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REVIEW ARTICLE

Surfactants in the Management of Respiratory Distress Syndrome in Extremely Premature Infants

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Respiratory distress syndrome (RDS) is primarily due to decreased production of pulmonary surfactant, and it is associated with significant neonatal morbidity and mortality. Exogenous pulmonary surfactant therapy is currently the treatment of choice for RDS, as it demonstrates the best clinical and economic outcomes. Studies confirm the benefits of surfactant therapy to include reductions in mortality, pneumothorax, and pulmonary interstitial emphysema, as well as improvements in oxygenation and an increased rate of survival without bronchopulmonary dysplasia. Phospholipids (PL) and surfactant-associated proteins (SP) play key roles in the physiological activity of surfactant. Different types of natural and synthetic surfactant preparations are currently available. To date, natural surfactants demonstrate superior outcomes compared to the synthetic surfactants, at least during the acute phase of RDS. This disparity is often attributed to biochemical differences including the presence of surfactant-associated proteins in natural products that are not found in the currently available synthetic surfactants. Comparative trials of the natural surfactants strive to establish the precise differences in clinical outcomes among the different preparations. As new surfactants become available, it is important to evaluate them relative to the known benefits of the previously existing surfactants. In order to elucidate the role of surfactant therapy in the management of RDS, it is important to review surfactant biochemistry, pharmacology, and outcomes from randomized clinical trials.

KEYWORDS continuous positive airway pressure, premature infants, surfactant, respiratory distress syndrome, plasmalogen

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INTRODUCTION

Respiratory distress syndrome (RDS) is primarily due to decreased production of pulmonary surfactant by type II pneumocytes lining the alveoli that leads to atelectasis and impaired gas exchange.[1] It is associated with significant neonatal morbidity and mortality, and is now the most common, serious, and costly infant health problem in the United States. The incidence of RDS is inversely related to gestational age and birth weight; it occurs significantly more often in preterm infants born at less than 30 weeks gestational

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ABBREVIATIONS DPPC, dipalmitoylphosphatidylcholine; FiO_2, fraction of inhaled oxygen; PDA, patent ductus arteriosus; PL, phospholipids; PUFA, polyunsaturated fatty acid; RDS, respiratory distress syndrome; SP, surfactant-associated proteins

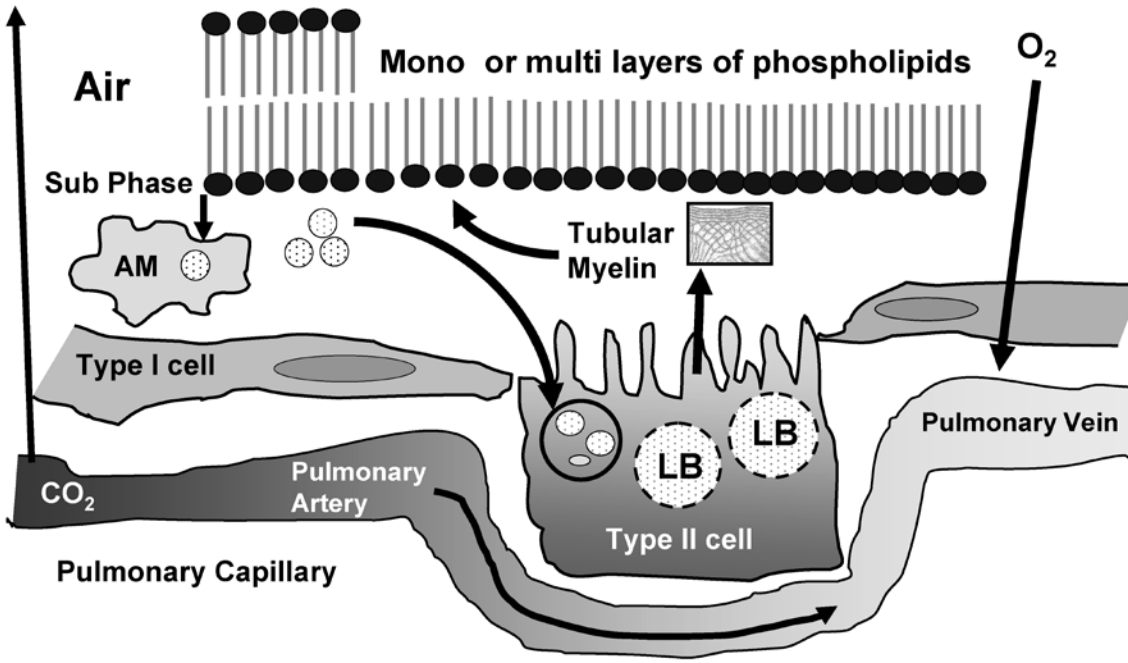

Figure 1. Life cycle of surfactant produced in the lung.
AM, alveolar macrophage; LB, lamellar bodies; PL, phospholipids; SA, small aggregate surfactant
Figure courtesy of Rangasamy Ramanathan, MD

age and in newborns weighing less than 1000 g at birth.

Advances in medical treatment, including the use of prenatal steroids, have decreased morbidity and improved the survival rate of preterm and low birth weight infants. Combined with a rise in multiple births associated with fertility treatment, the premature neonate population has expanded considerably. In spite of an overall decrease in the incidence and severity of RDS, due to increasing survival of extremely low birth weight (< 1000 g) infants[2] and reduced effect of antenatal steroids in twins and triplets as compared to singletons,[3] the number of at-risk patients has increased and has presented new challenges to neonatologists.

