Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome

Barry T. Bloom, MD*; John Kattwinkel, MD‡; Robert T. Hall, MD§; Paula M. Delmore, MSN*; Edmund A. Egan, MD‖; J. Richard Trout, PhD¶; Michael H. Malloy, MD#; David R. Brown, MD**; Ian R. Holzman, MD‡‡; Carl H. Coghill, MD§§; Waldemar A. Carlo, MD§§; Arun K. Pramanik, MD‖‖; Mary Anne McCaffree, MD¶¶; Paul L. Toubas, MD¶¶; Susan Laudert, MD§; Linda L. Gratny, MD§; Kathleen B. Weatherstone, MD##; John H. Seguin, MD##; Lynne D. Willett, MD***; Gary R. Gutcher, MD‡‡‡; Dawn H. Mueller, MD‡‡‡; and William. H Topper, MD§§§

ABSTRACT. *Objective.* **To compare the relative safety and efficacy of Infasurf (calf lung surfactant extract; ONY, Inc, Amherst, NY, IND #27169) versus Survanta (Beractant, Ross Laboratories, Columbus, OH) in reducing the acute severity of respiratory distress syndrome (RDS) when given at birth and to infants with established RDS.**

Design. **A prospective, randomized, double-blind, multicenter clinical trial.**

Setting. **Thirteen neonatal intensive care units participated in the treatment arm: seven of these concurrently participated in the prevention arm.**

Patients. **The treatment arm enrolled infants of 2000 g birth weight with established RDS, and the prevention arm enrolled infants of 29 weeks' gestation with birth weights <1250 g.**

Intervention. **Infants were randomly assigned to receive Infasurf (n = 303, treatment arm; n = 180, prevention arm) or Survanta (n = 305, treatment arm; n = 194, prevention arm) in accordance with the Survanta package insert instructions.**

Outcome Measures. **We projected a 25% reduction between groups in the need for a third dose of surfactant for infants with established RDS, and a 25% reduction in the need for a second dose of surfactant for infants who received prophylactic surfactant. Secondary outcomes included the severity of RDS measured by inspired oxygen concentrations and mean airway pressure, air leaks, complications associated with surfactant administration, and survival to 36 weeks' postmenstrual age without the need for oxygen supplementation.**

Results. **In the treatment arm, there was no difference between groups in the number of infants requiring more than two doses of surfactant. The interval between doses was significantly longer for Infasurf, suggesting an increased duration of treatment effect. The inspired oxygen concentration and mean airway pressure were lower in the Infasurf infants during the first 48 hours in the treatment arm.**

In the prevention arm, there were no differences with respect to the number of surfactant doses. The dosing intervals were longer for Infasurf infants after the second dose. No difference in inspired oxygen or mean airway pressure was noted during the first 72 hours.

There were no significant differences in the incidence of air leaks, complications associated with dosing, complications of prematurity, mortality, or survival without chronic lung disease in the prevention or treatment arm.

Conclusions. **Infants treated with Infasurf have a modest benefit in the acute phase of RDS. Infasurf seems to produce a longer duration of effect than Survanta.** *Pediatrics* **1997;100:31–38;** ***respiratory distress syndrome, surfactant, Infasurf, Survanta.***

ABBREVIATIONS. SP-B, surfactant apoprotein B; RDS, respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; MAP, mean airway pressure.

From the *Columbia Wesley Medical Center and University of Kansas School of Medicine–Wichita, Wichita, Kansas; ‡University of Virginia, Richmond, Virginia; §Children's Mercy Hospital and University of Missouri, Kansas City, Missouri; ‖ONY, Inc, Amherst, New York; ¶Rutgers University, Piscataway, New Jersey; #University of Texas Medical Branch at Galveston, Galveston, Texas; **Newark Beth Israel Medical Center, Newark, New Jersey; ‡‡Mount Sinai New York, New York, New York; §§University of Alabama at Birmingham, Birmingham, Alabama; ‖‖Louisiana State University in Shreveport, Shreveport, Louisiana; ¶¶The University of Oklahoma, Oklahoma City, Oklahoma; ##University of Kansas Medical Center, Kansas City, Kansas; ***University of Nebraska Medical Center, Omaha, Nebraska; ‡‡‡Medical College of Virginia, Richmond, Virginia; and §§§Research Medical Center, Kansas City, Missouri.

Presented in part at the annual meeting of the Society for Pediatric Research, Seattle, WA, May 1994 and at the American Academy of Pediatrics annual meeting San Francisco, CA, October, 1995.

Received for publication Apr 22, 1996; accepted Sep 11, 1996.

Reprint requests to (B.T.B.) Professor of Pediatrics, University of Kansas School of Medicine–Wichita, Columbia Wesley Medical Center, 550 N Hillside, Wichita, KS 67214.

Clinical trials with natural surfactant preparations have documented reductions in acute respiratory disease, air leaks, bronchopulmonary dysplasia, and mortality in preterm infants.[1–9] Variations in patient selection criteria, total dose, timing of the initial dose, and dosing schedules preclude a comparison of relative efficacy or safety of these surfactants from previous trials.

Differences in the characteristics of available surfactant preparations have been documented by in vitro biophysical measurements and physiological animal experiments.[10–13] Infasurf and Survanta both use bovine lung as a source. They are similar in that both contain phospholipids, neutral lipids, fatty acids, and hydrophobic surfactant apoproteins, but the proportions of the active ingredients are different.

