. Median age at first treatment was about 3 hours in both groups and in all patients treatment was started before the age of 15 hours. Overall, 51.5% in the poractant alfa group and 62.5% in the beractant group required multiple doses. The cumulative doses were 273mg/kg for poractant alfa and 218mg/kg for beractant and the proportion of patients requiring more than two doses was greater in the beractant group (40.0 vs. 18.2%,  $p=0.07$ ). Both treatments induced a rapid improvement in oxygenation and ventilatory requirements but infants treated with poractant alfa had a higher arterial to alveolar oxygen tension ratio ( $a/APO_2$ ) and required a lower peak inspiratory pressure and mean airway pressure at several time points in the 24-hour post-randomisation period ( $p<0.05$ – $0.001$ ) [Figure 1]. Median  $FiO_2$  could be lowered within 5 minutes from 0.90 to 0.34 in infants receiving poractant alfa and from 0.90 to 0.50 in those treated with beractant. Between 5 minutes and 6 hours poractant alfa-treated infants needed less oxygen compared with beractant-treated infants and this difference was sustained for 24 hours. There was a trend towards a lower incidence of complications in the poractant alfa group, but due to the relatively small number of patients these differences did not reach significance [Table 1].

Figure 1. Oxygen requirements in preterm infants treated with multiple doses of poractant alfa (n=33) or beractant (n=40)

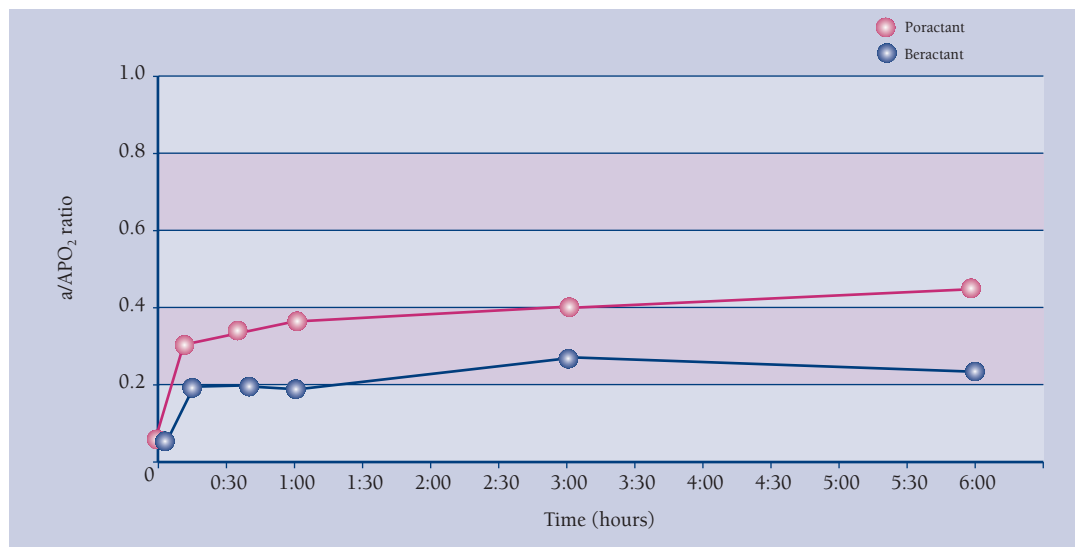


Table 1. Comparison of 28 day outcome measurements in preterm infants treated with multiple doses of poractant alfa (n=33) or beractant (n=40)

	Poractant alfa (%)	Beractant (%)	p-value
Pulmonary Interstitial emphysema	3	10	0.33
Pneumothorax	6.1	12.5	0.43
Intracerebral haemorrhage:			
Total	21.2	35	0.15
Grade III-IV	3	12.5	0.14
Mortality	3	12.5	0.23

### Key points

- Preterm infants with RDS treated with poractant alfa had improved oxygenation and reduced ventilatory requirements during the first 24 hours compared with those treated with beractant.
- There was a trend towards a lower incidence of serious and non-serious pulmonary complications with poractant alfa compared with beractant.
- The biochemical and biophysical properties of the two surfactants may account for the clinical differences observed.



# Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome

Baroutis G, Kaleyias J, Liarou T et al.

