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A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome

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Abstract. We performed a multicenter prospective randomized controlled trial to determine the efficacy and safety of the surfactant preparation, Survanta (Abbott Laboratories, Chicago, USA), for 750–1750 g infants with idiopathic respiratory distress syndrome, (IRDS) receiving assisted ventilation with 40% or more oxygen. One hundred and six eligible infants from the eight participating centers were randomly assigned between March 1986 and June 1987 to receive either surfactant (100 mg phospholipid/kg, 4 ml/kg) or air (4 ml/kg) administered into the trachea within 8 h of birth (median time of treatment 6.2 h, range 3.2–9.1 h). The study was stopped before enrollment was completed at the request of the United States Food and Drug Administration when significant differences were observed in incidence of periventricular-intraventricular hemorrhage (PIH), between the surfactant treated and control infants. Surfactant treated infants had larger average increases in the arterial-alveolar oxygen ratio, (a/A ratio) ($P < 0.0001$), and larger average decreases in FiO_2 ($P < 0.0001$) and mean airway pressure, (MAP) ($P < 0.017$) than controls over the 48 h following treatment. The magnitude of the differences between the surfactant and control groups were 0.19 (SE = 0.03) for a/A ratio, −0.28 (SE = 0.04) for FiO_2 and −1.7 cm H_2O (SE = 0.70) for MAP. The clinical status on days 7 and 28 after treatment was classified using four predefined ordered categories: (1) no respiratory support; (2) supplemental O_2 with or without continuous positive airway pressure (CPAP); (3) intermittent mandatory ventilation; and (4) death. There were no statistically significant differences in the status categories on days 7 or 28 between surfactant and control infants. There were no significant differences between the groups with respect to the incidence of patent ductus arteriosus, bronchopulmonary dysplasia, necrotizing enterocolitis, air leaks or death. There was a statistically significant difference between treated and control infants in the frequency and severity of periventricular-intraventricular hemorrhage (PIH) (Cochran-Mantel-Haenszel χ^2adj=6.36, $P = 0.01$). Hemorrhages occurred in 59.6% of surfactant treated infants and 26.9% of controls. Severe hemorrhages (grades 3 or 4) occurred in 38.5% of surfactant treated infants and 15.4% of controls (χ^2adj = 4.01, $P = 0.045$). We conclude that the intratracheal administration of Survanta prior to 8 h of age to infants with IRDS receiving assisted ventilation with 40% or more oxygen results in a reduction in the severity of respiratory distress during the 48 h after therapy. Because of the difference in incidence of PIH between surfactant and control infants in this study, we recommend that future clinical trials of surfactant include more frequent prospective serial ultrasound evaluations for diagnosis of hemorrhage.

Key words: Surfactant – Idiopathic respiratory distress syndrome – Clinical trial – Randomization

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Abbreviations: a/A ratio = arterial-alveolar pO_2 ratio; ANOVA = analysis of variance; BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen; IRDS = idiopathic respiratory distress syndrome; MAP = mean airway pressure; NEC = necrotizing enterocolitis; PaO_2 = partial pressure of oxygen in arterial blood; PAO_2 = partial pressure of oxygen in the alveolus; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PDA = patent ductus arteriosus; PIH = periventricular-intraventricular hemorrhage

Introduction

In 1980, Fujiwara and coworkers [4] first described improvements in oxygenation and ventilation following surfactant treatment of infants with hyaline membrane disease. Since then, the ability of exogenous surfactants from human or

other animal sources to modify the course of respiratory disease in infants with or at risk for developing idiopathic respiratory distress syndrome, (IRDS) has been subsequently confirmed in 13 randomized controlled trials [1, 3, 5, 6, 8, 10, 13, 15, 17, 20, 23, 25, 26]. These trials have varied in terms of patient selection criteria, surfactant preparations, and the timing and dosage schedule for surfactant administration. Despite the differences in study design, intratracheal surfactant administration resulted in improved blood gases and reduced oxygen requirements or ventilator settings in all of these trials. The optimal strategy for using surfactant, however, is currently unknown. Furthermore, the impact of surfactant therapy on mortality and serious morbidity remains uncertain. Serious adverse effects have not been observed.

We report the results of a multicenter prospective randomized controlled trial designed to determine the efficacy and safety of a single dose of a new surfactant preparation, Survanta (Abbott Laboratories, Chicago, USA).