Survanta has a modified lipid profile as compared with the lung tissue mince extract. Cholesterol is removed and dipalmitoyl-phosphatidylcholine, palmitic acid, and tripalmitin are added, so free fatty acid and neutral lipids are each approximately 10% of total phospholipids (wt/wt).[14] Total protein in Survanta is 1% of the phospholipid (wt/wt) of which 99% is surfactant apoprotein C. Surfactant apoprotein B (SP-B) is present in trace amounts, <.5% of total protein (wt/wt).[15,16]

Infasurf is an extract of the surfactant lavaged from the alveolar spaces and contains the same lipid profile as natural surfactant including cholesterol 5% by weight. It contains minimal free fatty acid, approximately 1% of total phospholipids (wt/wt). Total protein is approximately 2% of total phospholipid (wt/wt) with 40% SP-B and 60% surfactant apoprotein C.[15,16]

In biophysical testing, Infasurf develops lower surface tension than Survanta.[17] In the excised lung model, Infasurf restores total surfactant activity, whereas Survanta restores only a portion of full activity.[10] Mizuno and co-workers[18] improved the activity of Survanta in the premature rabbit by adding large amounts of SP-B (2% by weight) to Survanta. In premature surfactant deficient lambs, Infasurf was more active than Survanta in improving oxygenation and increasing compliance and its activity was sustained longer.[10]

Because of the biochemical and functional differences, we believed a clinical trial to compare these two surfactants was warranted. We conducted this comparison to test for differences in the acute course of RDS which we considered relevant in a comparison of relative surfactant activity.

METHODS

This prospective, randomized, and double-blind clinical trial was divided into a treatment arm (infants of ≤2000 g birth weight with established RDS) and a prevention arm (infants of ≤29 weeks gestation with birth weights <1250 g treated at birth). Both arms were developed to test the effects of the two surfactants in reducing the acute severity of RDS.

The treatment arm was conducted in 13 neonatal centers (participants listed in the Acknowledgments). Seven of the 13 simultaneously participated in the prevention arm. Informed written parental consent was required and protocols were approved by the Institutional Review Boards of all participating institutions. Informed consent was explicit that parents could choose to have their infants treated with an approved surfactant if they did not wish to enroll in the prospective trial.

The design variable for the treatment arm was a 25% reduction in the need for a third dose of surfactant. The design variable for the prevention arm was a 25% reduction in the need for a second dose of surfactant. As a result of the predicted sample size requirements, we could not reasonably have used chronic lung disease or mortality as the primary outcome.

Secondary outcome variables included ventilation and oxygen use during the first 3 days, the frequency of air leaks, complications associated with the dosing process, and survival to 36 weeks' postmenstrual age without the need for oxygen supplementation.

TABLE 1. Population Characteristics (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Birth weight (mean ± SD)	1162 ± 408 g	1166 ± 401 g	.92
Gestational age (mean ± SD)	29.2 ± 2.8 wk	29.2 ± 2.8 wk	.80
Male	57	58	.94
Race, % white	51	48	.47
Singleton births	74	78	.30
Small for gestational age	12	10	.69
Born at study site	66	64	.73
Maternal hypertension	19	16	.29
Maternal temperature >38°C	11	10	.79
Previa or abruption	18	21	.35
Rupture of membranes >24 h	20	20	.92
Mg, Indocin or β agonists	49	46	.63
Vaginal delivery	46	50	.33
Prenatal steroids ≥48 h	12	9	.31
1-Minute Apgar ≤3	27	32	.14
5-Minute Apgar ≤3	5	6	.49

* Unless otherwise noted numbers represent percent.

Enrollment and Randomization

Infants <2000 g birth weight (no minimum) and <48 hours of age, with radiographically confirmed RDS, requiring endotracheal intubation and an F_{IO_2} ≥.4 with a Pa_{O_2} < 80 Torr or an a/A oxygen ratio of ≤.22 were enrolled into the treatment arm.

Mothers who presented in labor or were expected to deliver before 30 weeks gestation (no minimum) were asked to enroll their infants in the prevention arm. Exclusion from enrollment was required if the infant was >1250 g birth weight or >15 minutes old before resuscitation was successful. Outborn infants were excluded from analysis in the prevention arm.

Infants were excluded from either arm if they had a major anomaly which interfered with lung development or function, eg, cyanotic congenital heart disease, diaphragmatic hernias or other causes of pulmonary hypoplasia, hydrops fetalis, or chromosomal anomaly. Exclusion after surfactant treatment occurred if more than one type of surfactant was used during the retreatment process, a dosage error of greater than 50% occurred, a major malformation was recognized after study entry, or congenital sepsis or pneumonia was diagnosed. Exclusions were made without the participant's knowledge of surfactant assignment and randomization codes were not reused after posttreatment exclusions.

Infants were randomly assigned to Survanta or Infasurf by selecting the next vial from a box of sequentially numbered vials. Surfactant was administered within 2 hours of meeting the treatment arm criteria or within 15 minutes of birth in the prevention arm. Stratification into three birth weight groups (≤750, 751 to 1250, and 1251 to 2000 g) was performed in the treatment arm and into two gestational age groups (<27 weeks and 27 to 29 weeks) in the prevention arm. Each center was assigned its own randomization schedule. Variable block size randomization was performed by a pseudo-random number generator and the Moses-Oakford algorithm.