*European Journal of Pediatrics* 2003;162:476–480

## Background

There are many clinical comparisons between synthetic and natural surfactants but at the time this study was designed there were few studies comparing different natural surfactants. This prospective study was conducted to compare outcome of neonates with respiratory distress syndrome (RDS) treated with three natural surfactants.

## Aim

To compare the efficacy of alveofact, poractant alfa (Curosurf®, Chiesi Farmaceutici), and beractant in the treatment of neonatal RDS.

## Methods

Preterm infants of  $\leq 32$  weeks' (birth weight  $\leq 2000$ g), established RDS requiring artificial ventilation and with a  $FiO_2 \geq 0.30$ , were randomised to receive at least two doses of alveofact, poractant alfa or beractant (100mg/kg per dose). Infants who still required artificial ventilation with a  $FiO_2 \geq 0.30$  received up to two

additional doses (100mg/kg each). The initial dose of surfactant was given as soon as possible after intubation but within 4 hours of birth while the second was given 12 hours later.

## Results

Eighty infants were randomised to receive either alveofact (n=27), poractant alfa (n=27) or beractant (n=26). There were no significant differences in mortality, chronic lung disease, air leaks, necrotising enterocolitis, retinopathy of prematurity or intraventricular haemorrhage among the three groups. Mortality rates before discharge were 25.9%, 18.5% and 23.0% in infants treated with alveofact, poractant alfa and beractant, respectively. Infants treated with alveofact and poractant alfa spent fewer days on a ventilator, needed fewer days of oxygen administration and spent fewer days in hospital compared with those treated with beractant. The length of stay in hospital for infants without chronic lung disease was similar for all three groups.

## Key points

- Neonates with RDS treated with poractant alfa spent fewer days on the ventilator, needed fewer days of oxygen administration and spent fewer days in hospital than those treated with beractant.
- Differences in the composition of the three natural surfactants studied may account for the different clinical efficacies observed.



# Randomized trial comparing natural and synthetic surfactant: increased infection rate after natural surfactant?

Kukkonen AK, Virtanen M, Jarvenpaa A-L et al.  
*Acta Paediatrica* 2000;89:556–561

## Background

Natural surfactants have a more rapid and greater effect on oxygenation than synthetic surfactants. When this trial was designed, no clinical study comparing the effects of poractant alfa and synthetic surfactant had been reported. The effects of poractant alfa (Curosurf®, Chiesi Farmaceutici), and Exosurf Neonatal on the duration of oxygenation supplementation and mechanical ventilation (MV) in neonates with respiratory distress syndrome (RDS) were compared.

## Aim

To compare the efficacy of poractant alfa and Exosurf Neonatal in infants with RDS.

## Methods

Newborn infants with clinical and radiological documented RDS and an arterial to alveolar oxygen tension ratio ( $a/APO_2$ )  $<0.22$ , were enrolled from three tertiary intensive care units in Finland. Infants were randomised to receive either poractant alfa (100mg/kg) or Exosurf Neonatal (5mL/kg). Additional doses (up to three) were administered if necessary ( $a/APO_2$   $<0.22$ ) at 6–12 hour intervals.

## Results

A total of 235 infants were enrolled and 228 (113 poractant alfa, 115 Exosurf Neonatal) were available for analysis. Seventy-eight infants had a birth weight of 1000g or less. The mean number of doses of poractant alfa was 2.1 vs. 2.0 in the Exosurf Neonatal group, while 36 infants received one dose, 45 received two and 32 received three. Corresponding figures for the Exosurf Neonatal group were 35, 54 and 26, respectively. Following treatment with poractant alfa the fraction of inspired oxygen ( $FiO_2$ ) was lower from 15 minutes (0.45 vs. 0.70,  $p=0.0001$ ) to 6 hours (0.48 vs. 0.64,  $p=0.0001$ ) and the mean airway pressure was lower at 1 hour (8.3 vs. 9.4  $cmH_2O$ ,  $p=0.01$ ). Thereafter, respiratory parameters were similar. The duration of MV (median 6 vs. 5 days) and the duration of oxygen supplementation (median 5 vs. 4 days) were similar in both groups. Analysis of infection markers in 220 infants showed that 45% of those treated with poractant alfa had high C-reactive protein levels ( $>40mg/L$ ) compared with 12% in the Exosurf group ( $p=0.0001$ ) while 52% had leukopenia (vs. 28%,  $p=0.001$ ) and 11% had bacteraemia (vs. 4%,  $p<0.05$ ).

