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ORIGINAL ARTICLES

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

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Abstract

A randomised trial was conducted in 82 centres using the porcine surfactant extract, Curosurf, to compare two regimens of multiple doses to treat infants with respiratory distress syndrome and arterial to alveolar oxygen tension ratio <0·22. Infants were randomly allocated to a low dosage group (100 mg/kg initially, with two further doses at 12 and 24 hours to a maximum cumulative total of 300 mg/kg; n=1069) or a high dosage group (200 mg/kg initially with up to four further doses of 100 mg/kg to a maximum cumulative total of 600 mg/kg; n=1099). There was no difference between those allocated low and high dosage in the rates of death or oxygen dependency at 28 days (51·1% *v* 50·8%; difference −0·3%, 95% confidence interval (CI) −4·6% to 3·9%), death before discharge (25·0% *v* 23·5%; difference −1·5%, 95% CI −5·1% to 2·2%), and death or oxygen dependency at the expected date of delivery (32·2% *v* 31·0%; difference −1·2%, 95% CI −5·2% to 2·7%). For 14 predefined secondary measures of clinical outcome there were no significant differences between the groups but the comparison of duration of supplemental oxygen >40% did attain significance; 48·4% of babies in the low dose group needed >40% oxygen after three days compared with 42·6% of those in the high dose group.

The total amount of surfactant administered in the low dose regimen (mean 242 mg phospholipid/kg) was probably enough to replace the entire pulmonary surfactant pool. Adopting the low dose regimen would lead to considerable cost savings, with no clinically significant loss in efficacy.

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There is now ample evidence from over 30 randomised controlled trials, involving more than 6000 babies, that surfactant replacement, either at birth[1] or later when signs of respiratory distress have developed,[2 3] reduces the odds of neonatal mortality in preterm babies by about 40%. Multiple doses of surfactant appear to be more effective than single doses,[4 5] but the optimal dose of surfactant has not been clearly defined. Recently the OSIRIS trial of Exosurf (Wellcome Foundation Ltd) failed to demonstrate differences in outcome between two and four dose regimens.[6] Konishi and colleagues found improved oxygenation and a reduced incidence of bronchopulmonary dysplasia in babies treated with 120 mg Surfactant-TA (Tokyo Tanabe)/kg compared with 60 mg/kg.[7] Gortner and coworkers found improved oxygenation with 100 mg Alveofact (Boehringer-Thomae)/kg compared with 50 mg/kg.[8] These studies were relatively small and did not address the question of whether multiple doses of surfactant for babies who relapse would give further benefits.

Curosurf is a porcine surfactant extract which, when given to babies with established severe respiratory distress syndrome in a single dose of 200 mg/kg, reduces neonatal mortality by 40% and the incidence of pneumothorax by half.[9] Two additional doses of 100 mg/kg 12 and 24 hours after initial treatment lead to a further reduction in neonatal mortality and pneumothorax.[5] This study, Curosurf 4, was designed to determine if a maximal cumulative dose of 300 mg/kg administered in up to three doses over 24 hours was as good as a total of up to 600 mg/kg administered in up to five doses over 72 hours.

Patients and methods

The surfactant used, Curosurf, was prepared by Chiesi Farmaceutici, Italy and supplied to trial collaborators. The preparation and composition of Curosurf have been previously described.[10] The criteria for entry were: (1) age <72 hours, (2) clinical[11] and radiological[12] diagnosis of respiratory distress syndrome, (3) endotracheal intubation, (4) arterial to alveolar oxygen tension (a/APO_2) ratio <0·22,[13] (5) no contraindication, such as a major malformation, as judged by the clinician responsible for care, and (6) parental consent. The trial was approved by the research ethics committees of each of the collaborating hospitals.

Table 1 Comparison of study groups at entry

	Low dose (n=1069)	*High dose (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)
Multiple births (%)	253/1069 (23·7)	291/1099 (26·5)
Age at randomisation (hours)		
Median (IQR)	6 (3, 14)	6 (3, 15)
No of babies	1043	1069
Inborn (%)	776/1065 (72·9)	815/1089 (74·8)
Antenatal steroids (%)	173/1061 (16·3)	189/1070 (17·7)
Caesarean section (%)	636/1060 (60·0)	643/1083 (59·4)
Apgar score 1 min		
Median (IQR)	5 (3, 7)	5 (3, 7)
No of babies	1043	1069
Apgar score 5 min		
Median (IQR)	8 (6, 9)	8 (6, 9)
No of babies	1037	1063
Chest radiography grades 3/4 RDS* (%)	670/1050 (63·8)	677/1074 (63·0)
FIO_2		
Mean (SD)	0·77 (0·18)	0·76 (0·19)
No of babies	1044	1067
PaO_2 (kPa)		
Mean (SD)	7·4 (2·5)	7·4 (2·4)
No of babies	1041	1060
$PaCO_2$ (kPa)		
Mean (SD)	5·7 (1·5)	5·7 (1·7)
No of babies	1044	1064
a/APO_2 ratio		
Mean (SD)	0·12 (0·05)	0·12 (0·06)
No of babies	1037	1054