Surfactants

Survanta (Beractant) is a Food and Drug Administration approved drug and is supplied as a 25 mg/mL suspension.[14] Infasurf (calf lung surfactant extract; IND# 27169) has been used in clinical studies at 35 mg/mL concentrations; however, a special 25 mg/mL concentration was used in this trial to maintain masking. The surfactants were therefore of similar consistency, concentration, and color. In addition, the vials were covered by two layers of opaque labels.

Administration, storage, and dispensing of surfactant followed the Survanta package insert. Both surfactants were administered at the recommended dose for Survanta of 100 mg/kg. Three repeat treatments, at least six hours apart, during the first 96 hours were to be given if the infant remained intubated for RDS and in ≥.3 F_{IO_2}. An infant, who received four doses from the assigned surfactant could be crossed over to the other surfactant at the discretion of the attending physician.

Sample Size, Data Collection, and Analysis

It had been shown that 64% of infants with RDS who received Survanta treatment required more than two doses.[19] It was determined that 320 infants with RDS were necessary to detect a 25% difference (α, .05; β, .2) in the treatment arm. Sixty percent of infants who received Survanta prophylaxis had required more

TABLE 2. Respiratory Status (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Study entry status			
Age at entry			
Mean ± SD	7.5 ± 8.1 h	6.4 ± 6.4 h	.08
Median (25th, 75th percentile)	4.7 (3.3, 7.3)	4.3 (2.6, 7.5)	
FIO_2 at entry			
Mean ± SD	74 ± 22 h	76 ± 23 h	.88
Median (25th, 75th percentile)	74 (54, 100)	80 (55, 100)	
Mean airway pressure at entry			
Mean ± SD	8.8 ± 2.9 cm H_2O	9.0 ± 2.8 cm H_2O	.57
Median (25th, 75th percentile)	8 (7, 10)	9 (7, 10)	
$PaCO_2$ at entry			
Mean ± SD	44 ± 12 Torr	43 ± 11 Torr	.25
Median (25th, 75th percentile)	42 (37, 48)	43 (36, 48)	
a/A Pao_2 at entry			
Mean ± SD	0.15 ± 0.06	0.15 ± 0.06	.79
Median (25th, 75th percentile)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	
Change in FIO_2 after 1st dose			
Mean ± SD	−18.3 ± 21.1	−13.0 ± 20.0	.01
Median (25th, 75th percentile)	−22 (0, −48)	−13 (0, −34)	
Change in mean airway pressure after 1st dose			
Mean ± SD	−0.4 ± 1.9 Torr	−0.1 ± 1.9 Torr	
Median (25th, 75th percentile)	0 (0, −10)	0 (0, −6)	
Number of surfactant doses			
Only one dose	30	34	
Only two doses	27	21	
Only three doses	21	12	
Four or more doses	22	33	.002
Dose intervals			
Hours dose 1 to dose 2			
Mean ± SD	13 ± 11 h	10 ± 9 h	<.001
Median (25th, 75th percentile)	8 (7, 15)	7 (6, 8)	
Hours dose 2 to dose 3			
Mean ± SD	13 ± 11 h	9 ± 5 h	<.001
Median (25th, 75th percentile)	8 (7, 17)	7 (6, 10)	
Hours dose 3 to dose 4			
Mean ± SD	12 ± 11 h	8 ± 5 h	.006
Median (25th, 75th percentile)	8 (7, 11)	7 (6, 9)	
Duration of intermittent mechanical ventilation			
Mean ± SD	13 ± 21 d	13 ± 21 d	.99
Median (25th, 75th percentile)	5 (2, 23)	5 (2, 26)	
Duration of supplemental oxygen			
Mean ± SD	29 ± 40 d	30 ± 37 d	.9
Median (25th, 75th percentile)	21 (5, 44)	24 (4, 45)	
Time weighted averages (0 to 72 hours)			
FIO_2	41 ± 16 Torr	44 ± 20 Torr	.03
Mean airway pressure	5.9 ± 2.8 cm H_2O	6.4 ± 3.1 cm H_2O	.04

* Unless otherwise noted numbers represent percent.

than one dose.[19] Therefore, 372 infants were required to detect a 25% difference (α, .05; β, .2) in the prevention arm.

A data coordinator and a neonatologist collected data at each center. Information was recorded for each mother's demographic profile, medical and obstetric history, labor, and delivery. Data from the infant's clinical course were collected daily for the first 45 days, at 36 weeks' postconceptional age, and at discharge to home or death.

