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

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Abstract

Aims—To compare treatment regimens of two widely used natural surfactant preparations Curosurf and Surfactant in respiratory distress syndrome (RDS).

Methods—The effects of the two treatment regimens on gas exchange, ventilatory requirements, and 28 day outcome in infants with RDS were compared. Seventy five preterm infants (birth weight 700–1500 g) with RDS requiring artificial ventilation with an FiO_2 of ≥ 0.4 , were randomly selected at 1–24 hours of age. One group received an initial dose of Curosurf (200 mg/kg); the other group Surfactant (100 mg/kg). Patients who remained dependent on artificial ventilation with an FiO_2 of ≥ 0.3 received up to two additional doses of Curosurf (each of 100 mg/kg) after 12 and 24 hours or up to three additional doses of Surfactant (each of 100 mg/kg) between six and 48 hours after the initial dose.

Results—There was a rapid improvement in oxygenation and ventilatory requirements were reduced in both groups. However, infants treated with Curosurf had a higher arterial:alveolar oxygen tension ratio and required a lower peak inspiratory pressure and mean airway pressure at several time points within 24 hours of randomisation ($p < 0.05$ – 0.001). The incidences of pneumothorax in the Curosurf and Surfactant groups were 6% and 12.5%, respectively; the corresponding figures for grades 3–4 intracerebral haemorrhage were 3% and 12.5%, respectively. Mortality was 3% in the Curosurf group and 12.5% in the Surfactant group. However, these differences did not reach significance.

Conclusion—The Curosurf treatment regimen resulted in a more rapid improvement in oxygenation than Surfactant and reduced ventilatory requirements up to 24 hours after start of treatment. This was associated with a trend towards reduced incidence of serious pulmonary and non-pulmonary complications.

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Surfactant treatment with natural or synthetic preparations reduces the incidence of neonatal

mortality and pneumothorax in babies with respiratory distress syndrome (RDS).¹ Natural surfactants seem to improve oxygenation and lung function more rapidly than synthetic surfactants,² but there have been no studies comparing the effects of two natural surfactants.

We designed a pilot trial to compare the acute effects of the bovine preparation Surfactant (Beractant, Ross Laboratories, Columbus, Ohio, USA) and the porcine surfactant Curosurf (Chiesi Farmaceutici, Parma, Italy). The two surfactant preparations have been carefully evaluated in clinical trials^{3–6 7–9}; they are licensed in Europe and have several features in common but differ in some potentially important biophysical characteristics.¹⁰

In preparation for a trial comparing therapeutic regimens involving these two natural surfactants, the present study was performed to test case record forms, compliance with randomisation guidelines in the collaborating centres, feasibility of monitoring procedures, adherence of centres to general good clinical principles, and for sample size calculations of a large definitive trial.

Methods

Curosurf is a natural surfactant, prepared from pig lungs. It contains almost exclusively polar lipids – in particular phosphatidylcholine (about 60% of the total phospholipids) and 1% of the specific hydrophobic low molecular weight apoproteins SP-B and SP-C. Further details of the composition and the physical properties have been described before.¹¹ Surfactant is a bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant associated apoproteins SP-B and SP-C. Dipalmitoylphosphatidylcholine, palmitic acid, and tripalmitin are added to standardise the composition, and to mimic the surfactant properties of natural lung surfactant.¹²

The present pilot study was designed to determine possible differences between the two surfactant treatment regimens. It was planned to recruit at least 35 infants for each treatment group. No short term endpoints relating to oxygenation or ventilator settings were defined. Five German neonatal intensive care units collaborated in this trial which started 1 December 1991 and ended 15 July 1992. The number of patients randomised by each unit varied because of differences in the

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Table 1 Number of patients randomised in each contributing unit

Contributing units	No of patients		Total
	Curosurf	Surfanta	
Bochum	2	5	7
Braunschweig	1	3	4
Essen	9*	9	18
Göttingen	9	9	18
Cologne	14*	14	28

*One patient treated with Curosurf was excluded (violation of entry criteria).

size of the population from which they were recruited and because of differences in admission policies (table 1).