The primary goals of this study were to determine whether surfactant administered within 8 h after birth to infants weighing 750–1750 g with IRDS requiring assisted ventilation and a fraction of inspired oxygen (FiO_2) ≥ 0.40:

1. Improves oxygenation during the first 48 h after treatment as measured by the alveolar/arterial (a/A) oxygen ratio.

2. Decreases the need for respiratory support during the first 48 h following treatment as demonstrated by decreases in FiO_2 and mean airway pressure (MAP).

3. Leads to improved clinical status on days 7 and 28.

Secondary goals were to determine whether the administration of surfactant was associated with any adverse clinical events.

Methods

Eligibility

Eligibility criteria were: (1) birthweight of 750–1750 g inclusive; (2) a clinical diagnosis of IRDS made between 3 and 6 h after birth based on clinical evidence of respiratory distress associated with a chest X-ray showing decreased lung volumes and a diffuse reticulogranular pattern; (3) assisted ventilation with an $FiO_2 \geq 0.4$; (4) presence of an arterial catheter; (5) normotension [30]; (6) blood glucose ≥ 40 mg/dl; (7) absence of seizures at time of study entry; (8) written informed parental consent.

Exclusion criteria were: (1) major congenital malformations or diseases (other than IRDS) of the cardiorespiratory, gastrointestinal, genitourinary or central nervous system; (2) pneumothorax or pneumopericardium; and (3) maternal use of intravenous narcotics at any time during gestation.

Blinding

In order to keep the physicians and nurses providing clinical care to study infants blinded as to treatment assignment, a physician, called the dosing investigator, was assigned for each subject. The dosing investigator was responsible for randomization of eligible infants and preparation and administration of the study treatment. The dosing investigator was aware of treatment assignment, but was not supposed to participate in the clinical care or post-treatment study assessments of enrolled infants.

Randomization

Infants were enrolled and randomized between 3 and 6 h after birth. They were stratified by birthweight (750–799 g, 1000–1249 g, 1250–1499 g, 1500–1750 g) and randomized by the dosing investigator who opened the next sequential opaque sealed envelope for the appropriate weight stratum. Separate randomization schedules were generated for each center.

Surfactant

Survanta is an organic solvent extract of minced cow lung which has been supplemented with dipalmitoyl phosphatidylcholine, palmitic acid and tripalmitin and dispersed in aqueous saline (25 mg of phospholipid per ml). The surfactant is autoclaved for sterilization and stored frozen. Survanta, which is thawed to a liquid state prior to use, is a modification of Surfactant-TA (Tokyo-Tanabe Co., Tokyo, Japan) which is stored as a lyophilized powder and dispersed in saline by sonication prior to administration [4, 27].

Treatment

After randomization, the dosing investigator prepared and administered the study treatment. Survanta was thawed for 20 min at room temperature or by holding the vial in the hand for 8 min. The liquid surfactant (100 mg phospholipid/kg of body weight, 4 ml/kg) was then drawn into a syringe through a needle. A similar syringe of air was prepared for placebo treatments. Treatment was administered as soon after randomization as possible and before 8 h of age, unless the infant, suffered clinical deterioration defined as either pneumothorax, pneumopericardium, hypotension, bradycardia, hypoglycemia or seizures. If deterioration occurred, treatment was administered following restabilization.

Survanta or air placebo was administered by the dosing investigator and a temporarily assigned nurse not providing clinical care to the patient. The infant's bed was screened from nursery personnel. The clinical caretakers were not present during treatment and remained blinded to treatment assignment.

The treatment protocol was standardized at an investigator's meeting, and by providing written instructions and a detailed videotaped demonstration to each center. Prior to treatment, blood and tracheal aspirate cultures, complete blood counts and serum electrolytes were obtained. Five minutes before the study treatment was administered, arterial blood gases and blood glucose were obtained and vital signs, ventilator settings, FiO_2 and MAP were recorded. Then, just prior to treatment, the ventilator settings were changed to a rate of 60 breaths/min, and an inspiratory time of 0.5 s. Pretreatment pressures were maintained. If the pretreatment rate was greater than 60/min, it was not changed, but the inspirator: expiratory time (I:E) ratio was adjusted to 1:1.