Cranial ultrasonography, echocardiograms, and chest radiographs were performed as necessary. Results were interpreted by the cardiologists and radiologists at the participating centers. A diagnosis of patent ductus arteriosus required ultrasound verification. Cranial ultrasounds were classified by the method of Papile.[20] The treatment and occurrence of other complications of prematurity were recorded. Pneumonia was diagnosed when any lung disease was associated with a positive blood culture. As in the Survanta prevention studies, RDS was defined as $FIO_2 > .40$ at any retreatment.[19]

Posthoc analysis of the time-weighted average of FIO_2 and mean airway pressures (MAPs) were done to permit comparison with the National Institutes of Health Exosurf-Survanta study report.[21]

One interim analysis was conducted for each arm by the Data Monitoring and Advisory Committee. The identity of the treatment groups was not revealed to either the committee or the investigators. The number of surfactant doses per patient was lower than expected suggesting that the sample size should be increased. The Data Monitoring Advisory Committee approved an increase in sample size to 600 for the treatment arm. The prevention arm interim analysis indicated a potential difference in mortality. However, the death rate in the low mortality group was much lower than previously reported in other surfactant studies. The enrollment plan of the prevention arm was not modified.

Quantitative variables were compared using analysis of variance and the Mann-Whitney *U* test. For qualitative variables, the Cochran-Mantel-Haenszel χ^2 test was used. The appropriateness of pooling the data from all centers was tested by the Breslow-Day method. All analyses were performed using the Statistical Analysis System (SAS, SAS Institute, Cary, NC).

RESULTS

Treatment Arm

Enrollment started during the spring of 1992 and was completed in August 1993. Six hundred sixty-five infants were enrolled. Three were not randomized. Thirty-seven infants were excluded because of

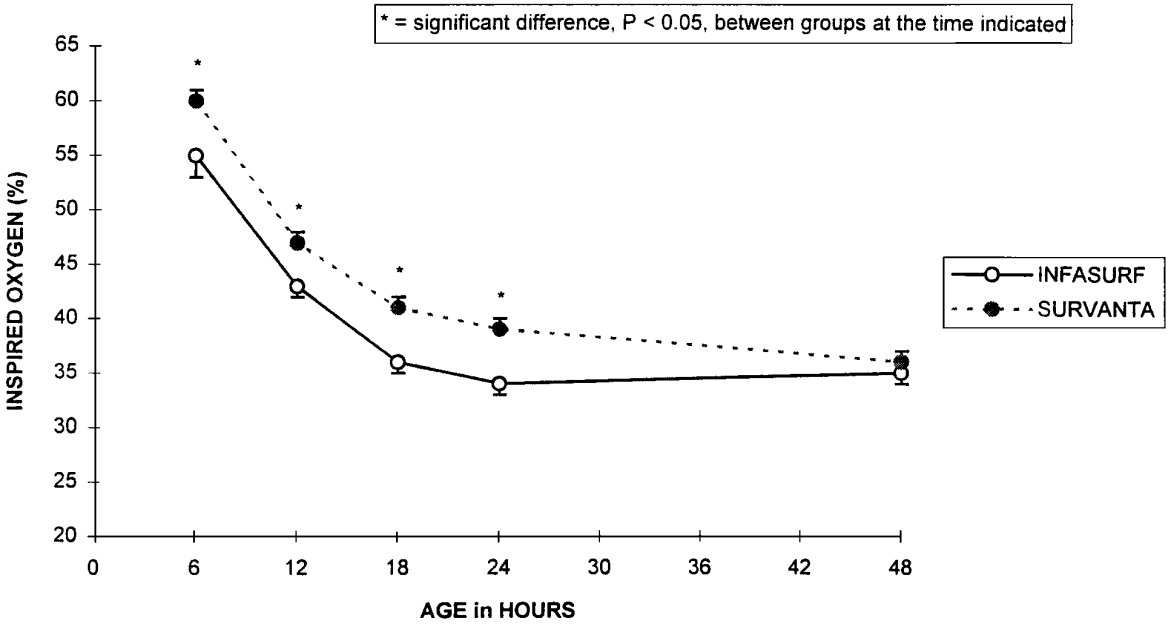

Fig 1. Treatment arm: Inspired oxygen concentration in the Infasurf and the Survanta groups. The mean and standard error is graphed. *Significant difference ($P < .05$) between groups at time indicated.

protocol-defined exclusions and seventeen because of major protocol violations. The primary cause of exclusion for protocol violation was retreatment with the incorrect drug. Center-to-center comparisons of the major outcomes did not reveal any significant difference; therefore, the data from all centers were pooled for analysis. The intent-to-treat analysis results were similar to the evaluable population results that are presented.

The populations were similar in birth weight, gestational age, sex and racial distribution, maternal conditions, prenatal, intrapartum, and delivery room variables including Apgar scores (Table 1).

The age and respiratory status of the two groups were similar at study entry. However, infants receiving Infasurf required significantly less oxygen and had significantly lower MAPs within 1 hour of administration (Table 2). The differences in FIO_2 (Fig 1) and MAP (Fig 2) were sustained throughout the first 24 hours. Time-weighted averages of MAP and FIO_2 were significantly less in the Infasurf group for the first 72 hours (Table 2). There were no differences in the duration of intermittent mechanical ventilation or use of supplemental oxygen throughout the remainder of the hospital stay (Table 2).