Pulmonary surfactant therapy demonstrates the best clinical and economic outcomes in preterm patients with RDS and is currently the treatment of choice. Surfactant use significantly decreases RDS-associated morbidity and mortality by reducing surface tension at the air-liquid interface in the lung and preventing collapse of the alveoli. Several different surfactant preparations are available for the treatment of RDS. Surfactant may be synthetic or derived from natural sources, although only natural surfactant products (poractant alfa [Curosurf, DEY LP, Napa, CA], calfactant [Infasurf, Forest Laboratories, St. Louis, MO], and beractant [Survanta, Ross Products Division, Abbott Laboratories, Inc, Columbus, OH]) remain on the market in the United States. To date, natural surfactants demonstrate superior outcomes compared to synthetic surfactants during the acute phase of RDS.[4-6] A meta-analysis comparing natural and synthetic surfactants showed reductions in the risk of pneumothorax (RR 0.63 [95% CI, 0.53-0.75]) and death (RR 0.87 [95% CI, 0.76-0.98]) with the natural products.[6]

In order to fully elucidate the role of surfactant therapy in the management of RDS, it is important to understand the biochemistry and pharmacology of surfactants and to review the pivotal clinical trials.

THE BIOCHEMISTRY OF SURFACTANTS

Pulmonary surfactant is a complex mixture of phospholipids (PL), neutral lipids, and proteins that covers the alveoli and reduces surface tension.[7,8] Type II pneumocytes that

Table 1. Commercially available natural surfactants vary widely in their composition

	SF-RI1	Poractant alfa	Beractant	Calfactant
Total Phospholipids	76% ± 2%	89% ± 1%	56% ± 2%	Not studied
Total Neutral Lipids	24% ± 2%	11% ± 1%	44% ± 2%	Not studied

Adapted with permission from The American Physiological Society.[15]

line the alveolar surface synthesize surfactant PL and proteins[1] (Figure 1) and store them as lamellar bodies. Four types of surfactant-associated proteins (SP) have been identified to date including two hydrophilic proteins, SP-A and SP-D, and two hydrophobic proteins, SP-B and SP-C. Surfactant lipids, SP-B, and SP-C from lamellar bodies are secreted into the airspace by a process of exocytosis. In the presence of calcium and SP-A, lamellar bodies unravel to form tubular myelin. SP-B and SP-C enhance and stabilize the formation of mono- or multiple layers of PL that are generated at the air-liquid interface from tubular myelin. The type II pneumocytes recycle surfactant, and alveolar macrophages break down surfactant lipids and proteins.

The primary lipid element in human surfactant is phosphatidylcholine, which comprises about 80% of the total lipid component.[9] About half of this component is dipalmitoylphosphatidylcholine (DPPC), which is a PL that plays a major role in lowering surface tension.[9] Other PL constituents contribute to adherence and adsorption to the air-liquid interface. The size of the surfactant layer changes with respiration, taking up PL during inspiration and exuding phosphatidylcholine when compressed during expiration.[10] These PL interactions reduce surface tension, stabilize the alveoli, and maintain end-expiratory lung volume.[11] With insufficient or absent surfactant, the alveoli collapse, resulting in ventilation-perfusion mismatch and poor gas exchange.[10]

The surfactant-associated proteins are endogenous proteins that contribute to the physiological function of surfactant. SP-A is the most abundant surfactant protein. It functions in immune modulation, pulmonary surfactant turnover, and in conjunction with SP-B to form tubular myelin and surface film.[1,9] Surprisingly, SP-A knock-out model in mice showed no major abnormalities in lung function.[12] Although not essential for normal lung function and survival, SP-A is clearly required for tubular myelin formation and has a regulatory role in surfactant turnover and metabolism. SP-B is a hydrophobic protein that plays a role in membrane binding, lysis and fusion of lipid vesicles, and surfactant homeostasis by promoting adsorption of lipid molecules to the air-liquid interface.[9,11,13] SP-C is another hydrophobic protein with many functions similar to those of SP-B, and it also contributes to monolayer film stability.[9] SP-D plays a role in innate host defense of the lung and may also be associated with surfactant metabolism.[9] The currently available synthetic surfactants do not contain these specific surfactant-associated proteins.[14]

The composition of surfactants has been studied extensively. Rüdiger et al.[15] quantified the lipid components of three natural surfactant preparations: beractant, poractant alfa, and SF-RI1 (Alveofact, Boehringer Ingelheim, Biberach, Germany), and found significant differences in their composition and surface viscosities. The balance between neutral lipids and PL varied widely among the three products (Table 1). Further, the composition of any subgroup of lipids differed greatly between the surfactants analyzed. The mean PL content (expressed in mol%) of SF-RI1, a natural bovine surfactant, was only 23% saturated PL and 66% monoene PL.[15] Beractant, also a bovine derivative, was comprised of 66% saturated PL and 28% monoene PL. Poractant alfa, a porcine lung derivative, consisted of 31% saturated PL, 39% monoene PL, and 26% polyunsaturated PL. In comparison, the content of polyunsaturated PL in SF-RI1 and beractant was 11% and 6%, respectively. Unsaturated lipids, particularly polyunsaturated fatty acid (PUFA)-containing PL, have been shown to enhance the fluidity of lipid layers at physiological temperature.[15]

Plasmalogen is another lipid component that may significantly improve surfactant properties.[16] Plasmalogens, SP-B and cholesterol

regulate the surfactant monolayer stability and viscosity in a synergistic manner.[17] The role of plasmalogen has been studied extensively in cardiovascular and neurological disorders. Plasmalogens are not only structural membrane components and a reservoir for second messengers but may also be involved in membrane fusion and ion transport.[18] Plasmalogens may also act as antioxidants, thus protecting cells from oxidative stress.[19] Rüdiger and colleagues[15] reported the highest concentration of plasmalogens in poractant alfa (3.8 mol%), which is 2.5 times greater than beractant and 4 times greater than SF-RI1. On an *in-vitro* basis, plasmalogens and PUFA-PL contribute substantially to the lowering of surface viscosity.[16] In a comparative *in-vitro* trial, Rüdiger et al.[15] confirmed that poractant alfa maintains a lower surface viscosity at low surface tension than SF-RI1 and beractant, although this may reflect the higher SP-B content of poractant alfa. The plasmalogen content of calfactant has not been studied.