Survanta (4 ml/kg) or air placebo (4 ml/kg) was administered in four equal aliquots through a 5-French feeding tube measured and cut to length so that it would be positioned at the end of the endotracheal tube. For each treatment, the infant was briefly disconnected from the ventilator while the surfactant or air was instilled. Four positions with the infant at

a 45° incline were used in sequence: (1) head down, body turned to right side; (2) head down, body turned to left side; (3) head up, body turned to right and; (4) head up, body turned to the left. Following each aliquot the infant was held in position and reconnected to the ventilator for 30 s before the next aliquot was given. Following the final aliquot, the infant was placed in a supine position. The dosing investigator remained with the infant for 5 min during which time only the FiO_2 was adjusted to maintain PaO_2 or $TcPO_2$ less than 100 mm Hg. Responsibility for the infant's care was then returned to the clinical staff. The trachea was not suctioned during the 2 h following treatment administration unless tube obstruction was suspected.

Assessment schedule

Arterial blood gases were obtained 5 min, 30 min, and 1, 4, 12, 24, 36, and 48 h after treatment. Ventilator settings, FiO_2, and MAP were recorded at those times and then daily for the 1st week. The MAP was measured at the endotracheal tube connector using a respirator monitor (Pneumogard Model 1200, Novametrix Medical Systems, Inc., Wallingford, USA).

Cardiopulmonary assessment was recorded at 4 and 12 h after treatment and then daily for 28 days. This assessment included systolic, diastolic and mean blood pressure (oscillometric or arterial catheter) and examination for systolic murmur, hyperdynamic precordium and increased brachial or femoral pulses.

A cranial ultrasound was scheduled between 7 and 10 days after birth. Laboratory studies including complete blood count, serum electrolytes, total and direct bilirubin and serum creatinine were obtained at 1, 3 and 10 days after treatment. Serial blood samples for determination of antibodies to surfactant proteins were also obtained at scheduled intervals during the 28 day study period.

Study infants were classified at the end of each 24 h interval following completion of study treatment using 4 ordered categories: (1) no supplemental O_2 or respiratory support; (2) supplemental O_2 with or without continuous positive airway pressure (CPAP); (3) intermittent mandatory ventilation at any rate; and (4) death.

Post-treatment evaluations were performed by clinicians blinded to treatment assignment.

Analysis

The major null hypotheses for which statistical testing was prospectively planned were:

1. There are no differences in the average changes over 48 h from pretreatment baselines between surfactant and air placebo treated infants regarding a/A ratio, FiO_2 and MAP.

2. There are no differences in clinical status on days 7 and 28 defined using a scale for four ordered categories between surfactant and air placebo treated infants.

The arterial/alveolar oxygen ratio was calculated as a/A ratio = PaO_2/PAO_2, where PaO_2 is the partial pressure of oxygen in arterial blood. The alveolar partial pressure of oxygen, PAO_2, was calculated using the modified alveolar air equation [3]:

$$PAO_2 = FiO_2\,(713) - PaCO_2/0.8,$$

where $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood, 713 mm Hg is an estimate of barometric pressure minus the vapor pressure of water at body temperature and 0.8 is the respiratory quotient.

The average changes over 48 h from pretreatment levels for a/A ratio, FiO_2 and MAP were determined for each individual study infant by computing the area under the time curve for each parameter using the trapezoidal rule, then dividing the result by 48 h and finally subtracting the pretreatment (−5 min) value. The resulting average changes from pretreatment baseline for individual infants were analyzed using analysis of variance (ANOVA) to compare the effects of surfactant and air placebo. The ANOVA model included main effects for treatments, center, birthweight group and the 2-way interactions of treatment with center and birthweight group. By prior design, for infants dying before 48 h, the last available post-treatment values for a/A ratio, FiO_2 or MAP were utilized for observations beyond the point of death. Infants breathing spontaneously without an endotracheal tube were assigned an MAP of 2 cm H_2O.

The clinical status on days 7 and 28 post-treatment were analyzed by the Cochran-Mantel-Haenzel test for ordered categories.

The diagnoses of patent ductus arteriosus, bronchopulmonary dysplasia, periventricular-intraventricular hemorrhage, necrotizing enterocolitis and air leak were standardized by protocol. The frequencies of these diagnoses in the two groups were compared using the Fisher's Exact test.

The diagnosis of hemodynamically significant patent ductus arteriosus was made when all of the following were present: (1) systolic or continuous murmur; (2) hyperdynamic precordium; and (3) increased brachial or femoral pulses or a pulse pressure of 35 mm Hg or more.

Bronchopulmonary dysplasia (BPD) was diagnosed given: (1) primary pulmonary disease requiring positive pressure ventilation within the first 3 days of life; (2) continued respiratory insufficiency due to pulmonary pathology requiring daily oxygen supplementation to maintain $PaO_2 > 50$ mm Hg at day 28 of life; and (3) pulmonary parenchymal abnormalities on chest X-ray at 28 days after birth [18]. Abnormalities were defined as either alternating areas of hyperinflation and atelectasis, fibrosis or cystic change.