Criteria for entry were:

- (i) birth weight 700–1500 g;
- (ii) clinical and radiological findings typical of RDS;
- (iii) age at randomisation of 1–24 hours;
- (iv) requirement of artificial ventilation with a fraction of inspired oxygen (FIO_2) of ≥ 0.4 ;
- (v) no complicating diseases; and
- (vi) parental consent.

Complicating diseases leading to exclusion of infants were: (i) prolonged rupture of membranes (>3 weeks); (ii) intracranial haemorrhage (ICH) grade III–IV before randomisation; and (iii) severe birth asphyxia (Apgar score of ≤ 3 at five minutes, umbilical arterial cord blood pH of < 7.1), or major congenital anomalies. Anaemia, hypotension, hypoglycaemia, acidosis, and pneumothorax and neonatal infection (with group B streptococci, for example) were treated by appropriate measures before surfactant replacement. Infants were excluded if they had persistent physiological instability such as hypotension, hypoglycaemia, and pneumothorax.

At randomisation, all infants were mechanically ventilated with an FIO_2 of ≥ 0.4 (entry criterion), a frequency of 40–80 breaths/minute, a peak inspiratory pressure (PIP) of < 30 cm H_2O , a positive end expiratory pressure (PEEP) of 2–5 cm H_2O , and an inspiration to expiration ratio of 1:1 to 1:2.

On a random basis, infants with RDS who met eligibility criteria were allocated to treatment with Curosurf or Surfanta by means of sealed opaque envelopes. Stratified randomisation within each centre was applied with regard to birth weight (700–999 g and 1000–1500 g). After randomisation of a patient each contributing centre contacted the Biometric Centre at the University of Göttingen to provide centre number, patient's number, date of birth and treatment group. This informed the Biometric Centre of the inclusion of a new patient into the study, ensuring an objective verification of the randomisation sequence. Because the recommended doses, volumes, dose interval and dose procedures differed between both surfactant preparations, blinding of surfactant administration was not feasible.

All infants randomised to Curosurf treatment received 200 mg of Curosurf/kg bodyweight (2.5 ml/kg), divided in two portions instilled into each main bronchus.³ Retreatment with 100 mg/kg per dose was performed at 12 hours and 24 hours after the

first treatment if the babies required an FIO_2 of ≥ 0.3 to keep PaO_2 to ≥ 50 mm Hg (≥ 6.7 kPa) on mechanical ventilation. Details of the instillation manoeuvre have been described before.⁴ The maximal cumulative dose was 400 mg/kg.

Surfanta was administered intratracheally at a dose of 100 mg/kg (4.0 ml/kg) divided into four equal amounts, instilled into the four quadrants of the lung, as recommended by the manufacturer. Retreatment with Surfanta was performed as early as 6 hours after the initial dose, provided the baby required an FIO_2 of ≥ 0.3 and was still on the ventilator. Six hours after the first dose until 48 hours of age, the patients could receive up to three additional treatments, no more than every six hours if they remained intubated and required an FIO_2 of ≥ 0.3 to maintain PaO_2 of ≥ 50 mm Hg (≥ 6.7 kPa). Each of these doses was 100 mg/kg which means the maximum cumulative dose of Surfanta was the same as for Curosurf – 400 mg/kg. The retreatment doses (if required) were administered in two doses into each lung quadrant. Details of the instillation procedure have been reported.^{9 11}

No suctioning of the airways was performed during the first six hours after instillation of Curosurf or Surfanta. After surfactant administration the baby was reconnected to the ventilator, and FIO_2 and ventilator settings were immediately adjusted according to clinical response to maintain adequate blood gases (PaO_2 of 50–70 mm Hg); (PaCO_2 40–50 mm Hg, pH ≥ 7.3) with the lowest possible level of FIO_2 and PIP. To obtain this goal, FIO_2 was lowered first; subsequent adjustments included reduction of insufflation pressure and inspiration:expiration ratio. A PEEP of 2–5 cm H_2O was maintained during the first hours after surfactant instillation.