Theoretically, lower surfactant viscosity may enhance clinical response to therapy and explain some of the differences seen in clinical trials comparing different surfactants with respect to onset of action, duration of action, and the need for additional doses to maintain a functional reservoir of surfactant in the lungs. Furthermore, a lower viscosity may contribute to the ease of administration and the time required delivering the surfactant dose into the lungs. Studies to confirm these theoretical benefits, and whether a dose-response relationship exists, remain to be performed. Differences in viscosity and composition may have other consequences as well. Observational study results indicate that a higher PUFA-PL and plasmalogen content in tracheal aspirates at birth is associated with a reduced risk of developing bronchopulmonary dysplasia.[20] Poractant alfa contains a relatively high proportion of these components compared to other available surfactants,[15] although the relative concentrations in calfactant have not been compared directly to poractant alfa. This study did not demonstrate that exogenously administered surfactant increased PUFA-PL or plasmalogen concentrations in tracheal aspirates after treatment. The relevance of these results is an important area for future research. It is also important to note that SP-B reduces the surface viscosity of lipid mixtures,[17] therefore, relative SP-B concentration may affect surfactant characteristics. Certainly the benefits and contributions of the surfactant components are an area of continuing clinical interest.

CLINICAL STUDIES OF SURFACTANT

Early Trials

Early pilot trials that examined the efficacy of surfactants focused on one of two types: synthetic surfactants without surfactant-associated proteins and surfactants derived from natural sources. Fujiwara et al. demonstrated improved oxygenation in infants with severe hyaline-membrane disease.[21] They used an artificial surfactant of naturally occurring surfactant lipids and synthetic lipids that contained dipalmitoyl lecithin and phosphatidylglycerol.[21] The following year, Morley and colleagues demonstrated improved mortality and decreased need for ventilation with a dry powder preparation of pure DPPC and phosphatidylglycerol at a 7:3 ratio.[7] A 1998 Cochrane meta-analysis by Soll[22] examined six studies that utilized synthetic surfactant. The overall results were significant reductions in pneumothorax (RR 0.64 [95% CI, 0.55-0.76]), pulmonary interstitial emphysema (RR 0.62 [95% CI, 0.54-0.71]), bronchopulmonary dysplasia (RR 0.75 [95% CI, 0.61-0.92]), and neonatal mortality (RR 0.73 [95% CI, 0.61-0.88]).[22] After the introduction of colfosceril palmitate (Exosurf, [GlaxoSmithKlein, Research Triangle, NC, no longer in market]) in the United States, infant mortality dropped by 6% from 1989 to 1990, with as much as half of the decline directly attributable to surfactant use.[23]

A number of uncontrolled trials in infants with RDS have examined natural surfactants derived from calf lungs, human amniotic fluid, and pig lungs.[24-28] The promising evidence gained from these trials suggested a need for further controlled studies, and several small, randomized clinical trials ensued. These early trials lacked sufficient power to yield meaningful data individually. However, meta-analyses of their pooled data found a significant reduction in neonatal mortality with the use of synthetic or natural surfactant.[4]

During this time, a pivotal multicenter clini-

Table 2. Summary of 14 trials comparing synthetic and natural surfactants for RDS treatment in preterm infants.

Reference	Surfactant	Number of Patients	Type	Patients	Results
30	Beractant vs. colfosceril palmitate	617	Treatment	500-1500 g	Beractant: Lower 0-72 h FiO_2 & MAP
31	Beractant vs. colfosceril palmitate	66	Treatment	< 1500 g	Beractant: Decreased duration of PPV, O_2, LOS
32	Beractant vs. colfosceril palmitate	121	Treatment	Any with RDS	No differences in any outcomes
33	Beractant vs. colfosceril palmitate	41	Treatment	600-1750 g	No differences in any outcomes
34	Beractant vs. colfosceril palmitate	1296	Treatment	501-1500 g	Beractant: Lower FiO_2 at 72 h, lower 0-72 h MAP, fewer air leaks
35	Calfactant vs. colfosceril palmitate	1126	Treatment	All with RDS	Calfactant: Lower 0-72 h FiO_2 & MAP, fewer air leaks
36	Calfactant vs. colfosceril palmitate	846	Prophylaxis	< 29 wks	Calfactant: Less RDS, lower 0-72 h FiO_2 & MAP, fewer air leaks, more IVH
37	Beractant vs. colfosceril palmitate	122	Treatment	< 1500 g	Beractant: Lower FiO_2, MAP, & OI
38	Beractant vs. colfosceril palmitate	89	Treatment	< 37 wks, 1000 g	No difference
39	Poractant alfa vs. colfosceril palmitate	66	Treatment	All with RDS	Poractant alfa: Lower FiO_2, and improved a/A ratio; Increase in IVH with colfosceril palmitate
40	Poractant alfa vs. colfosceril palmitate	228	Treatment	All with RDS	Poractant alfa: Lower FiO_2, and MAP
41	Poractant alfa vs. pumactant	212	Treatment	< 30 wks	Poractant alfa: Decreased mortality (Trial stopped after interim analysis)
42	Lucinactant vs. poractant alfa	252	Prophylaxis	600-1250 g	Noninferiority trial, early trial closure, original sample size 496, no differences in any outcomes
43	Lucinactant vs. colfosceril palmitate vs. beractant	1294	Prophylaxis	600-1250 g	Lucinactant more effective than colfosceril palmitate and similar to beractant

FiO_2, fraction of inspired oxygen; IVH, intraventricular hemorrhage; LOS, length of stay; MAP, mean airway pressure; OI, oxygenation index; PPV, positive pressure ventilation
Adapted from data in Soll and Blanco,[6] Copyright Cochrane Library with permission.

cal trial of 146 infants was conducted in Europe.[29] A single dose of poractant alfa (200 mg/kg) was delivered as rescue therapy to infants with severe RDS. The researchers found that application of the natural surfactant decreased 28-day mortality from 51% to 31% ($P < .05$) compared to controls. In addition to the mortality benefit, there were also improvements in oxygenation and percentage of survivors without bronchopulmonary dysplasia (55% vs. 26%, $P < .001$), as well as a decreased incidence of pulmonary interstitial emphysema (23% vs. 39%, $P < .05$) and pneumothorax (18% vs. 35%, $P < .05$). These results in cases of severe RDS stimulated interest in further clinical trials.