The distribution of surfactant dosing is shown in Table 2. Forty-three percent of Infasurf and 45% of Survanta infants received three or more doses ($P = .33$). However, 33% of Survanta-treated infants were given a fourth dose as compared with 22% of Infa-

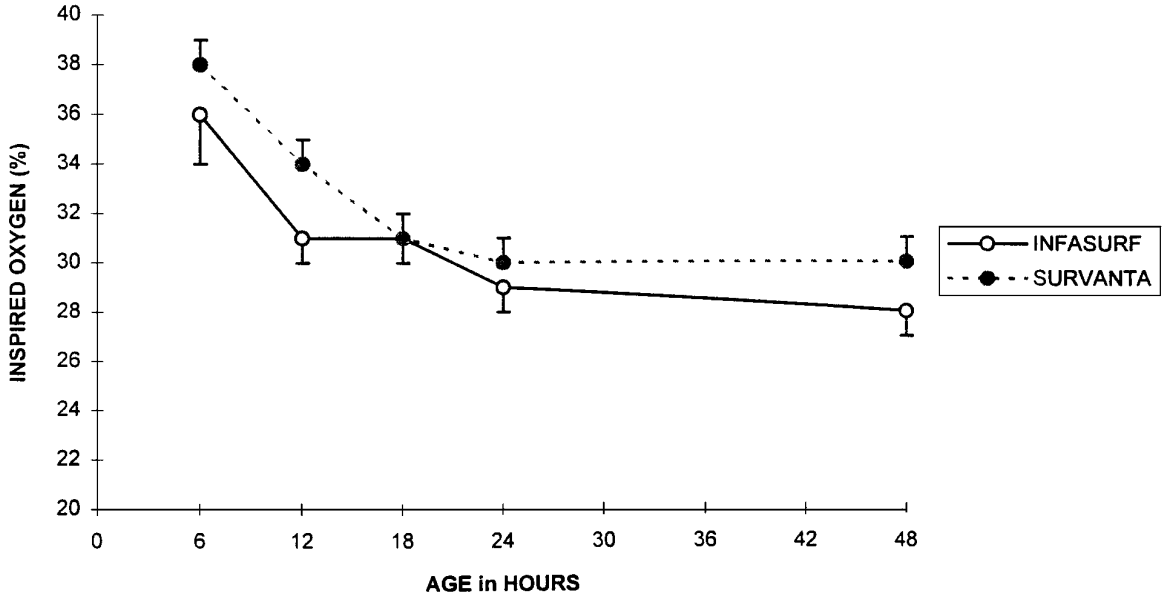

Fig 2. Prevention arm: Inspired oxygen concentration in the Infasurf and the Survanta groups. The mean and standard error is graphed. *Significant difference ($P < .05$) between groups at time indicated.

TABLE 3. Event Reports (Treatment Arm)*

	Infasurf (n = 303)	Survanta (n = 305)	*P* Value
Dosing complications			
Bradycardia during any dose	16	14	.50
Airway obstruction during any dose	2	1	.11
Extubated during any dose	1	0	.12
δ blood pressure ± 5 mm Hg during any dose	16	14	.57
Any dosing complication during any dose	29	26	
Pneumothorax	6	10	.07
Pulmonary interstitial emphysema	10	14	.13
Any air leak	15	18	.27
Pulmonary hemorrhage	6	6	1.00
Patent ductus arteriosus evaluated for patent ductus arteriosus	114/168	118/157	.18
Necrotizing enterocolitis	11	15	.15
Apnea	71	68	.25
Retinopathy of prematurity	17	14	.37
Sepsis	23	24	.85
Number with neuroimaging	275	268	
Grades I and II	30	35	.20
Grades III and IV	11	10	.68
Alive at discharge	82	83	.83
Respiratory distress syndrome deaths	13	13	.9
Alive at 36 wk, no oxygen	63	59	.3

* Unless otherwise noted, numbers represent percent.

surf-treated infants ($P = .002$). The duration of treatment effect was longer for Infasurf infants as measured by the longer dosing interval (Table 2).

No significant differences were noted in the incidence of mortality, chronic lung disease, dosing-related events, or complications of prematurity (Table 3).

Prevention Arm

Enrollment started during the spring of 1992 and was completed in January 1994. Four hundred sixty-three infants were recruited for the study. Six infants were not randomized. Sixty were excluded because of protocol defined exclusions and 23 because of major protocol deviations. Center-to-center comparisons of the major outcomes did not reveal any significance difference; therefore, the data from all centers were pooled for analysis. The intent-to-treat analysis results were similar to the evaluable population results which are presented.

The mean gestational age of the 181 Infasurf and 195 Survanta infants who successfully completed the study was similar, although the mean birth weight of Infasurf infants was greater. No significant differences were noted in gender, race, the number of singletons, or small-for-date infants. Comparison of maternal conditions, prenatal, intrapartum, and delivery room information did not show significant differences (Table 4).

RDS occurred in 43% of Infasurf and 44% of the Survanta infants ($P = .92$). Infasurf infants had significantly longer interdose intervals after dose two, but there was no difference in the number of infants who required the full treatment course (Table 5).

Survival to discharge occurred in 86% of the Infasurf and 92% of the Survanta infants ($P = .06$). However, mortality <600 g birth weight was extremely low in the Survanta group (6 out of 23, 26%) compared with the Infasurf group (19 out of 30, 63%) ($P = .007$).

Supplemental oxygen and MAP were similar throughout the first 72 hours. Survanta infants required more days of intermittent mechanical ventilation and oxygen supplementation (Table 5), primarily because of the survival of those <600 g at birth. There were no significant differences in the incidence of adverse events, survival to 36 weeks' postmenstrual age without the need for oxygen supplementation, or dosing complications (Table 6).