Periventricular-intraventricular hemorrhage (PIH) was assessed by a cranial ultrasound or autopsy and graded using the criteria of Papile et al. [22].

Necrotizing enterocolitis was diagnosed at surgery or postmortem or if at least one clinical sign (bilious gastric aspirate, emesis, abdominal distension, occult or gross blood in the stool) and at least one radiologic finding (pneumatosis intestinales, hepato-biliary gas, or pneumoperitoneum) were present.

Air leaks, defined as either pneumothorax or pneumopericardium, were diagnosed radiologically or by emergency evacuation of air prior to obtaining an X-ray.

A decision was made when the study was designed to exclude from primary analysis any infant with a positive pretreatment blood culture for an organism on a predetermined list of pathogens.

Study administration, data monitoring, and statistical analysis were performed by Abbott Laboratories. All analyses were done using SAS [24]. The Cochran-Mantel-Haenszel tests were done with the SAS procedure FREQ using the chi squared and CMH options. All analyses of the average change in a/A ratio, FiO_2 and MAP during the first 48 h were done with the SAS procedure GLM using type IV sums of squares.

SAS procedures *T*-test and FREQ were used where appropriate for comparisons of treatment groups with respect to baseline, concurrent diagnoses and laboratory variables.

The study was approved by the institutional review boards at all participating centers and written informed parental consent was obtained for all study infants.

Results

There were 586 infants weighing 750–1750 g admitted to the eight participating units between March 1986 and June 1987. One hundred and six of these infants were enrolled in the study. The number of infants enrolled per center ranged from 9 to 17. The study was stopped prior to enrolling the planned 169 infants at the request of the United States Food and Drug Administration when an increased incidence of intracranial hemorrhage was observed in surfactant treated infants.

One infant randomized to the control group died prior to treatment and is excluded from analysis. Two infants weighing less than 750 g were mistakenly enrolled and randomized to receive surfactant. They are included in the analysis in the 750–999 g weight group if data for a specific variable was collected. Two infants in the surfactant group with positive pre-

Table 1. Maternal and obstetrical characteristics of the study groups

	Surfactant		Control		*P*-value
	n	(%)	*n*	(%)	
Maternal race:					0.15
Black	2	(3.8)	0	(0)	
Caucasian	50	(94.3)	49	(92.4)	
Other	1	(1.9)	4	(7.6)	
Tocolytic therapy	34	(64.2)	31	(58.5)	0.69
Steroid therapy	20	(37.7)	26	(49.1)	0.33
Mode of delivery:					0.53
vaginal	14	(26.4)	13	(24.5)	
elective C/S	11	(20.8)	16	(30.2)	
emergency C/S	28	(52.8)	24	(45.3)	
Birth at study center	36	(67.9)	34	(66.7)	1.00

Table 2. Characteristics of study infants

	Surfactant ($n = 53$)	Control ($n = 53$)	*P*-value
Birthweight[a] (g)	1172 ± 287	1131 ± 236	0.43
Gestational age[a] (weeks)	28.6 ± 2.0	28.6 ± 2.0	0.96
Sex			0.70
Male	32 (60.4%)	29 (54.7%)	
Female	21 (39.6%)	24 (45.3%)	
Apgar score[a]			
1 min.	4.2 ± 2.0	4.7 ± 2.2	0.21
5 min.	7.1 ± 1.9	7.4 ± 1.7	0.34
Treatment administered[b] (h)	6.3 (3.3–9.1)	6.0 (3.2–9.0)	0.55

[a] Mean ± SD
[b] Median (range), data missing for 1 control infant

Table 3. Five minute pretreatment values for a/A ratio, FiO_2 and MAP

	Surfactant	Control	*P*-value[a]
a/A ratio[b]			
n	51	52	
Mean ± SE	0.13 ± 0.01	0.15 ± 0.01	0.31
FiO_2[b]			
n	51	52	
Mean ± SE	0.77 ± 2.7	0.72 ± 3.0	0.28
MAP[c]			
n	48	52	
Mean ± SE	11.7 ± 0.5	12.6 ± 0.5	0.19

[a] Based on F-test results for treatment differences
[b] Analysis excludes 1 infant who died prior to treatment, 2 with pretreatment sepsis
[c] MAP data missing for 3 infants