Comparative Trials among Surfactants

Many comparative trials have been conducted using the available surfactants. Studies have examined parameters such as onset and duration of response, need for additional doses, importance of timing on efficacy, prophylactic application of surfactants in infants at high risk for RDS versus early or delayed rescue therapy in infants with established RDS, and the effects of combining surfactant

Table 3. Summary of 8 trials comparing surfactants derived from natural sources for RDS treatment in preterm infants

Reference	Surfactant	Number	Type	Patients	Results
44	Beractant vs. calfactant	374	Prophylaxis	< 1250 g	No differences in any variables; Calfactant: Increased mortality in infants < 600 g
44	Beractant vs. calfactant	608	Treatment	< 2000 g	Calfactant: Lower average 0-72 h FiO_2 and MAP
46	Beractant vs. poractant alfa (200 mg/kg)	73	Treatment	700-1500 g	Poractant alfa: Lower FiO_2, PIP, and MAP at 12-24 hrs
47	Alveofact vs. poractant alfa (100 mg/kg) vs. beractant	80	Treatment	< 2000 g	Poractant alfa: fewer days on O_2 and PPV; decreased LOS
5	Poractant alfa (100 or 200 mg/kg) vs. beractant	293	Treatment	750-1750 g	Poractant alfa: lower FiO_2, fewer doses, decreased mortality
48	Poractant alfa (200 mg/kg) vs. beractant	58	Treatment	< 37 wks with RDS	Poractant alfa: lower FiO_2 up to 48 hours; fewer doses; lower volume of surfactant given; fewer PDA
45	Beractant vs. calfactant	749	Prophylaxis	23-29 wks	Early trial closure; original sample size 2000; Infants alive with BPD 34% VS. 33%; No differences in any outcomes
45	Beractant vs. calfactant	1361	Treatment	401-2000 g	Early trial closure; original sample size 2080; Infants alive with BPD 31% VS. 31%; No differences in any outcomes

BPD, bronchopulmonary dysplasia; FiO_2, fraction of inspired oxygen; LOS, length of stay; MAP, mean airway pressure; OI, oxygenation index; PDA, patent ductus arteriosus; PIP, peak inspiratory pressure; PPV, positive pressure ventilation; RDS, respiratory distress syndrome

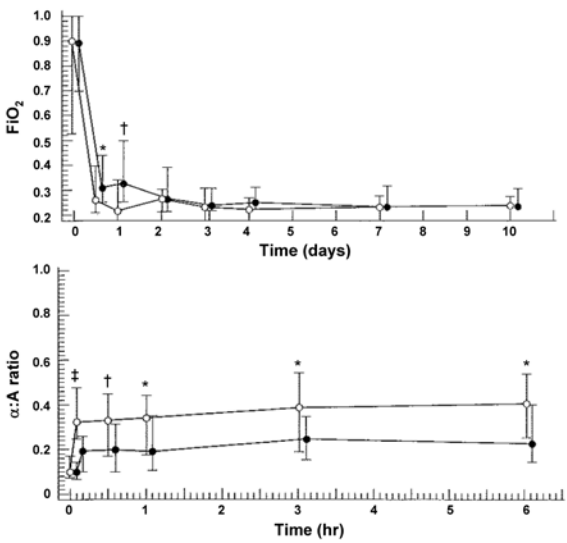

Figure 2. Oxygenation measurements in preterm infants with RDS treated with multiple doses of Curosurf (○) or Survanta (●) at various time points after randomization. Values are given as median and 25th and 75th percentiles. The points for the two groups are offset for clarity.
** P < .5*
† P < .01
‡ P < .001
conversion factor: 10 cm H2O = 0.98 kPa.
Adapted with permission from BMJ Publishing Group Ltd.[46]

therapy with various respiratory interventions such as continuous positive airway pressure (CPAP).

Synthetic versus Natural Surfactants

The efficacy of synthetic surfactants has been compared to that of natural surfactants in 14 clinical trials as of 2006.[30-43] For infants with RDS, natural surfactants improved survival and had fewer associated comorbidities compared to synthetic products (Table 2).[6] Further benefits of the natural products included faster onset of action and decreased dependence on supplemental oxygen and mechanical ventilation. The superior outcomes associated with natural surfactants were likely due to the presence of the surfactant-associated proteins, particularly SP-B. The favorable results associated with the natural preparations led many clinicians to conduct comparative trials of these products.