DISCUSSION

Three clinical surfactant comparison studies have been reported. The Vermont-Oxford and National Institutes of Health networks tested Exosurf Neona-

TABLE 4. Population Characteristics (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Birth weight (mean ± SD)	891 ± 221 g	845 ± 205 g	.04
Gestational age (mean ± SD)	27.1 ± 2.2 wk	27.1 ± 2.1 wk	.5
Male	53	46	.18
Race, % white	46	40	.35
Singleton births	79	85	.18
Small for gestational age	12	10	.74
Maternal hypertension	14	16	.57
Maternal temperature >38°C	17	13	.30
Previa or abruption	22	26	.40
Rupture of membranes >24 h	26	30	.38
Mg, Indocin or β agonists	67	63	.39
Vaginal delivery	45	48	.54
Prenatal steroids ≥48 h	28	26	.82
1-Minute Apgar ≤3	30	29	.7
5-Minute Apgar ≤3	4	3	.7

* Unless otherwise noted, numbers represent percent.

TABLE 5. Respiratory Status (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Surfactant doses			
Only one dose	52	51	
Only two doses	16	13	
Only three doses	13	10	
Four or more doses	19	26	.30
Dose intervals (mean ± SD)			
Dose 1 to dose 2			
Mean ± SD	15 ± 12 h	12 ± 12 h	.10
Median (25th, 75th percentile)	9 (7, 19)	8 (7, 12)	
Dose 2 to dose 3			
Mean ± SD	18 ± 19 h	11 ± 8 h	.005
Median (25th, 75th percentile)	9 (7, 20)	8 (7, 11)	
Dose 3 to dose 4			
Mean ± SD	17 ± 16 h	11 ± 8 h	.04
Median (25th, 75th percentile)	8 (7, 22)	8 (7, 14)	
Duration of intermittent mechanical ventilation			
Mean ± SD	20 ± 22 d	27 ± 26 d	.012
Median (25th, 75th percentile)	25 (2, 38)	29 (3, 45)	
Duration of supplemental oxygen			
Mean ± SD	36 ± 39 d	46 ± 48 d	.02
Median (25th, 75th percentile)	40 (16, 45)	43 25, 45)	
Time weighted averages (0 to 72 h)			
FIO_2	32 ± 14 Torr	32 ± 11 Torr	.90
Mean airway pressure	5.8 ± 2.8 cm H_2O	5.5 ± 2.3 cm H_2O	.26

* Unless otherwise noted, numbers represent percent.

TABLE 6. Event Reports (Prevention Arm)*

	Infasurf (n = 180)	Survanta (n = 194)	*P* Value
Dosing complications			
Bradycardia during any dose	14	14	.88
Airway obstruction during any dose	4	2	.13
Extubated during any dose	2	2	1.00
δ blood pressure ± 5 mm Hg during any dose	1	1	.36
Any dosing complication during any dose	18	18	1.00
Any air leak	13	10	.41
Pulmonary hemorrhage	6	6	1.00
Patent ductus arteriosus/evaluated for patent ductus arteriosus	94/120	107/138	1.00
Necrotizing enterocolitis	26	24	.72
Apnea	87	89	.53
Retinopathy of prematurity	27	29	.42
Sepsis	33	32	.91
Number with neuroimaging	175	193	
Grades I and II	37	31	.13
Grades III and IV	5	5	.82
Alive at discharge	86	92	.06
Birth weight <600 g–alive at discharge	37	74	.007
Respiratory distress syndrome deaths	7	2	.01
Alive at 36 wk, no oxygen	67	69	.66

* Unless otherwise noted, numbers represent percent.

tal versus Survanta[21,22] and Hudak and colleagues[23] tested Infasurf versus Exosurf. Each concluded that treatment with natural surfactant, as compared with a synthetic, resulted in a greater reduction in the severity of RDS, two comparisons documented a difference in air leaks, but survival without chronic lung disease was not significantly altered. In this study which compared the two natural (bovine) surfactants, similar differences between surfactants were observed in the treatment arm but not in the prophylaxis arm.

The treatment arm showed that Infasurf, when administered according to the Survanta protocol, produced a greater initial improvement in respiratory status that was better sustained at every dose as evidenced by lower oxygen and MAP and by longer intervals between doses. In addition, there were fewer patients who required the full Infasurf treatment course. Only the longer duration between doses could be replicated in the prevention arm.

In the prevention arm, Survanta-treated infants had longer duration of mechanical ventilation and oxygen supplementation most likely as a result of an unprecedented survival rate in those of <600 g birth weight. The survival rate of this subset of Survanta infants (13 out of 19, 74%) is probably not reproducible because all other published data report that a majority of infants <600 g die whether treated with

TABLE 7. Association of Time-Weighted Percent Oxygen and Mean Airway Pressure to Intact Cardiopulmonary Survival

	Infasurf	Survanta
% FIO_2 0 to 72 hours		
Survived	37 ± 12	36 ± 11
Died or oxygen at 36 weeks	51 ± 21	56 ± 24
P value	<.001	<.001
Mean airway pressure		
Survived	5.3 ± 2.2	5.1 ± 2.3
Died or oxygen at 36 weeks	8.3 ± 3.5	7.8 ± 3.0
P value	<.001	<.001

surfactant or not.[24] Beyond this subgroup's unexplained difference in mortality, safety outcomes, adverse events at administration, and serious complications of prematurity, including chronic lung disease, occurred at similar rates in both treatment groups in both arms of the study.