## Key points

- Compared with Exosurf Neonatal, poractant alfa provided a greater initial improvement in infants with RDS.
- The difference in infection markers between the two groups requires additional study.



# Pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25–29 weeks' gestation: a randomised trial

Ainsworth SB, Bereford MW, Milligan DWA et al.

*Lancet* 2000; 355:1387-1392

## Background

Poractant alfa (Curosurf®, Chiesi Farmaceutici), a porcine-derived natural surfactant has been shown to more rapidly improve lung function in preterm infants with RDS than beractant (Survanta) a bovine surfactant. A trend towards reduced incidence of serious pulmonary and non-pulmonary complications has also been observed. Pumactant, a synthetic surfactant, is widely used in the UK but there is a lack of clinical trials comparing it with other surfactants.

## Aim

To compare the effects of pumactant and poractant alfa in the treatment of RDS in neonates.

## Methods

In this multicentre study neonates (born between 25 and 29 weeks of gestation) with presumed surfactant deficiency were randomised to receive either poractant alfa (100 mg/1.25mL) or pumactant (100mg/1.2mL). Surfactant was administered as soon as possible after delivery and within 30 minutes of intubation according to local-unit guidelines. The second dose was given 12 hours later if the oxygenation index ( $\text{FiO}_2$  [%] x mean arterial pressure [ $\text{cmH}_2\text{O}$ ]/ $\text{PaO}_2$  [mmHg]) was  $\geq 5\%$ . Further doses were given at the supervising clinician's discretion. Primary outcome was days spent in high-dependency care and the secondary outcome was neonatal mortality (death within 28 days). A data and safety monitoring

committee (DSMC) met when half of the neonates had been recruited.

## Results

The DSMC met 19 months after the trial started and reviewed recruitment data, exclusions after randomisations and available outcome data for 189 neonates. At this time there was a highly significant difference in predischage mortality not explained by possible confounding variables (differences in gestational age or sex) and the trial was stopped. A total of 212/403 eligible neonates had been randomised to receive poractant alfa (n=105) or pumactant (n=107) and of these 13 (6 poractant alfa and 7 pumactant) were excluded before treatment. Outcome data were analysed for 199 infants (99 poractant alfa, 100 pumactant). Neonatal mortality (OR 0.38, 95% CI 0.17–0.81,  $p=0.011$ ) and predischage mortality (0.37, 0.18–0.74,  $p=0.004$ ) were lower in neonates who received poractant alfa than in those who received pumactant [Table 1]. These differences remained significant after adjustment for centre, gestational age, birth weight, sex, plurality and use of antenatal steroids (neonatal mortality 0.32, 0.13–0.77,  $p=0.011$ ); predischage mortality (0.27, 0.11–0.64,  $p=0.003$ ) and were consistent across centres. The proportions of deaths attributed to respiratory causes were 5% (5/99) in the poractant alfa group and 21% (21/100) in the pumactant group ( $p=0.001$ ). Median duration of high-dependency care among survivors were 22 and 18 days in the pumactant and poractant alfa groups, respectively.

*Table 1.* Neonatal and predischARGE mortality in analysed neonates receiving poractant alfa (n=99) or pumactant (n=100)

	Poractant alfa	Pumactant
<b>Neonatal mortality</b>		
Overall	11/99 (11%)	25/100 (25%)
25 weeks' gestation	4/12 (33%)	6/13 (46%)
26 weeks' gestation	3/17 (18%)	6/22 (27%)
27 weeks' gestation	0	4/17 (24%)
28 weeks' gestation	2/24 (8%)	6/24 (25%)
29 weeks' gestation	2/32 (6%)	3/24 (13%)
<b>PredischARGE mortality</b>		
Overall	14/99 (14%)	31/100 (31%)
25 weeks' gestation	4/12 (33%)	8/13 (62%)
26 weeks' gestation	5/17 (29%)	7/22 (32%)
27 weeks' gestation	0	5/17 (29%)
28 weeks' gestation	3/24 (13%)	7/24 (29%)
29 weeks' gestation	2/32 (6%)	4/24 (17%)

### Key points

- Neonates of 25 to 29 weeks gestation treated with poractant alfa soon after birth had much better survival rates than those treated with pumactant.
- PredischARGE mortality differed significantly between groups in favour of poractant alfa (14.1 vs. 31.0%).
- Differences in mortality were independent of all the variables assessed.
- The authors conclude that the reductions in mortality with poractant alfa have implications for clinical practice.