Natural versus Natural Surfactants

Eight clinical trials have examined different natural surfactants commercially available:

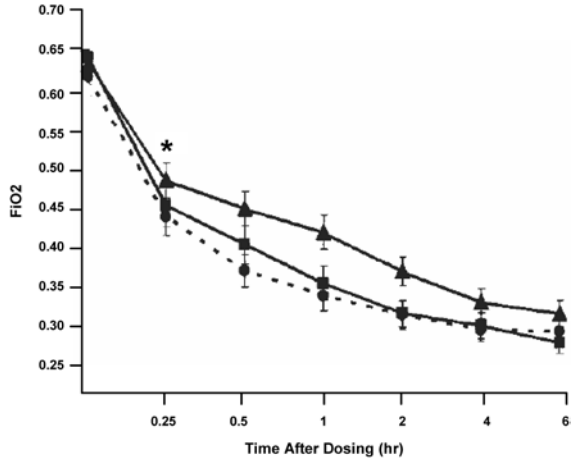

Figure 3. FiO_2 versus time after dosing for beractant (▲), poractant alfa 100 (●), and Poractant alfa 200 (■) in all 293 infants. Data are presented as mean ± SEM.
** P < .05 at all posttreatment time points in the poractant alfa groups compared with beractant.*
Adapted with permission from Ramanathan and Thieme Medical Publishers.[5]

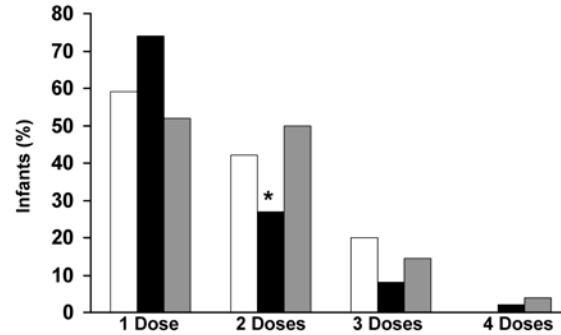

Figure 4. Percent of infants receiving one or more doses of surfactant in the three groups (n = 293). ■, Poractant alfa 100 mg/kg; ■, Poractant alfa 200 mg/kg; ▒, beractant 100 mg/kg.
** P < .002 poractant alfa 200 mg/kg versus beractant 100 mg/kg group.*
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beractant, poractant alfa, Alveofact and calfactant (Table 3).[5,44-49] In an early trial comparing natural surfactants, Bloom et al. examined the relative efficacy of calfactant and beractant in neonates with RDS.[44] In the treatment arm of the trial the researchers noted a longer interval between doses and improvements in initial oxygenation requirements in the calfactant treatment group. In the prevention arm of the trial the dosing intervals for calfactant were also longer, but there was no difference in initial ventilatory requirements. In a subsequent study, Bloom and colleagues set out to examine potential mortality differences between calfactant and beractant, but this evaluation ended early due to insufficient recruitment.[45]

Another early pilot trial by Speer and colleagues evaluated the effects of poractant alfa and beractant in 73 preterm infants with RDS.[46] Patients received either poractant alfa at an initial dose of 200 mg/kg with up to two additional doses of 100 mg/kg or beractant at 100 mg/kg for up to four total doses. The researchers determined that infants treated with poractant alfa had less oxygen and ventilator requirements during the first 24 hours than those treated with beractant (Figure 2). Furthermore, trends were established towards fewer instances of redosing and fewer complications such as reflux and oxygen saturation < 85% with poractant alfa, although these observations did not reach statistical significance likely due to the small sample size.

A multicenter, randomized, controlled trial of 293 preterm infants with RDS conducted in the United States also compared poractant alfa and beractant.[5] Infants less than 35 weeks gestation and with a birth weight of 750-1750 g were randomized to receive an initial dose of either 100 mg/kg or 200 mg/kg poractant alfa or 100 mg/kg beractant within 6 hours of birth. All repeat doses were given at 100 mg/kg regardless of drug. Where necessary, the second dose of surfactant was administered within 48 hours of the first, with repeat doses given at least 12 hours apart for poractant alfa and 6 hours apart for beractant. Infants in both poractant alfa groups demonstrated a significantly faster weaning of supplemental oxygen compared to the beractant treatment group at all points during the 6 hours after the first dose (P < .05), with a significant difference in FiO_2 area under the curve between 0 and 6 hours (P < .005) (Figure 3). Additionally, this study confirmed the observation of Speer et al.[50] in that only 36% of patients that received poractant alfa 200 mg/kg required two or more doses compared to 68% in the beractant group (P = .002) (Figure 4).[5] Furthermore, in infants born ≤ 32 weeks gestation, mortality was significantly lower at 36 weeks postconceptional age for those that received 200 mg/kg poractant alfa than with beractant (3% vs. 11%, P = .034) and poractant alfa 100 mg/kg (3% vs. 11%, P = .046) (Table 4). The larger amounts

Table 4. Mortality at 28 days of life (n = 293) for the groups as randomized and at 36 weeks postmenstrual age for infants born at ≤ 32 weeks gestational age (n = 270)

Mortality	Treatment Groups			P 200 vs. P 100 OR (95% CI)	P 100 vs. B 100 OR (95% CI)	P 200 vs. B 100 OR (95% CI)
	P 100 (n = 96)	P 200 (n = 99)	B 100 (n = 98)			
At day 28; n, (%)	6 (6%)	3 (3%)	8 (8%)	0.47 (0.11-1.93)	0.75 (0.25-2.25)	0.35 (0.09-1.37)
P value				.28	.61	.11
At 36 weeks PMA; n, (%)	9 (11%)	3 (3%)	10 (11%)	0.28 (0.07-1.05)	0.95 (0.36-2.46)	0.26 (0.07-0.98)
P value				.046	.912	.034

B 100, beractant 100 mg/kg; CI, confidence interval; n, number; OR, odds ratio; PMA, postmenstral age; P 100, poractant alfa 100 mg/kg; P 200, poractant alfa 200 mg/kg
Adapted with permission from Ramanathan and Thieme Medical Publishers.[5]

of polar lipids and SP-B in a smaller volume of poractant alfa may have accounted for the faster response observed with this surfactant. At present, poractant alfa is the only product available with the ability to deliver a 200 mg/kg dose in a smaller volume.