Arterial or transcutaneous blood gas values were determined at regular intervals (five, 30, 60 minutes; three, six, 12, 24 hours, and two, three, four, seven, and 10 days after surfactant replacement). The Curosurf and Surfanta groups were compared with respect to the following measurements: FIO_2 , PaO_2 , PaCO_2 , pH, $\text{PaO}_2/\text{FIO}_2$ ratio, arterial to alveolar pO_2 ratio (a/APO_2), PIP, mean airway pressure (MAP), inspiration:expiration ratio, PEEP, ventilatory efficiency index,⁴ and arterial blood pressure. The groups were also compared with respect to the following complications diagnosed within 28 days: pulmonary interstitial emphysema (PIE); pneumothorax; patent ductus arteriosus (PDA); intracerebral haemorrhage (ICH); pulmonary haemorrhage; septicaemia; bronchopulmonary dysplasia (BPD); and death. Furthermore, total time of exposure to supplemental oxygen and complete duration of mechanical ventilation during hospital stay were recorded. Chest x ray pictures were examined by a local paediatric radiologist who was not involved in the study and was blinded to the randomisation of the patients. PIE and pneumothorax were diagnosed according to recent definitions.¹³ Sequential echocardiograms and Doppler measurements to assess shunting across the ductus arteriosus were obtained every 24 hours during the first week

Table 2 Patient details

	Curosurf (n=33*)	Survanta (n=40)
Gestational age, weeks (mean (SD))	28.9 (2.3)	28.8 (2.2)
Birth weight g (mean (SD))	1095.3 (226.4)	1082.4 (252.2)
Male sex (%)	11 (33.3)	22 (55.0)
Prenatal steroids (%)	14 (42.4)	15 (37.5)
Umbilical cord pH (mean (SD))	7.31 (0.06)	7.27 (0.14)
Rectal temperature on admission (°C)†	36.5 (36–37)	36.3 (35.6–37)
Age at treatment, hours‡	3.2 (2.7–6.1)	3.0 (2.6–4.1)
FiO ₂ ‡ at randomisation‡	0.9 (0.55–1.0)	0.9 (0.7–1.0)

*No of patients included in the final calculations after exclusion of two patients (violation of entry criteria). †Median (25th–75th percentile). ‡Fraction of inspired oxygen.

of life and whenever clinical signs of PDA were present. Ultrasonographic examinations of the head were performed daily for the first seven days and on day 10, and ICH was classified according to Papile *et al*¹⁴; in surviving infants a further cranial ultrasound scan was performed at 28 days to look for ischaemic lesions.¹⁵ Pulmonary haemorrhage was defined as the appearance of bright red blood in the endotracheal tube associated with signs of clinical deterioration of the baby. Septicaemia was defined as clinical signs of systemic infection and positive blood culture.¹⁶ BPD was defined as oxygen requirement at a postconceptional age of 36 completed weeks.

The trial was approved by the ethics committee of the University of Göttingen and was performed in compliance with good clinical practice guidelines. This compliance took into account approval by relevant regulatory bodies, written informed consent of a parent before randomisation, and the ‘CPMP Working Party on Efficacy of Medicinal Products: Notes for Guidance’ on ‘Good Clinical Practice for Trials on Medicinal Products in the European Community’.

Figure 1 Oxygenation measurements in preterm infants with RDS treated with multiple doses of Curosurf or Survanta at various time points after randomisation. Values are given as median and 25th and 75th percentiles. The points for the two groups are offset for clarity. **p*<0.5, ***p*<0.01, ****p*<0.001; conversion factor: 10 cm H₂O=0.98 kPa.

STATISTICAL ANALYSIS

The statistical treatment of the trial data was approached by an intention-to-treat analysis of all eligible study subjects.¹⁷ Differences between the two randomised groups with respect to gas exchange and ventilatory settings at different time points were evaluated using the Wilcoxon-Mann-Whitney test. When the overall measures of ventilatory requirement and oxygen dependence were compared, the log-rank test, with the data from all patients (not only the survivors), was used.¹⁸ As specified in the study protocol, logistic regression analysis was used to assess the effect of the surfactant treatment regimen on the 28 day outcome variables while simultaneously controlling for the confounding influence of birth weight, sex, and allocation to different hospitals. The resulting adjusted odds ratios (OR) represent approximate relative risks and are accompanied by their 95% confidence intervals.¹⁹