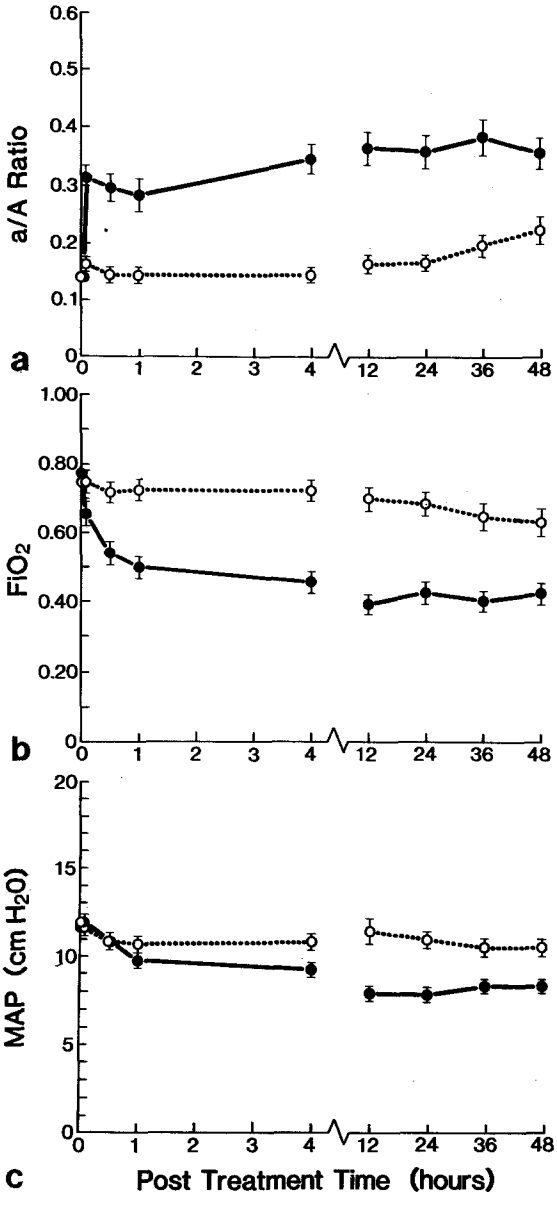

Fig. 1a–c. 48 h time course of a/A ratio (**a**), FiO_2 (**b**) and MAP (**c**) for Survanta (●) and control (○) infants. *Bars* represent mean ± SEM

Table 4. Analysis of variance results for average change form baseline over 48 h for a/A ratio, FiO_2 and MAP[a]

Effect	Degree of freedom	a/A ratio		FiO_2		MAP	
		F	*P*	F	*P*	F	*P*
Treatment	1	51.0	0.0001*	50.7	0.0001*	5.97	0.017*
Birthweight	3	1.73	0.168	0.93	0.43	0.07	0.98
Center	7	2.28	0.036*	1.41	0.21	2.50	0.025*

[a] ANOVA model included 3 main effects and the 2-way interactions of treatment with center and birthweight group. There were no significant interaction terms. F-statistics and *P*-values are shown for the main effects
* $P < 0.05$

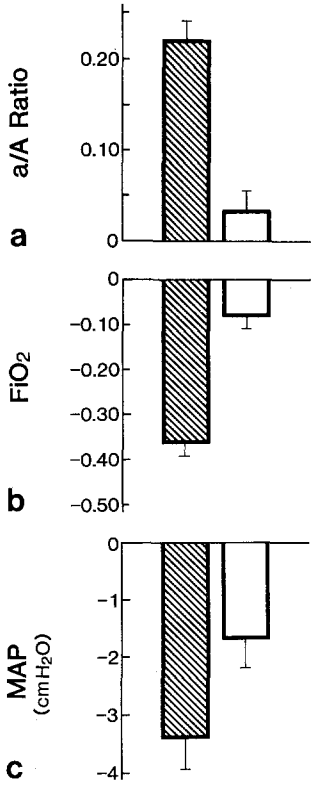

Fig. 2a–c. Average change over 48 h (± SEM) from pre-treatment baseline for a/A ratio (**a**), FiO_2 (**b**) and MAP (**c**) for Survanta (▨) and control (□) infants. Differences between groups were significant for all three parameters (a/A ratio $P < 0.0001$; FiO_2 $P < 0.0001$; MAP, $P = 0.017$)

treatment blood cultures were excluded from the efficacy analyses, but included in the analyses of adverse effects.