FIO_2=Fractional inspired oxygen; PaO_2=arterial oxygen tension; $PaCO_2$=arterial carbon dioxide tension. IQR=interquartile range.
*Grades of respiratory distress syndrome (RDS) according to Giedion *et al.*[12]

Eligible babies were enrolled using a 24 hour telephone randomisation service based in Belfast, except in Israel where babies were randomised in Beersheva. Randomisation to low and high dose groups was stratified by centre using lists comprised of balanced blocks of 10 babies. Participating centres were unaware of the way that these lists were drawn up. Babies in the low dose group received 100 mg of surfactant/kg at entry and were eligible to receive up to two further doses of 100 mg/kg at intervals of 12 hours provided that they continued to need mechanical ventilation with supplemental oxygen. Babies in the high dose group received 200 mg of surfactant/kg at entry and were eligible to receive up to four further doses of 100 mg/kg at intervals of 12 hours. The total possible dose of surfactant allowed in the low dose group was 300 mg/kg and in the high dose group 600 mg/kg. Surfactant was administered as a bolus or boluses into the lower trachea as previously described.[5 9] After administration babies in both groups were treated similarly by first lowering inspired oxygen concentrations and inspiratory times, and later inspiratory pressures as indicated by clinical findings and blood gas analyses.

There were three primary measures of outcome: (1) death or oxygen dependence at 28 days, (2) death at any time before hospital discharge, and (3) death or oxygen dependence at expected date of delivery.

There were a number of prespecified secondary outcome measures: duration of hospital stay, duration of oxygen supplementation, duration of need for oxygen >40%, duration of endotracheal intubation, incidence of major cerebral abnormality on ultrasound scan (parenchymal haemorrhagic lesions, porencephalic cysts, cystic leukomalacia, hydrocephalus: more than 4 mm >97th centile,[14] or intraventricular haemorrhage complicated by ventricular dilatation >97th centile[14]) at 1 and 6 weeks, pneumothorax or other pulmonary air leak, pulmonary haemorrhage, patent ductus arteriosus requiring treatment, recurrent apnoea, necrotising enterocolitis, acquired pneumonia and sepsis, neonatal seizures treated with anticonvulsants, and retinopathy of prematurity graded according to the international classification.[15] In addition, oxygenation was assessed by measuring blood gases and calculating a/APO_2 ratios.[13]

The sample size was calculated on the basis of the third primary outcome measure. A trial of 2000 babies (1000 in each group) would have 80% power to detect as statistically significant ($p<0·05$; two tailed) a difference in the incidence of death or prolonged oxygen dependency of 15% in one treatment group versus 20% in the other. The strategy for the single planned interim analysis required that a major outcome be significant at the 0·3% level for early termination of the trial.[16] The data monitoring committee considered this interim analysis which was based on the results from the first 1000 babies and recommended completion of the trial. All final analyses were conducted on an 'intention to treat' principle and tests were performed at the 5% level of significance (two tailed). Results from the two groups were compared using the χ^2 test, the independent samples Z test, and the Mann-Whitney U test. For each of the primary end points confidence intervals for the differences in proportions were calculated. Logistic regression analysis was used to adjust the between-group comparisons of primary end points (the dependent variables in the analyses) for chance imbalances in baseline characteristics (the independent variables).

Results

A total of 2168 babies was enrolled in the trial from 82 collaborating hospitals in 13 countries. Study group characteristics at trial entry are shown in table 1. No comparison between the groups for any of these variables attained significance.

Results for the three primary outcomes are shown by group in table 2. There were no

*Table 2 Primary outcome measures by group; values are number (%)**

	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)	243 (22·8)
Not known	13	24
>37 weeks	9	9

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

Table 3 Summary of odds on an unfavourable outcome in the low dose group relative to the high dose group before and after adjustment for differences in baseline characteristics by multiple logistic regression analysis

	Unadjusted		*Adjusted for gestation, birth weight, and gender*	
Primary outcome	*Relative odds (95% CI)*	*p Value*	*Relative odds (95% CI)*	*p Value*
Status at 28 days	1·01 (0·86 to 1·20)	0·87	1·10 (0·88 to 1·37)	0·42
Status at discharge	1·08 (0·89 to 1·32)	0·42	1·19 (0·96 to 1·48)	0·13
Status at expected date of delivery	1·06 (0·88 to 1·27)	0·54	1·17 (0·94 to 1·44)	0·17