Malloy et al. also compared the effects of beractant and poractant alfa on oxygen requirements in 58 neonates with RDS.[48] The researchers found that infants in the poractant alfa group had a lower FiO_2 requirement in the first 48 hours after initial treatment compared to those who received beractant (P = .018). Also, infants who had received poractant alfa required a lower mean number of surfactant doses compared to the beractant group (1.2 vs. 1.7, P = .004). One interesting observation is that there was a significantly lower incidence of patent ductus arteriosus (PDA) requiring treatment with indomethacin in the poractant alfa group compared to the group that received beractant (17% vs. 45%, P = .02), although this has not been consistent with findings in other studies and should be interpreted appropriately. Three deaths, none associated with respiratory failure, were observed in the beractant group with no deaths among those who received poractant alfa. This difference was not statistically significant (P = .08); however, this study was not designed to evaluate mortality. The results of this study further support the observations that a higher initial surfactant dose is beneficial and reduces the need for subsequent treatments.

A meta-analysis including five publications representing six comparative trials of beractant and poractant alfa has been published.[4] Even though this meta-analysis represents a relatively small number of patients, 301 beractant-treated and 301 poractant alfa-treated neonates, the results were impressive. When the United States dosing regimen for poractant alfa (200 mg/kg) was compared to beractant 100 mg/kg, the mortality rate was significantly decreased (RR 0.29 [95% CI, 0.10-0.79]) (Table 5). The NNT associated with this outcome was low at 14 (95% CI, 8-50). Even when the initial dose was only 100 mg/kg, the NNT was 20, but the 95% CI was wide (11-1000). In aggregate, the evidence would suggest that treatment with poractant alfa at 200 mg/kg was more effective than beractant at 100 mg/kg. A summary of neonatal mortality data from the studies comparing poractant alfa and beractant is shown in Table 6.[4] These results further supported the superiority of natural surfactants in the reduction of morbidity and mortality associated with neonatal RDS. Table 7 summarizes

Table 5. Relative risks and numbers needed to treat for neonatal mortality: poractant alfa vs. beractant

	n	RR	95% CI	NNT	95% CI
All studies*	602	0.57	0.34-0.96	20	11-1000
Poractant alfa 200 mg/kg	328	0.29	0.10-0.79	14	8-50

CI, confidence interval; NNT, number needed to treat; RR, relative risk
**beractant dose was 100 mg/kg*
Adapted with permission from S. Karger AG, Basel.[4]

Table 6. Studies comparing mortality at 28 days in neonates given poractant alfa and beractant

	Number of Deaths (patients in study)	
Reference	**Poractant alfa**	**Beractant**
46	1 (33)	5 (40)
51	5 (17)	3 (10)
47	5 (27)	6 (26)
5	3 (99)	8 (98)
5	6 (96)	8 (98)
48	0 (29)	3 (29)
Total	**20 (301)**	**33 (301)**

Adapted with permission from S. Karger AG, Basel.[4]

the outcomes from all available comparative surfactant trials to date.

Other Considerations

Despite continued efforts to develop synthetic surfactants, they have yet to perform with the efficacy of the natural derivatives. Recently a new synthetic surfactant, lucinactant (Surfaxin; Discovery Laboratories, Doylestown, PA), was examined in phase III clinical trials.[42,43] This surfactant preparation contains a synthetic polypeptide intended to mimic the action of SP-B. However, this peptide behaves more like SP-C than SP-B, and acts as a transmembrane protein at the air-liquid interface.[52,53] The trial by Moya et al.[43] compared prophylactic use of lucinactant to beractant and the synthetic surfactant colfosceril palmitate in the rate of RDS at 24 hours and the rate of RDS-related death during the first 14 days after birth. The trial by Sinha et al.[42] used a non-inferiority design and compared prophylactic use of lucinactant to poractant alfa in the rate of survival without BPD through 28 days of age.

Shortcomings in these studies have prevented acceptance of this new synthetic surfactant as a replacement for proven, natural surfactants. The first study[43] was underpowered to detect equivalency to beractant in the primary endpoint, and although the trial was sufficiently powered to compare to colfosceril, that surfactant is no longer used in the United States.[54] The second study[42] was halted halfway through enrollment and was therefore also underpowered to sufficiently compare efficacy versus poractant alfa in the primary endpoint.[54] Further research is warranted to address these issues.

Furthermore, there are variations in the quantities of PL and the volumes of surfactant administered in each dose in the trials.[54] For example, Sinha and colleagues did not utilize the accepted and Food and Drug Administration-approved poractant alfa starting dose of 200 mg/kg, and when redosing they did not administer doses containing equal amounts of PL.[42] Some practical aspects of lucinactant may also be of concern. In the trials examined herein, lucinactant is dosed at 5.8 mL/kg.[42,43] In comparison, poractant alfa is dosed at 2.5 mL/kg for the first dose and 1.25 mL/kg for the second and subsequent doses.[5] A larger volume load may impede the ability to administer lucinactant quickly in an emergent situation, and a larger volume may contribute to adverse effects such as reflux or endotracheal tube obstruction. Furthermore, lucinactant requires heating at 44°C in a warming cradle for 15 minutes and subsequent shaking to convert it to liquid form for administration.[42,43] The biological fate of exogenously administered synthetic surfactants largely remains unknown. Although the development of a synthetic surfactant that contains synthetic peptides is intriguing, certainly further investigation is required before synthetic surfactant can be regarded as a suitable alternative to more proven natural surfactant preparations.