There were no statistically significant differences between infants randomized to the surfactant and control groups with respect to maternal or obstetrical factors (Table 1), infant characteristics (Table 2) or pretreatment baseline values for a/A ratio, FiO_2 or MAP (Table 3).

The 48 h time courses of a/A ratio, FiO_2 and MAP are shown in Fig. 1. The results of the analysis of variance for the 48 h average change from pretreatment baseline for a/A ratio, FiO_2 and MAP are shown in Table 4. There were statistically significant differences between surfactant treated and control infants with respect to a/A ratio ($P < 0.0001$), FiO_2 ($P < 0.0001$) and MAP ($P = 0.017$). There were also significant center differences for a/A ratio ($P = 0.036$) and MAP ($P = 0.023$). There were no statistically significant differences among the four birthweight categories and there were no significant interactions between treatment group and any other main effect.

The magnitude of the average 48 h changes from pretreatment baseline for a/A ratio, FiO_2 and MAP are shown in Fig. 2. The treatment differences (surfactant-control, mean ± SE) were 0.19 ± 0.3 for a/A ratio, -0.28 ± 0.04 for FiO_2 and -1.7 ± 0.7 cm H_2O for MAP. Thus surfactant treated infants had a greater average increase in a/A ratio and larger average decreases in FiO_2 and MAP over the 48 h following treatment than controls.

Table 5. Clinical status on day 7

	Surfactant		Control	
	n	(%)	*n*	(%)
No respiratory support	2	(4.0)	1	(1.9)
Supplemental O_2 and/or CPAP	7	(14.0)	3	(5.8)
Intermittent mandatory ventilation	33	(66.0)	38	(73.1)
Death	*8*	(16.0)	*10*	(19.2)
Total	50	(100)	52	(100)

Cochran-Mantel-Haenzel $x^2 = 1.92$, $P = 0.17$

Table 6. Clinical status on day 28

	Surfactant		Control	
	n	(%)	*n*	(%)
No respiratory support	16	(32.0)	13	(25.0)
Supplemental O_2 and/or CPAP	11	(22.0)	16	(30.8)
Intermittent mandatory ventilation	11	(22.0)	7	(13.4)
Death	*12*	(24.0)	*16*	(30.8)
Total	50	(100)	52	(100)

Cochran-Mantel-Haenzel $x^2 = 0.43$, $P = 0.51$

Table 7. Concurrent diagnoses through day 28

	Surfactant (%)	Control (%)	*P*-value
Patent ductus arteriosus	21/52 (40.4)	22/52 (42.3)	1.00
Necrotizing enterocolitis	4/52 (7.7)	4/52 (7.7	1.00
Air leaks	10/52 (19.2)	16/52 (30.8)	0.26
Bronchopulmonary dysplasia[a]	13/40 (32.5)	7/36 (19.4)	0.30

[a] Denominators include infants alive on day 28

Table 8. Periventricular intraventricular hemorrhage in study subjects

	Surfactant		Control	
	n	(%)	*n*	(%)
None	21	(40.4)	38	(73.1)
Grade I or II	11	(21.2)	6	(11.5)
Grade III or IV	*20*	(38.5)	*8*	(15.4)
Total	52		52	

Adjusted Cochran-Mantel-Haenzel x^2adj = 6.36, $P = 0.01$

Table 9. Periventricular-intraventricular hemorrhage, (PIH) and severe (grades 3 and 4) PIH by center

Center	ANY PIH				Severe PIH			
	Surfactant		Control		Surfactant		Control	
Zürich	5/8	(63%)	0/6	(0%)	3/8	(38%)	0/6	(0%)
Berlin	2/7	(29%)	0/9	(0%)	2/7	(29%)	0/9	(0%)
Milan	5/6	(83%)	0/4	(0%)	4/6	(67%)	0/4	(0%)
Heidelberg	5/7	(71%)	2/7	(29%)	5/7	(71%)	1/7	(14%)
Frankfurt	4/6	(67%)	2/6	(33%)	2/6	(33%)	0/6	(0%)
Düsseldorf	3/6	(50%)	3/7	(43%)	1/6	(17%)	2/7	(29%)
Munich[a]	5/7	(71%)	4/9	(44%)	2/7	(29%)	3/9	(33%)
Munich[b]	2/5	(40%)	3/4	(75%)	1/5	(75%)	2/4	(50%)
Total	31/52	(59.5%)	14/52	(26.9%)	20/52	(38.5%)	8/52	(15.4%)