Table 4 Secondary outcome measures by treatment group

	Low dose (n=1069)	*High dose (n=1099)*
Duration of hospital stay (days)		
Median (IQR)	44 (19, 75)	45 (19, 76)
No of babies	1058	1087
Duration of supplemental oxygen (days)		
Median (IQR)	10 (4, 34)	8 (4, 34)
No of babies	1014	1035
Duration of >40% oxygen (days)		
Median (IQR)	3 (1, 11)	3 (1, 12)*
No of babies	1057	1074
Duration of intubation (days)		
Median (IQR)	6 (3, 14)	5 (3, 15)
No of babies	1065	1083
Abnormal cerebral ultrasound nearest to 1 week (%)	143/896 (16·0)	154/929 (16·6)
Abnormal cerebral ultrasound nearest to 6 weeks	107/642 (16·7)	96/648 (14·8)
Pneumothorax or other air leak (%)	201/1061 (18·9)	178/1085 (16·4)
Pulmonary haemorrhage (%)	59/1061 (5·6)	74/1082 (6·8)
Patent ductus arteriosus (%)	380/1059 (35·9)	384/1081 (35·5)
Recurrent apnoea (%)	281/1048 (26·8)	287/1075 (26·7)
Necrotising enterocolitis (%)	56/1055 (5·3)	72/1076 (6·7)
Acquired pneumonia (%)	112/1057 (10·6)	131/1077 (12·2)
Acquired sepsis (%)	214/1056 (20·2)	230/1076 (21·4)
Retinopathy of prematurity stages 3, 4 (%)	44/937 (4·7)	36/935 (3·9)
Seizures (%)	92/1056 (8·7)	92/1073 (8·6)

*p<0·05 (Mann-Whitney U test). IQR=interquartile range.

Table 5 Blood gas changes at 1 hour, 12 hours, and values at 36 hours after the first dose by treatment group

	Low dose		*High dose*		
	No	*Mean (SD)*	*No*	*Mean (SD)*	*Difference (95% CI)*
Change at 1 hour					
F_{IO_2}	1039	−0·26 (0·20)	1063	−0·28 (0·21)	−0·02 (−0·04 to −0·01)**
Pa_{O_2} (kPa)	1028	+1·2 (4·0)	1054	+1·5 (4·3)	0·3 (0·0 to 0·7)
Pa_{CO_2} (kPa)	1034	−0·2 (1·5)	1059	−0·3 (1·7)	−0·1 (−0·2 to 0·1)
a/AP_{O_2} ratio	1024	+0·14 (0·14)	1045	+0·17 (0·16)	0·03 (0·02 to 0·04)***
Change at 12 hours					
F_{IO_2}	1007	−0·22 (0·23)	1028	−0·31 (0·23)	−0·09 (−0·11 to −0·07)***
Pa_{O_2} (kPa)	996	+0·2 (3·1)	1013	+0·5 (3·0)	0·3 (0·0 to 0·6)*
Pa_{CO_2} (kPa)	1001	−0·3 (1·8)	1021	−0·6 (1·9)	−0·3 (−0·4 to −0·1)***
a/AP_{O_2} ratio	991	+0·11 (0·14)	1005	+0·18 (0·17)	0·07 (0·06 to 0·08)***
Values at 36 hours					
F_{IO_2}	950	0·41 (0·22)	980	0·38 (0·20)	−0·03 (−0·05 to −0·02)***
Pa_{O_2} (kPa)	932	8·1 (2·2)	963	8·1 (2·0)	0·0 (−0·2 to 0·2)
Pa_{CO_2} (kPa)	945	5·6 (1·4)	977	5·5 (1·2)	−0·1 (−0·2 to 0·0)
a/AP_{O_2} ratio	929	0·34 (0·18)	961	0·37 (0·19)	0·03 (0·01 to 0·05)***

*p<0·05, **p<0·01, ***p<0·001.
F_{IO_2}=fractional inspired oxygen; Pa_{O_2}=arterial oxygen tension; Pa_{CO_2}=arterial carbon dioxide tension.

significant differences between the groups for any of these outcomes. For the first primary outcome 51·1% of the low dose group were either dead or oxygen dependent at 28 days compared with 50·8% of the high dose group (difference −0·3%, 95% confidence interval (CI) −4·6% to 3·9%); for the second primary outcome 25·0% of the low dose group and 23·5% of the high dose group were dead before hospital discharge (difference −1·5%, 95% CI −5·1% to 2·2%); and for the third primary outcome, 32·2% of the low dose group and 31·0% of the high dose group were dead or oxygen dependent at expected date of delivery (difference −1·2%, 95% CI −5·2% to 2·7%). Logistic regression showed that centre to centre variations in outcome were significant, but these did not confound the comparison of doses because the randomisation was stratified by centre. Adjustment for other statistically significant prognostic variables recorded at randomisation tended to favour the high dose group (reflecting the fact that they were slightly lighter and less mature) but none of the three end points differed significantly (p<0·05) between the low and high dose groups in the adjusted analyses (table 3).