# A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants

Ramanathan R, Rasmussen MR, Gerstmann D et al for the North American Study Group  
*American Journal of Perinatology* 2004;21(3):109–119

## Background

Three randomised trials comparing different natural surfactants have been previously published. These trials involving calf lung surfactant (Infasurf), bovine lung surfactant (Alveofact), beractant (Survanta) and poractant alfa (Curosurf®, Chiesi Farmaceutici) show that not all natural surfactants produce the same outcome. Infants treated with poractant alfa, for example, spent fewer days on a ventilator, required less supplemental oxygen and had shorter hospital stays compared with beractant. To further compare the effects of natural surfactants, a large multicentre trial evaluated the efficacy of poractant alfa (given at two different doses) and beractant.

## Aim

To evaluate the effectiveness of poractant alfa (100mg/kg), poractant alfa (200mg/kg) and beractant (100mg/kg) in the treatment of respiratory distress syndrome (RDS) in preterm infants.

## Methods

This prospective, masked comparison trial conducted in 20 centres in the United States, enrolled preterm infants (<35 weeks gestation and weighing 750–1750g at birth) with clinically and radiologically documented RDS, fraction of inspired oxygen ( $FiO_2 \geq 0.30$ ) and with an arterial to alveolar oxygen tension ratio ( $a/APO_2 \leq 0.33$ ). Infants were randomised to one

of three groups: an initial dose of 100mg/kg poractant alfa, 200mg/kg poractant alfa or 100mg/kg beractant. Additional doses of 100mg/kg (poractant alfa or beractant) were administered in infants who continued to require mechanical ventilation and an  $FiO_2 \geq 0.30$  to maintain an oxygen saturation of  $\geq 88\%$ . The onset of clinical response after the first dose was studied by comparing changes in the  $FiO_2$  (between 0 and 6 hours) measured using the area under the curve ( $FiO_2 AUC_{0-6}$ ).