[a] Klinikum Grosshadern der Universität
[b] Kinderklinik der Universität

The 7 and 28 day status of study infants is shown in Tables 5 and 6. There were no statistically significant differences on either day 7 or day 28. The concurrent diagnoses other than intraventricular hemorrhage are shown in Table 7. There were no statistically significant differences in the frequency of patent ductus arteriosus, necrotizing enterocolitis, or air leaks (pneumothorax or pneumomediastinum) between the groups. One surfactant treated infant who had a pneumothorax prior to treatment is included. A diagnosis of BPD was made in 13 of the 40 surfactant treated infants alive on day 28 and in 7 of the 36 control infants alive on day 28. There were no significant differences in the proportion of survivors on day 28 (76% for surfactant, 69.2% for controls, $\chi^2 = 0.56$, $P = 0.46$).

Table 8 shows the occurrence and severity of PIH in surfactant treated and control infants diagnosed either by ultrasound or autopsy. One infant in the control group died without either an autopsy or cranial ultrasound and was considered not to have PIH. Both the frequency and severity of PIH was greater in surfactant treated infants (χ^2 adj = 6.36, $P = 0.01$). Hemorrhages occurred in 59.6% of surfactant treated infants and 26.9% of controls. Severe hemorrhages (Grade 3 or 4) occurred in 38.5% of surfactant treated infants and 15.4% of controls (χ^2 adj = 4.01, $P = 0.045$). The adjusted χ^2 values, χ^2 adj, shown for these statistical comparisons maintain the Type I error rate of 5% planned for the completed study since enrollment was stopped prematurely [21]. The incidence of PIH was higher in the surfactant groups at 7 of the eight participating centers; the incidence of severe (Grades 3 or 4) PIH was higher in the surfactant groups at 5 of the 8 centers (Table 9).

Discussion

We have shown that a single intratracheal dose of Survanta given to infants with IRDS receiving assisted ventilation results in improved respiratory status during the 48 h following therapy. This result is consistent with the early respiratory improvement noted following surfactant therapy in numerous other clinical trials [1, 3, 5, 6, 8, 10, 13, 15, 17, 20, 23, 25, 26].

In comparing this trial to previous ones, it is useful to classify the trials into two broad categories. The "rescue" trials [3, 7, 13, 15, 20, 26, 29, 31], of which the current study is an example, have used surfactants to treat infants with established IRDS, whereas the "prevention" [3, 7, 13, 15, 20, 26, 29, 31] trials have used surfactant treatment prior to the first breath or within minutes of delivery to modify the course of IRDS in high risk infants. Other differences in study design which must be considered in comparing the results of previous surfactant trials include the type of surfactant used, the dose, timing and frequency of administration and the patient selection criteria.

Surfactant preparations have included protein-free synthetic surfactants [29, 31], surfactant extracted from human omniotic fluid [8, 17, 20], and surfactants extracted from other mammalian sources [1, 3, 5, 6, 10, 13, 15, 17, 23, 25, 26]. Several recent reviews of the results of the previously reported trials are available [2, 10, 28].

All eight of the previously reported rescue trials using natural surfactant extracts have demonstrated early respiratory improvement in the surfactant treated infants [1, 5, 6, 8, 10, 17, 23, 25]. Measures of acute respiratory efficacy have included measured blood gas values, ventilator parameters and several different derived indices of oxygenation and ventilation [9]. In this trial we used the average changes over 48 h from pre-treatment baseline as determined from the areas under the curves for a/A ratio, FiO_2 and MAP. Survanta treated infants have larger average increases in a/A ratio and larger average decreases in both FiO_2 and MAP compared to controls. These results are consistent with effects observed in the multicenter rescue trial of Survanta performed in the United States [10] using a nearly identical protocol where the observations were made over 72 h rather than 48 h.

The results of surfactant therapy with respect to mortality and serious morbidity are less certain than the effects on early respiratory course. We did not observe a reduction in neonatal mortality in this study or in the multicenter American trial of Survanta referred to above [10]. Decreases in mortality have been observed in two previous rescue trials [1, 23] and in two prevention trials [3, 20].

A primary goal of this study was to compare surfactant treated and control infants on days 7 and 28 with respect to four ordered categories of clinical status. No statistically significant differences were noted between the groups on either day 7 or 28 in this study or in the multicenter American trial of Survanta which used a five category scale to classify clinical status [10].