There were 74 protocol deviations, 40 in the low dose group and 34 in the high dose group. Forty five babies, 19 in the low dose group and 26 in the high dose group, were not given surfactant after randomisation and 12 babies in the low dose group were given more than three doses of surfactant. The other major reason for protocol violation was congenital malformations (eight in the low dose group and five in the high dose group). The four remaining babies, one in the low dose and three in the high dose group, were randomised after 72 hours, did not have respiratory distress syndrome or could not be traced. The primary outcomes, after exclusion of these 78 babies, were very similar and there remained no significant differences between groups.

One prespecified secondary outcome measure did differ significantly between groups, fewer days being spent in >40% oxygen in the high dose group. The relative crudeness of the median masks the difference detected by the Mann-Whitney U test (table 4). However, 512 (48·4%) babies in the low dose were in >40% oxygen after 3 days compared with 458 (42·6%) of the high dose group (p<0·01). There were no differences in cerebral abnormality rates based upon ultrasound scans at 1 and 6 weeks and complication rates were similar in both groups (table 4).

Oxygenation of babies in the high dose group was better during the first 36 hours after treatment (table 5). Babies in the low dose group had a mean (SD) of 2·4 (0·8) doses of surfactant (242 (81) mg phospholipid/kg) compared with 2·8 (1·5) doses (380 (147) mg phospholipid/kg) in the high dose group. Of the 1050 babies in the low dose group who were given a first dose of surfactant, 813 (77·4%) received a second and 651 (62·0%) a third dose compared with 740 (69·1%) and 580 (54·2%) respectively of the 1071 babies in the high dose group (both p<0·001).

Discussion

In this trial a low dose surfactant regimen was found to be as effective as a high dose regimen to treat babies with severe respiratory distress syndrome. For Exosurf, a synthetic, protein-free surfactant, two doses (up to 135 mg phospholipids/kg) were as good as four doses (up to 270 mg/kg).[6] For Curosurf, a porcine lung extract, an average total dose of 242 mg/kg was as good as 380 mg/kg, and was probably enough to replace the total pool of surfactant phospholipids in the neonatal lung[17] and to overcome inactivation or inhibition by other proteins leaking into the airways.[18] This

dose is about 80 times that of the estimated amount of phospholipids needed to form an alveolar monolayer.[19] This may explain why the higher dosage achieved no further benefit. It is unlikely that the higher dose led to overloading of the surfactant system as increased doses of phospholipid lead to faster clearance and turnover in the rabbit with no evidence of accumulation.[20]

Of the three primary and 15 secondary comparisons of clinical outcome, only one, the number of days receiving >40% oxygen, significantly favoured the high dose group and then only weakly ($p<0.05$). As no adjustment was made to allow for the large number of comparisons performed, this isolated secondary result should be interpreted with caution.

There were dose-dependent effects of surfactant on oxygenation with blood gas measurements favouring the high dose group during the first 36 hours after treatment. These early benefits of high dose treatment were not reflected in improved long term outcome, although fewer babies needed retreatment compared with the low dose group.

This study is one of the largest ever performed in neonatology. Its inability to detect a difference in efficacy between the two dose regimens is an important finding as the sample size was sufficiently large to ensure that any clinically worthwhile difference would be detected with high probability. The extra 140 mg of surfactant/kg used in the high dose group could cost up to £800[21] so that adoption of the low dose regimen would be considerably more cost effective.

Furthermore, this study helps to define the optimal dose regimen for a natural surfactant. This information, together with overviews of trials of prophylaxis versus 'rescue' treatment with natural surfactant and data from the OSIRIS trial[6] of Exosurf should provide a sound basis for the planning of any future comparative study of these surfactants. Such a trial is necessary because of the apparent superiority of natural surfactants compared to synthetic surfactants in animal studies.[22] Direct comparison of outcomes between babies enrolled in the OSIRIS and Curosurf 4 trials is not valid because of the lack of randomisation and the well documented differences in outcome which exist from centre to centre.[23] Any comparative trial will need to be large and to involve many centres. For example, a trial of 7500 infants (3750 per group) will be necessary to have 80% power to detect a difference in the rate of death or prolonged oxygen dependency of 29% with one surfactant versus 32% with the other. As about 30% of babies in both the OSIRIS and Curosurf 4 trials were oxygen dependent at 28 days any future comparative trial should probably also study in a factorial design the early use of dexamethasone in an attempt to reduce chronic lung morbidity.[24]

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