The body of knowledge surrounding optimal surfactant use in RDS and other conditions is constantly evolving. Clinical trials continue to explore different aspects of surfactant therapy. In neonates with RDS, studies have shown that surfactant administration within the first hour of life reduces the need for additional surfactant doses while improving gas exchange and decreasing the need for ventilatory support.[55] Furthermore, in an effort to decrease the risk of barotrauma and BPD, clinicians are increasingly attempting to extubate preterm infants following surfactant therapy. Dani et al. demonstrated that in infants less than 30 weeks gestational age, early extubation following poractant alfa resulted in decreased need for mechanical ventilation and additional surfactant doses, fewer days in the neonatal intensive care unit, and lower cost compared to continued mechanical ventilation.[56] Certainly there is much to learn regarding the optimal use of surfactant therapy for RDS, and as new

Table 7. Overview of surfactant trials and outcome

Parameter	Beractant vs. colfosceril palmitate	Calfactant* vs. colfosceril palmitate	Calfactant† vs. beractant	Poractant alfa vs. colfosceril palmitate	Poractant alfa‡ vs. pumactant	Poractant alfa‡ vs. beractant	Alveofact vs. Poractant alfa‡ vs. beractant	Lucinactant vs. colfosceril palmitate vs. vs. beractant vs. poractant alfa
BPD	ND	ND	ND	ND	ND	ND	ND	Less BPD§
IVH	ND	¶Total IVH increased*	ND	Increase in IVH#	ND	ND	ND	ND
Mortality	ND	ND	Increased†	ND	Decreased‡	Decreased‡	ND	ND
Doses	ND	ND	ND	ND	ND	Fewer doses‡	ND	ND
PPV days	ND	ND	ND	ND	ND	ND	Fewer days‡	ND
O_2 days	ND	ND	ND	ND	ND	ND	Fewer days‡	ND
LOS	ND	ND	ND	ND	ND	ND	Fewer days‡	ND

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; LOS, length of stay; ND, no difference; PPV, positive pressure ventilation
** Observed with calfactant*
† Observed with calfactant in <600 g infants in the prophylaxis trial
‡ Observed with poractant alfa
§ Observed with lucinactant in the only trial that compared two synthetic surfactants (40.2% and 45%, P=.045)
¶ Prophylaxis trial
 # Observed with colfosceril palmitate
Table provided courtesy of Rangasamy Ramanathan, MD.

surfactant products are introduced into practice it is prudent to evaluate them and consider all these parameters.

CONCLUSIONS

Surfactants are a complex mixture of saturated and unsaturated PL, neutral lipids, plasmalogens, and proteins. The physiological mechanism by which surfactants reduce surface tension throughout the respiratory cycle remains poorly understood. Nevertheless, surfactants derived from natural sources repeatedly have shown high efficacy and safety as treatment for RDS in preterm infants. As premature infants survive at progressively lower gestational ages, the need to effectively treat associated pulmonary comorbidities will continue to grow. A review of the literature provides strong evidence of the vital importance of early surfactant therapy for increasing survival and minimizing morbidity in preterm infants. Future attempts to produce an optimal synthetic surfactant preparation should take into account the constituents in the preparation, especially the compounds that replace the role of surfactant proteins, the stability, viscosity, and the volume to be administered to preterm infants with RDS.

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REFERENCES

1. Gal P, Ransom JL. Acute respiratory distress syndrome. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 6th ed. New York, NY: McGraw-Hill;2005:557-75.
2. El-Metwally D, Vohr B, Tucker R. Survival and neonatal morbidity at the limits of viability in the mid 1990s: 22 to 25 weeks. J Pediatr 2000;137:616-622.
3. Blickstein I, Shinwell ES, Lusky A, et al. Plurality-dependent risk of respiratory distress syndrome among very-low-birth-weight-infants and antepartum corticosteroids treatment. Am J Obstet Gynecol 2005;192:360-364.
4. Halliday HL. History of surfactant from 1980. Biol Neonate 2005;87:317-322.
5. Ramanathan R, Rasmussen MR, Gerstmann DR, et al. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol 2004;21:109-119.

6. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD000144. DOI: 10.1002/14651858.CD000144. Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000144/frame.html. Accessed August 2006.
7. Morley CJ, Bangham AD, Miller N, et al. Dry artificial lung surfactant and its effect on very premature babies. Lancet 1981;1:64-68.
8. Bangham AD. Lung surfactant: how it does and does not work. Lung 1987;165:17-25.
9. Poynter SE, LeVine AM. Surfactant biology and clinical application. Crit Care Clin 2003;19:459-472.
10. Clements JA, Hustead RF, Johnson RP, et al. Pulmonary surface tension and alveolar stability. J Appl Physiol 1961;16:444-450.
11. Whitsett JA, Weaver TE. Hydrophobic surfactant proteins in lung function and disease. N Engl J Med 2002;347:2141-2148.
12. Ikegami M, Korfhagen TR, Whitsett JA, et al. Characteristics of surfactant from SP-A deficient mice. Am J Physiol 1998;275: L247-L254.
13. Hawgood S. Surfactant protein B: structure and function. Biol Neonate 2004;85:285-289.
14. Pfister RH, Soll RF. New synthetic surfactants: the next generation? Biol Neonate 2005;87:338-344.
15. Rudiger M, Tolle A, Meier W, et al. Naturally derived commercial surfactants differ in composition of surfactant lipids and in surface viscosity. Am J Physiol Lung Cell Mol Physiol 2005;288:L379-L383.
16. Tolle A, Meier W, Greune G, et al. Plasmalogens reduce the viscosity of a surfactant-like phospholipid monolayer. Chem Phys Lipids 1999;100:81-87.
17. Tolle A, Meier W, Rudiger M, et al. Effect of cholesterol and surfactant protein B on the viscosity of phospholipid mixtures. Chem Phys Lipids 2002;114:159-168.
18. Farooqui AA, Horrocks LA. Plasmalogens: Workhorse lipids of membranes in normal and injured neurons and glia. Neuroscientist 2001;7:232-245.
19. Maeba R, Ueta N. Ethanolamine plasmalogens prevent the oxidation of cholesterol by reducing the oxidizability of cholesterol in phospholipid bilayers. J Lipid Res 2003;44:164-171.
20. Rudiger M, von Baehr A, Haupt R, et al. Preterm infants with high polyunsaturated fatty acid and plasmalogen content in tracheal aspirates develop bronchopulmonary dysplasia less often. Crit Care Med 2000;28:1572-1577.
21. Fujiwara T, Maeta H, Chida S, et al. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980;1:55-59.
22. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews 1998, Issue 3. Art. No.: CD001149. DOI: 10.1002/14651858.CD001149. Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001149/frame.html. Accessed August 2006.
23. Schwartz RM, Luby AM, Scanlon JW, et al. Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500 g. N Engl J Med 1994;330:1476-1480.
24. Cochrane CG, Revak SD, Merritt TA, et al. The efficacy and safety of KL4-surfactant in preterm infants with respiratory distress syndrome. Am J Respir Crit Care Med 1996;153:404-410.
25. Gortner L, Bernsau U, Hellwege HH, et al. A multicenter randomized controlled clinical trial of bovine surfactant for prevention of respiratory distress syndrome. Lung 1990;168 Suppl:864-869.
26. Hallman M, Merritt TA, Schneider H, et al. Isolation of human surfactant from amniotic fluid and a pilot study of its efficacy in respiratory distress syndrome. Pediatrics 1983;71:473-482.
27. Noack G, Berggren P, Curstedt T, et al. Severe neonatal respiratory distress syndrome treated with the isolated phospholipid fraction of natural surfactant. Acta Paediatr Scand 1987;76:697-705.