Secondary goals of the study included comparing surfactant and control infants with respect to complications of neonatal intensive care including PIH, BPD, patent ductus ar-

teriosus, (PDA), necrotizing enterocolitis, (NEC) and air leak syndromes.

We did observe differences between treated and control infants in the incidence and severity of PIH. Hemorrhages occurred in 59.6% of surfactant treated infants and 26.9% of the controls; severe hemorrhages (Grades 3 or 4) occurred in 38.5% of surfactant treated infants and 15.4% of controls. Subsequent evaluation suggested that the incidence of PIH in Survanta-treated infants was similar to previous experience in the same centers and was consistent with the wide range of incidences reported in the literature. An analysis of ventilator settings and blood gas values before and after surfactant administration did not demonstrate any effect of these variables on the occurrence of PIH.

What inferences can be drawn from the observed differences in the incidence and severity of PIH following Survanta treatment? First, PIH was not a primary outcome measure in this or any other clinical surfactant trial, and observed differences in incidence must therefore be interpreted with caution. Second, no increase in the frequency of PIH has been observed in the other multicenter trials of Survanta [10, 26] or other surfactants [1, 6, 8, 13, 15, 20, 23, 29]. Several groups, however, have reported decreases in PIH following surfactant treatment. Enhorning et al. [3] and one center participating in the multicenter Curosurf trial [19] have reported a decreased incidence of PIH in surfactant treated infants. Fujiwara et al. [5] have reported a decreased incidence of PIH in the subgroup of their study infants weighing less than 1250 g. The Ten Centre Study Group [29] has reported a trend towards a decrease in cerebral parenchymal hemorrhages in surfactant treated infants. Konishi et al. [14] have reported a decreased incidence of PIH following high dose (120 mg/kg) versus low dose (60 mg/kg) treatment with Surfactant-TA. The reasons for contradictory observations regarding PIH in these trials and the current study are unknown. It is possible that management practices, particularly those affecting ventilators, at different centers interact in varying ways with surfactant treatment to influence the risk for PIH. Because of this, we recommend that future surfactant trials include more frequent prospectively planned serial ultrasound evaluation for the diagnosis of PIH.

We did not observe statistically significant differences between the groups with respect to BPD, PDA or NEC. These results are consistent with those of the American multicenter rescue trial of Survanta [10]. We did not observe a statistically significant reduction in the frequency of pneumothoraces in this trial, whereas surfactant therapy was associated with a decrease in pneumothoraces in the American rescue trial of Survanta [10] as well as four other surfactant rescue trials [5, 6, 8, 23].

No other adverse reactions were observed in association with surfactant treatment. No problems were associated with the dosing procedure.

Major unanswered questions concerning surfactant relate to the optimal dose and instillation method, timing and frequency of surfactant administration. We used a single dose of 100 mg/kg of surfactant phospholipid. Konishi et al. [14] have recently shown greater efficacy of a 120 mg of lipid/kg dose compared to that of 60 mg lipid/kg. The optimal single dose therapy is unknown, nor is it known if multiple doses will change long-term outcome.

The optimal instillation method for surfactant has not been determined. Ventilation at rapid rates and with short inspiratory times may not be optimal for infants receiving surfactant [16].

The relative benefits of early preventive therapy compared to later treatment of infants with established IRDS are unclear. Late treatment may be less effective as a result of respirator induced lung injury and the inactivation of surfactant by proteins present in alveolar edema fluid [11, 12]. On the other hand, prophylactic treatment will necessitate surfactant administration for many infants who would not progress to severe respiratory disease. No prospective trial comparing prevention and rescue strategies had yet been performed and the optimal time to treat with surfactant has not been determined.

The efficacy of retreatment for infants with a poor response to their first dose of surfactant, or who deteriorate following initial improvement is not clear. Multiple dose schedules may be beneficial and should be carefully evaluated.

In conclusion, we have shown that a single intratracheal dose of Survanta administered before 8 h of age to infants weighing 750–1750 g at birth with IRDS receiving assisted ventilation with 40% or more oxygen results in improved respiratory status during the subsequent 48 h. We did not observe any differences in clinical status on days 7 or 28 after treatment. We did observe unexplained differences in the frequency and severity of PIH between Survanta treated and control infants.

The efficacy of exogenous surfactants in modifying the initial course of IRDS is well established. The next phase of surfactant research will require clinical trials comparing different surfactant treatment strategies to determine whether the acute respiratory improvement following surfactant treatment can be translated into reductions in mortality and serious neonatal morbidity.

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