Early administration of any surfactant to preterm infants at high risk of RDS is more effective than waiting until development of severe respiratory symptoms, as evidenced by lower severity of acute disease and lower incidence of death and chronic lung disease.[25,26] Although this study did not compare prophylaxis to treatment, we note that the duration of effect, for both surfactants, was substantially longer in the prevention arm as compared with the treatment arm.

There are three major compositional differences between Infasurf and Survanta, two of which we speculate account for the biophysical activity and clinical differences. Survanta contains phospholipids from lung cells as well as lung surfactant, it has higher levels of nonphosphatidylcholine phospholipids such as sphingomyelins and phosphatidylethanolamines, and these phospholipids limit the lowest surface tension attainable in bovine surfactant preparations.[27] There is a step in the Survanta process that removes cholesterol which probably also removes the surfactant apoprotein B, the apoprotein most critical for full biophysical activity.[28] Mizuno and associates[18] have shown the levels of SP-B in Survanta to be subthreshold for biologic effect and Survanta activity is improved by supplementing it with SP-B.

The differences between surfactants in biophysical testing and animal models with virtual surfactant depletion are difficult to document in a clinical trial in which almost all patients have endogenous surfactant. It has been proposed that all surfactant drugs, in addition to their independent surfactant activity, interact with existing endogenous surfactant and may serve as substrate for improved endogenous production.[29] The effect in a clinical trial of any surfactant is a combination of surfactant activity, its interaction with endogenous surfactant, and the time at which adequate endogenous material begins to be secreted from the Type II cells. In addition, it is likely that this diminished difference is a reflection of the larger number of confounding variables introduced by the clinical practice arena.

Trials such as this one and others that have compared surfactants, which have treatment groups in the hundreds, not thousands, have only demonstrated the differences in activity of surfactants during the acute phase of RDS. They have not been able to document differences in ultimate outcome. The failure to detect differences in chronic lung disease or mortality could come from inadequate sample size or the lack of effect. Insight can be gained by examining the relationship of the time-weighted averages with ultimate outcome (Table 7). Infants who die or develop chronic lung disease had significantly more severe RDS, in both treatment groups. Based upon this association we speculate that all of these comparison studies would have revealed differences in chronic lung disease and death if they had enrolled enough patients.

This study detected differences in the time interval between doses in a protocol that followed the Survanta package insert guidelines for redosing. Many clinicians are choosing to wait longer, or for more severe lung disease to reappear before retreating than recommended in the Survanta package insert. It is unclear how this practice influences the interpretation of our findings. We are currently conducting a follow-up clinical comparison trial to examine optimum redosing strategies.

SUMMARY

In conclusion there was a modest improvement in the acute phase of respiratory distress measured by MAP, FIO_2, and duration of effect in infants receiving Infasurf in the treatment group. Only the longer duration of effect of Infasurf seems is replicated in the prevention arm. Survival to 36 weeks' postmenstrual age without the need for supplemental oxygen was similar for both surfactants. Both surfactants are associated with marked improvement in severity of RDS and Infasurf seems to have a longer sustained effect.

ACKNOWLEDGMENTS

In addition to the authors, this study was conducted by Richard Krouskop, and John Baier at Louisiana State University in Shreveport; and Mary Bussey, MD, at the University of Nebraska Medical Center.

Edmund Egan, MD, is the President of ONY, Inc, the manufacturer of Infasurf. Dr J. Richard Trout, PhD, statistician of Rutgers University, was funded by Forest Laboratories, Inc. The study center and each of the study sites were funded by ONY, Inc.

The authors appreciate the assistance and support of the nursing and respiratory care staff at their institutions.

REFERENCES

1. Gitlin JD, Soll RF, Parad RB, et al. Randomized controlled trial of exogenous surfactant for hyaline membrane disease. *Pediatrics*. 1987;79: 31–37
2. Merritt TA, Hallman M, Bloom BT et al. Prophylactic surfactant in the moderation of neonatal respiratory distress syndrome. *N Engl J Med*. 1986;315:785–790
3. Enhorning G. Prevention of the neonatal respiratory distress syndrome by tracheal instillation of surfactant. Ross Special Conference; November 29, 1984
4. Raju TN, Vidyasagar D, Bhat R, et al. Double blind controlled trial of single-dose treatment with bovine surfactant in severe hyaline membrane disease. *Lancet*. 1987;1:651–655
5. Hoekstra RE, Jackson JC, Myers TF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. *Pediatrics*. 1991;88:10
6. Leichty EA, Donovan E, Purchit D, et al. Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. *Pediatrics*. 1991;88:19–28
7. Enhorning GE, Shennan A, Possmayer F, et. al. Prevention of neonatal

respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. *Pediatrics.* 1985;76:145–153
8. Kwong MS, Egan EA, Notter RH, Shapiro DL. Double blind clinical trial of calf lung surfactant extract for the prevention of hyaline membrane disease in extremely premature infants. *Pediatrics.* 1985;76:585–592
9. Shapiro DL, Notter RH, Morin FC III, et al. Double blind randomized clinical trial of a calf lung surfactant extract administered at birth to very premature infants to prevent respiratory distress syndrome. *Pediatrics.* 1985;76:593–599
10. Cummings JJ, Holm BA, Hudak ML, et al. A controlled clinical trial of four different preparations in surfactant-deficient preterm lambs. *Am Rev Respir Dis.* 1992;145:999–1004
11. Metcalf IL, Burgone R, Enhorning G. Surfactant supplementation in the preterm rabbit. Effects of applied volume on compliance and survival. *Pediatr Res.* 1982;16:834–839
12. Hall SB, Venkitaraman AR, Whitsett JA, et al. Importance of hydrophobic apoproteins as constituents of clinical exogenous surfactants. *Am Rev Respir Dis.* 1992;145:24–30
13. Whitsett JA, Ohning BL, Ross G, et al. Hydrophobic surfactant-associated protein in whole lung surfactant and its importance for biophysical activity in lung surfactant extracts used for replacement therapy. *Pediatr Res.* 1986;20:460–467
14. Survanta (Beractant):intratracheal suspension [package insert]. Ross Laboratories; 1994
15. Seeger W, Grube C, Gunther A, Schmidt A. Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations. *Eur Resp Journal*. 1993;6:971–977
16. Hamvas A, Cole FS, deMello DE, et al. Surfactant Protein B deficiency: antenatal diagnosis and treatment with surfactant replacement. *J Pediatr*. 1994;125:356–361
17. Hall SB, Venkitaraman AR, Whitsett JA, et al. Importance of hydrophobic apoproteins as constituents of clinical exogenous surfactants. *Am Rev Respir Dis.* 1992;145:24–30
18. Mizuno K, Ikegami M, Chen C-M, et al. Surfactant protein-B supplementation improves in vivo function of a modified natural surfactant. *Pediatr Res.* 1995;37:271–276
19. Neonatal Respiratory Distress Syndrome, [Monograph]. Ross Laboratories; 1991:21
20. Papile L, Burstein J Burnstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birthweights less than 1500 grams. *J Pediatr*. 1978;92:529–534
21. Horbar JD, Wright LL, Soll RF, et al. A Multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. *J Pediatr.* 1993;123:757–766
22. Vermont Oxford Neonatal Network. A multicenter, randomized trial comparing synthetic surfactant with bovine surfactant in the treatment of neonatal respiratory distress syndrome. *Pediatrics*. 1995;97:1–6
23. Hudak ML, Farrell EE, Rosenberg AA, et al. A multicenter randomized, masked comparison trial of natural versus synthetic surfactant for the treatment of respiratory distress syndrome. *J Pediatr*. 1996;128:396–406
24. Zola EM, Overbach AM, Gunkel JH. Treatment investigational new drug experience with Survanta (Beractant). *Pediatrics*. 1993;91:546–551
25. Kendig JW, Notter RH, Cox C, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. *N Engl J Med*. 1991;324:865–871
26. Kattwinkel J, Bloom BT, Delmore PM, et al. Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29–32 weeks' gestation. *Pediatrics*. 1993;92:90–98
27. Egan EA, Holm BA, Hiavaty LM, Egan ES. Cell wall phospholipids and lung biophysics. *Am Rev Respir Dis*. 1993;A987:147
28. Wang Z, Gurel O, Baatz JE, Notter RH. Differential activity and lack of synergy of lung surfactant proteins SP-B and SP-C in interactions with phospholipids. *J Lipid Res.* 1996;37:1749–1760
29. Holm BA. Surfactant replacement therapy, new levels of understanding. *Am Rev Respir Dis*. 1993;148:834–836

TECHNOLOGICAL DISASTER

In football, the rise of the plastic helmet in place of leather, around 1950, allowed the sport to become more brutal, more than tripling the number of neck injuries and doubling the deaths from cervical spine injuries.

Gelberg JN. The big technological tennis upset. *Invention and Technology*. Spring 1997.

Submitted by Student

Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome

Barry T. Bloom, John Kattwinkel, Robert T. Hall, Paula M. Delmore, Edmund A. Egan, J. Richard Trout, Michael H. Malloy, David R. Brown, Ian R. Holzman, Carl H. Coghill, Waldemar A. Carlo, Arun K. Pramanik, Mary Anne McCaffree, Paul L. Toubas, Susan Laudert, Linda L. Gratny, Kathleen B. Weatherstone, John H. Seguin, Lynne D. Willett, Gary R. Gutcher, Dawn H. Mueller and William. H Topper

Pediatrics 1997;100;31
DOI: 10.1542/peds.100.1.31

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome

Barry T. Bloom, John Kattwinkel, Robert T. Hall, Paula M. Delmore, Edmund A. Egan, J. Richard Trout, Michael H. Malloy, David R. Brown, Ian R. Holzman, Carl H. Coghill, Waldemar A. Carlo, Arun K. Pramanik, Mary Anne McCaffree, Paul L. Toubas, Susan Laudert, Linda L. Gratny, Kathleen B. Weatherstone, John H. Seguin, Lynne D. Willett, Gary R. Gutcher, Dawn H. Mueller and William. H Topper

Pediatrics 1997;100;31
DOI: 10.1542/peds.100.1.31