Results

CHARACTERISATION OF PATIENTS AND TREATMENT REGIMENS

Thirty five patients were randomised to the Curosurf group and 40 to the Survanta group. For two babies who were randomised to Curosurf, treatment entry criteria had been violated (birth weight was <700 g in one preterm infant and >1500 g in the other). These infants therefore had to be excluded from further analyses (neither of them had pulmonary or extrapulmonary complications until discharge from the hospital, outcome results including these babies would have favoured the Curosurf group). Table 2 shows that the baseline characteristics of both groups were quite well matched, with the exception that the Curosurf group had a higher percentage of female babies. Median age at first treatment was about 3 hours in both groups, and in all patients the treatment was initiated before the age of 15 hours.

In the Curosurf group 16 (49%) infants received a single dose, 11 (33%) received two doses, and six (18%) received three doses. The corresponding numbers in the Survanta group were 15 (38%), nine (23%), and eight (20%). Eight (20%) babies also received four doses of Survanta. Overall, 51.5% of the Curosurf and 62.5% of the Survanta babies needed multiple doses. The cumulative dose was 273 (SD 87) mg/kg in the Curosurf group and 218 (115) mg/kg in the Survanta group, and the number of patients requiring more than two doses was substantially larger in the Survanta group (40.0% *v* 18.2%; *p*=0.07 derived from Fisher's exact test). Due to dosing errors, one Curosurf infant received a lower initial dose; in another baby the second Curosurf dose was doubled. In two Survanta babies the initial dose was too low, and in one a repeat dose of Survanta was given after 48 hours of age. One infant received the last Survanta dose at an FiO₂ of <0.3.

GAS EXCHANGE AND VENTILATOR SETTINGS AFTER SURFACTANT REPLACEMENT

Initial treatment with Curosurf (200 mg/kg) or

Figure 2 Peak inspiratory pressure (PIP) (A) and mean airway pressure (MAP) (B) in patients treated with multiple doses of Curosurf or Survanta at various time points after randomisation. Values are given as median and 25th and 75th percentile. The points for the two groups are offset for clarity. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; conversion factor: $10 \text{ cm H}_2\text{O} = 0.98 \text{ kPa}$.

Survanta (100 mg/kg) resulted in improved oxygenation. Median FiO_2 could be lowered within five minutes, from 0.9 to 0.34, in Curosurf neonates and from 0.9 to 0.5 in babies receiving Survanta (fig 1). However, between five minutes and six hours the Curosurf treatment patients needed less oxygen than the Survanta group ($p < 0.05$ – 0.01); this difference was sustained until 24 hours ($p < 0.05$ – 0.001). During the first 24 hours after initial treatment the Curosurf babies also had a greater improvement in a: APO_2 ($p < 0.05$ – 0.001) (fig 1).

PIP and MAP could gradually be reduced in both groups; however, at various time points the Curosurf treatment patients needed a lower PIP and MAP than the Survanta treated neonates ($p < 0.05$) (fig 2). The differences in oxygenation and ventilatory support favouring Curosurf treated infants did not persist beyond 24 hours after start of treatment. At

representative time points the ventilatory efficiency index was not different between the groups: median values for the Curosurf and Survanta treatment babies before treatment were 0.12 v 0.13 , at 3 hours 0.16 v 0.14 , and at 6 hours 0.18 v 0.19 (ml/mm Hg/kg^{-1}), respectively. Values for inspiration:expiration ratio, PEEP, arterial blood pressure, PaO_2 , PaCO_2 , and pH showed no relevant differences between the groups (data not shown).

OUTCOME

Table 3 shows the values for duration of artificial ventilation and total time of exposure to supplemental oxygen in surviving patients: there were no differences between the groups. An identical number of patients in each group also had a supplemental oxygen requirement at 36 weeks' postconceptional age.

One Curosurf baby died at the age of 18 days from massive hepatic bleeding following surgical repair for spontaneous intestinal perforation. In the Survanta group two infants died from grade IV ICH, two from acute cardiocirculatory failure (one had tension pneumothorax), and one due to respiratory failure probably related to lung hypoplasia after premature rupture of the membranes 17 days before delivery. Age at death ranged between 1 and 2 days.