28. Smyth JA, Metcalfe IL, Duffty P, et al. Hyaline membrane disease treated with bovine surfactant. Pediatrics 1983;71:913-917.
29. Collaborative European Multicenter Study Group: Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. Pediatrics 1988;82:683-691.
30. Horbar JD, Wright LL, Soll RF, et al. A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1993;123:757-766.
31. Alvarado. Clinical Trial of Survanta versus Exosurf in infants < 1500 g with respiratory distress syndrome [abstract]. Ped Res 1993;33A.
32. Pearlman SA, Leef KH, Stefano JL, et al. A randomized trial comparing Exosurf versus Survanta in the treatment of neonatal RDS [abstract]. Pediatr Res 1993;33:340A.
33. Sehgal SS, Ewing CK, Richards T, et al. Modified bovine surfactant (Survanta) versus a protein-free surfactant (Exosurf) in the treatment of respiratory distress syndrome in preterm infants: a pilot study. J Natl Med Assoc 1994;86:46-52.
34. A multicenter, randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. Vermont-Oxford Neonatal Network. Pediatrics 1996;97:1-6.
35. 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.
36. Hudak ML, Martin DJ, Egan EA, et al. A multicenter randomized masked comparison trial of synthetic surfactant versus calf lung surfactant extract in the prevention of neonatal respiratory distress syndrome. Pediatrics 1997;100:39-50.
37. Modanlou HD, Beharry K, Padilla G, et al. Comparative efficacy of Exosurf and Survanta surfactants on early clinical course of respiratory distress syndrome and complications of prematurity. J Perinatol 1997;17:455-460.
38. da Costa DE, Pai MG, Al Khusaiby SM. Comparative trial of artificial and natural surfactants in the treatment of respiratory distress syndrome of prematurity: experiences in a developing country. Pediatr Pulmonol 1999;27:312-317.
39. Rollins M, Jenkins J, Tubman R, et al. Comparison of clinical responses to natural and synthetic surfactants. J Perinat Med 1993;21:341-347.
40. Kukkonen AK, Virtanen M, Jarvenpaa AL, et al. Randomized trial comparing natural and synthetic surfactant: increased infection rate after natural surfactant? Acta Paediatr 2000;89:556-561.
41. Ainsworth SB, Beresford MW, Milligan DW, et al. Pumactant and poractant alfa for treatment of respiratory distress syndrome in neonates born at 25-29 weeks' gestation: a randomised trial. Lancet 2000;355:1387-1392.
42. Sinha SK, Lacaze-Masmonteil T, Soler A, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics 2005;115:1030-1038.
43. Moya FR, Gadzinowski J, Bancalari E, et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. Pediatrics 2005;115:1018-1029.
44. Bloom BT, Kattwinkel J, Hall RT, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome. Pediatrics 1997;100:31-38.
45. Bloom BT, Clark RH. Comparison of Infasurf (calfactant) and Survanta (beractant) in the prevention and treatment of respiratory distress syndrome. Pediatrics 2005;116:392-399.

46. Speer CP, Gefeller O, Groneck P, et al. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 1995;72:F8-13.
47. Baroutis G, Kaleyias J, Liarou T, et al. Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Eur J Pediatr 2003;162:476-480.
48. Malloy CA, Nicoski P, Muraskas JK. A randomized trial comparing beractant and poractant treatment in neonatal respiratory distress syndrome. Acta Paediatr 2005;94:779-784.
49. Notter RH. Lung biology in health and disease. Lung Surfactants: Basic Science and Clinical Applications, vol 149. New York, NY: Marchel Dekker Inc.,2000:281-298.
50. Speer CP, Robertson B, Curstedt T, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. Pediatrics 1992;89:13-20.
51. Halahakoon CW. A Study of Cerebral Function following Surfactant Treatment for Respiratory Distress Syndrome; MD thesis, Queen's University of Belfast, 1999.
52. Gstafsson M, Vandenbussche G, Curstedt T, et al. The 21-residue surfactant peptide (LysLeu4)4Lys(KL4) is a transmembrane alpha-helix with a mixed nonpolar/polar surface. FEBS Lett 1996;384:185-188.
53. Curstedt T, Johansson J. New synthetic surfactant – how and when. Biol Neonate 2006;89:336-339.
54. Kattwinkel J. Synthetic surfactants: the search goes on. Pediatrics 2005;115:1075-1076.
55. Lefort S, Diniz EM, Vaz FA. Clinical course of premature infants intubated in the delivery room, submitted or not to porcine-derived lung surfactant therapy within the first hour of life. J Matern Fetal Neonatal Med 2003;14:187-196.
56. Dani C, Bertini G, Pezzati M, et al. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. Pediatrics 2004;113:e560-e563.