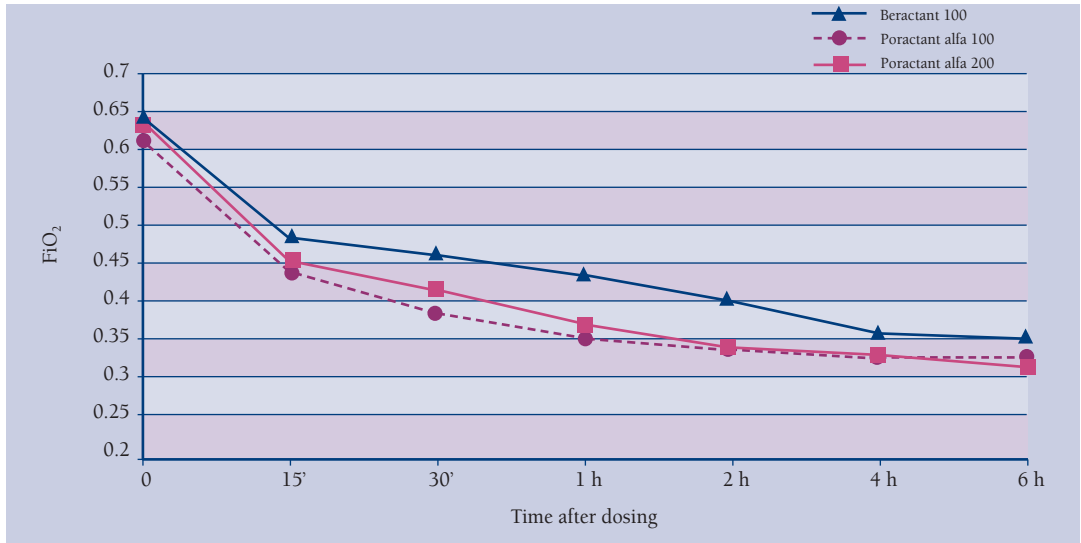
## Results

Of a total of 301 infants enrolled, 293 were evaluable for analysis (n=96 poractant alfa 100mg/kg, n=99 poractant alfa 200mg/kg and n=98 beractant 100mg/kg). The mean age when the first dose of surfactant was given was 3 hours in all groups. Mean  $FiO_2$  values for poractant alfa 100 and 200mg/kg were significantly lower than that for the beractant group at all time points until 6 hours ( $p < 0.05$ ) [Figure 1]. There were no significant differences between the poractant alfa groups. Mean  $FiO_2 AUC_{0-6}$  values for the poractant alfa 100 and 200mg/kg groups (1.956  $FiO_2$  hours;  $p < 0.001$  and 1.989  $FiO_2$  hours,  $p < 0.005$ , respectively) were significantly lower than those of the beractant group (2.237  $FiO_2$  hours) but not different from each other. Forty-five, 47 and 50 infants treated with 100mg/kg poractant alfa, 200mg/kg poractant alfa and 100mg/kg beractant, respectively received surfactant within 2.5 hours after birth. The need for more than

one dose of surfactant was significantly lower in infants treated with an initial dose of 200mg/kg poractant alfa compared with beractant-treated infants ( $p<0.002$ ) [Figure 2]. Mortality at 36 weeks postconceptional age for infants born at

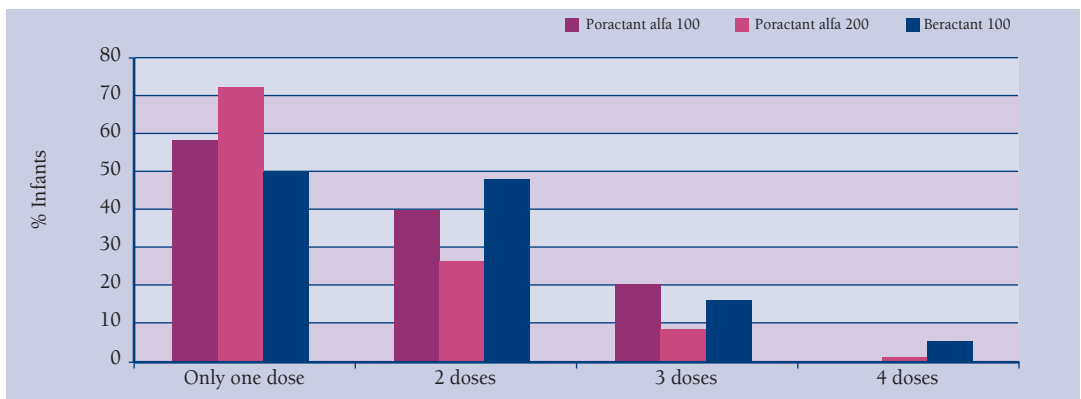
$\leq 32$  weeks' gestation, was significantly lower in the higher dose poractant alfa group than in either the beractant group (3 vs. 11%,  $p=0.034$ ) or in the lower poractant alfa group (3 vs. 11%,  $p=0.046$ ).

Figure 1. Fraction of inspired oxygen (FiO<sub>2</sub>) for the three treatment groups (n=293)



\* $p<0.05$  at all posttreatment time points in the poractant alfa groups compared with beractant

Figure 2. Infants (%) receiving one or more doses of poractant alfa 100mg/kg (n=96), poractant alfa 200mg/kg (n=99), beractant 100mg/kg (n=98)



## Key points

- Preterm infants (<35 weeks gestation) treated with poractant alfa at an initial dose of 200mg/kg are weaned from supplemental oxygen more rapidly during the first 6 hours post-treatment than infants treated with beractant (100mg/kg).
- Significantly fewer infants required additional doses if treated with poractant alfa at an initial dose of 200mg/kg compared with those receiving beractant 100mg/kg.
- Infants  $\leq 32$  weeks treated with an initial 200mg/kg poractant alfa had a survival advantage over those treated with beractant.
- The authors suggest that the combination of larger amounts of polar lipids and SP-B may have accounted for the faster response seen with poractant alfa compared with beractant.