Data on the treatment comparison for pulmonary and extrapulmonary complications are listed in table 4. The incidences of most of the complications were lower in the Curosurf group, but with the small number of patients these trends towards favourable outcome following Curosurf treatment did not reach significance. The adjusted ORs given in table 4 represent the results of risk calculations for the effect of the treatment regimen (Curosurf v Survanta) on the 28 day outcome variables controlled for the influence of birth weight, sex, and collaborating centre and thus do not reflect imbalances between treatment groups with respect to these prognostic factors.

Treatment administration problems were only observed in Survanta infants, probably reflecting the larger volume of the surfactant dose. Reflux of administered surfactant was observed in three, and oxygen saturation of less than 85% in two babies five minutes after administration.

Discussion

The results of our pilot trial show that infants treated with Curosurf had less oxygen and ventilator requirements than babies treated with Survanta. Although the long term measures of outcome favoured the Curosurf infants, the differences were not significant. These results, however, provide a sound basis for an accurate sample size calculation for the large scale trial to follow; a reduction from 25% to 15% for the occurrence of the primary endpoint 'death or BPD' is a reasonable assumption on the difference to be detected. Thus, a total of 708 infants is required in the definitive study to find

Table 3 Ventilatory requirement and oxygen dependency of surviving patients

	Curosurf (n=32)	Survanta (n=35)	p Value
Duration of artificial ventilation in survivors, days†	14 (6–20.5)	14 (5–27)	0.494‡
Total time of exposure to oxygen in survivors, days†	16.5 (3.5–38.5)	10 (3–28)	0.274‡

†Median (25th–75th percentile).

‡Derived from the log-rank test (including the censored information of dead patients).

Table 4 Comparison of 28 day outcome measurements with crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) as well as corresponding *p* values in Curosurf (*n*=33) and Survanta (*n*=40) treated babies

Outcome measurements	Curosurf No/%	Survanta No/%	OR crude*	OR adjusted**	95% CI of adjusted OR	<i>p</i> Value†
Pulmonary interstitial emphysema	1 (3.0)	4 (10.0)	0.28	0.30	0.03–3.42	0.33
Pneumothorax	2 (6.1)	5 (12.5)	0.45	0.49	0.08–2.88	0.43
Intracerebral haemorrhage						
Total	7 (21.2)	14 (35.0)	0.50	0.44	0.14–1.36	0.15
Grades 3–4	1 (3.0)	5 (12.5)	0.22	0.18	0.02–1.78	0.14
Persistent ductus arteriosus	18 (54.6)	12 (30.0)	2.80	2.83	0.98–8.21	0.06
Bronchopulmonary dysplasia‡	4 (12.5)	4 (11.4)	1.11	1.03	0.21–5.21	0.97
Pulmonary haemorrhage	0 (0)	1 (2.5)	–	–	–	–
Septicaemia:						
Total No	12 (36.4)	11 (27.5)	1.51	1.33	0.37–4.81	0.66
Onset ≤2 days	6 (18.2)	4 (10.0)	1.94	1.55	0.32–7.43	0.58
Onset >2 days	6 (18.2)	7 (17.5)	1.05	1.02	0.24–4.30	0.98
Mortality	1 (3.0)	5 (12.5)	0.22	0.23	0.02–2.54	0.23

*Derived from the fourfold table of treatment times outcome.

**Derived from the logistic model incorporating covariate information.

†Derived from the test in the logistic model whether the adjusted OR equals 1.

‡Oxygen dependency at 36 weeks' postconceptional age.

such a difference with 90% power using a two-sided test at a significance level of 5%.

In general, the data of the present pilot study must be interpreted with caution. The trend towards favourable 28 day outcome in Curosurf treated infants has to be viewed in the light of the small number of babies enrolled in the study and the non-blind trial design. Although we are not aware of any systematic bias in the assessment of outcome measures, we cannot rule out this possibility. However, additional data analysis stratified by collaborating centre did not indicate heterogeneity in our results. Thus, if systematic bias were present it would have to be the same in all centres, which seems unlikely.

There are at least three possible explanations for the improved lung function in the Curosurf treated babies during the first 24 hours. These are, firstly, that the trial collaborators had more experience with the porcine surfactant preparation; secondly, the Curosurf is a more effective surfactant than Survanta; and thirdly, that the dose of phospholipids – namely, 200 mg/kg *v* 100 mg/kg was critical.

The first explanation seems very unlikely. Although the collaborating neonatologists have participated in previous Curosurf trials,^{4,6} their expertise in administering Survanta is comparable as each of the centres had been using Survanta in routine clinical practice for many months before the trial started.

The two surfactant preparations used in the present trial differ in some potentially important biophysical characteristics. Curosurf and Survanta are both derived from minced animal lungs by washing and extraction with organic solvents; this latter procedure removes water soluble components including the surfactant associated apoproteins SP-A and SP-D, leaving only hydrophobic constituents with about 1% SP-B and SP-C. Curosurf is further 'purified' by a liquid-gel chromatography procedure removing neutral lipids such as triacylglycerol, cholesterol, and cholesteryl esters.¹¹ Survanta, in contrast, is enriched with synthetic DPPC, triacylglycerol, and palmitic acid to standardise lipid composition and reduce film compressibility. It is not clear how these different modifications of the surfactant preparations influence their physiological properties under *in vivo* conditions. Nohara *et al* confirmed that

in vitro film compressibility of a bovine equivalent to Curosurf could indeed be lowered by enrichment with synthetic lipids²⁰; however, this was associated with retarded spreading and did not seem to improve further physiological variables of lung mechanics in ventilated immature newborn rabbits.

The present trial was designed to investigate whether these differences in biochemical and biophysical properties between the two preparations would have an impact on their clinical effects in babies with RDS. We realise that, under optimal trial conditions, Curosurf and Survanta should have been given at identical doses and treatment intervals in a blind manner. However, this was not possible, as different treatment regimens were already established for each of the two surfactants. The trial design thus implied that Curosurf was given at a larger initial dose, whereas the maximum dose during the first two days of postnatal life was the same for the two preparations. We found that, after administration of either Curosurf or Survanta, there was a rapid improvement of gas exchange, as reflected by a significant increase in a:AP_O₂, and F_{IO}₂ could therefore be reduced in both groups of babies. However, five minutes to 24 hours after surfactant replacement Curosurf treated infants needed less oxygen than patients in the Survanta group and had a more noticeable improvement in a:AP_O₂. Apparently, the effect of the Survanta treatment regimen was delayed.

At some time points PIP and MAP were significantly lower in the Curosurf group than in the Survanta group. Five minutes after instillation of Survanta a slight increase in median PIP was observed; this phenomenon could have been due to the larger volume of the initial Survanta dose compared with the Curosurf dose. The superior improvement in oxygenation and ventilatory pressure in the Curosurf group may reflect the higher initial dose (200 mg/kg Curosurf *v* 100 mg/kg Survanta) or the different preparation. The difference in ventilatory requirements between the groups might explain the trend towards the lower incidence of PIE and pneumothorax in Curosurf babies compared with Survanta babies. There was also a trend towards lower incidence of ICH in the

Curosurf group; severe ICH was present in only one (3%) of the Curosurf treated infants and in five (12.5%) patients in the Survanta group. Our data support the concept that babies with RDS benefit from receiving a high initial dose⁴ and also indicate that a high initial dose reduces the need for retreatment. Each administration procedure, which involves disconnection from the ventilator and instillation of fluid into the airways, is potentially traumatic and usually associated with a slight drop in arterial blood pressure,²¹ and may even lead to transient depression of cerebroelectrical activity.²²

In summary, we feel confident in concluding that preterm infants with RDS treated according to the Curosurf regimen had improved oxygenation and reduced ventilatory requirements during the first 24 hours compared with Survanta treated neonates. There was also a trend towards lower incidence of air leaks and severe ICH in babies receiving Curosurf. These findings need to be confirmed in a larger randomised trial.

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The trial is dedicated to our friend and trial collaborator Dr Edgar Laufkötter, who died in April 1994.

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