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Is there a Difference in Surfactant Treatment of Respiratory Distress Syndrome in Premature Neonates? A Review

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Abstract

Exogenous surfactant treatment of premature infants with Respiratory Distress Syndrome (RDS) has been the standard of care for more than two decades. There are now many studies comparing various surfactant preparations. Data are clear that the synthetic surfactants without surfactant proteins are inferior to animal derived surfactant preparations. In the United States, commercially available surfactants are beractant, calfactant, poractant alfa, and lucinactant. Relative efficacy of the various available animal derived surfactants in the United States appear to favor poractant alfa, the surfactant preparation with the highest concentrations of phospholipids and high concentration of surfactant proteins, allowing a higher initial dose of phospholipids in preterm infants less than 32 weeks. A new synthetic surfactant with a surfactant protein analog, lucinactant, has been recently been approved for use in the United States. Synthetic surfactants hold the possibility of surfactant treatments without potential animal-born infectious agents or animal proteins that could induce an immune response in fragile premature infants with multiple medical problems. New surfactant administration strategies are described, complimenting new respiratory support strategies, designed to minimize invasive mechanical ventilation and decrease the frequency of chronic lung disease. Minimally invasive surfactant administration strategies are being developed to accommodate these new respiratory support strategies. The goal of this manuscript is to review the available surfactant preparations and their administration strategies.

Introduction

RDS was first characterized as surfactant deficiency disease of the newborn by Avery and Mead in 1959 [1]. The first clinical use of exogenous surfactant to treat RDS was by Fujiwara and colleagues in 1980 [2]. These sentinel reports lead to our current strategies for the surfactant treatment of RDS in premature infants that began in 1989, with the Food and Drug Administration (FDA) approval of the synthetic surfactant colfosceril palmitate suspension (Exosurf®), closely followed by approval of beractant (Survanta®), the first animal derived surfactant. These were the first commercially available surfactant preparations in the United States and were associated with a greater decline in mortality in premature infants with RDS than in any other years in recent decades [3,4]. Since 1989, several animal derived surfactant preparations have been developed, each surfactant being more concentrated and tending to have a more rapid onset and longer duration of action. The animal derived surfactant preparations contain surfactant protein B and C (SP-B and SP-C) and are superior to the early synthetic surfactants without surfactant protein. Nonetheless, RDS continues to be a leading cause of infant morbidity and mortality in the United States. Reviews on this topic are available from Logan and Moya [5], Pfister et al. [6], Ramanathan et al. [7], Seger and Soll [8], and Fujii and Carillo [9]. There is also a compelling review by Bassler and Poets [10] advocating for the inclusion of surfactants in the World Health Organization (WHO) model list of essential medicines. In the current review, we summarize the current state of the art, concentrating on the comparison of various animal derived surfactant preparations from a clinician's perspective. We briefly review what is known of the comparison between animal derived surfactants vs. the newer synthetic surfactant, lucinactant (Surfaxin®, Discovery Labs, Warrington, PA), approved by the FDA for use in the United States in 2012, and a brief discussion of the cost-benefit analysis of surfactant use. In addition, we discuss some of the novel surfactant administration strategies that are being used to support newer strategies of Minimally Invasive ventilation and Surfactant Therapy (MIST) in these fragile premature infants.

Background

Surfactant preparations for the treatment of RDS in premature infants are segregated into synthetic vs. animal derived surfactant preparations. The older synthetic surfactants, such as colfosceril palmitate (Exosurf®, Glaxo Wellcome, UK) and pumactant (ALEC®, artificial lung expanding compound, Britannia Pharmaceuticals, UK) are composed of phospholipids, with no surfactant proteins (Table 1). Animal derived surfactant preparations are extracted from either bovine or porcine lungs by mincing or lavaging surfactant from the animal lungs. Specifically, animal-derived surfactant preparations have surfactant proteins, SP-B and SP-C, responsible for spreading and adsorption of phospholipids at the alveolar air-liquid interface [11,12]. Animal derived surfactants with surfactant proteins induce a more rapid improvement in lung function than synthetic surfactants that lack surfactant proteins [13-19]. While synthetic surfactants without surfactant proteins are still being manufactured, the animal derived surfactants have become the standard of care. Animal derived surfactants have become progressively more concentrated, with higher concentrations of phospholipids and surfactant proteins, and a concomitant decrease in the volume of administration and increase in the rapidity of onset and duration of action (Table 2). Development of newer synthetic surfactants, such as lucinactant and rSP-C surfactant (Venticute®, ALTANA Pharma AG, Konstanz, Germany, not approved for use in the United States) have synthetic or recombinant polypeptides that may function similarly to that of animal derived surfactant preparations.

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SURFACTANT	PHOSPHOLIPID COMPOSITION	PHOSPHOLIPIDS (mg/mL)	Protein Mimicking Molecules (mg/mL)	DOSE VOLUME (mL/kg)
Pumactant (ALEC®) [19,20]	DPPC + PG	83.3	0	1.2
Colfosceril palmitate (Exosurf®) [21]	DPPC + Hexadecanol + Tyloxapol	13.5	0	5
Lucinactant (Surfaxin®) [22]	DPPC + 21 Synthetic aminoacids {5 Lysines (K) + 16 Leucines (L)}	30	0.862 (KL-4)	5.8

DPPC (phospholipid dipalmitoylphosphatidylcholine)
PG (Phosphatidylglycerol)

Table 1: Synthetic surfactants.

SURFACTANT	PREPARATION	PHOSPHO-LIPIDS (mg/mL)	DSPC (mg/mL)	Total Proteins (mg/mL)	SP-B (mg/mL)	PLMGN (mol% total PL)
Beractant (Survanta®) [23]	**Minced bovine lung extract +DPPC, Palmitic Acid, Tripalmitin**	**25**	**11-15.5**	**<1**	**Not specified**	**1.5 ± 0.2[26]**
Calfactant (Infasurf®) [23]	**Bovine Lung Lavage/DPPC, Cholesterol**	**35**	**16**	**0.7**	**0.26**	**Not specified**
Poractant alfa (Curosurf®) [25]	**Minced porcine lung extract-purified via Liquid Gel chromatography**	**76**	**30**	**1**	**0.45**	**3.4 ± 0.1[26]**

DPPC (phospholipid dipalmitoylphosphatidylcholine)
DSPC (Disaturated Phosphotidylcholine)
SP-B (Surfactant Protein B)
PLMGN (plasmalogens)
PL (Phospholipids)

Table 2: Animal-derived surfactants.

Overview of Surfactant Treatment of Rds

Human surfactant is composed of lipids and surfactant proteins that act to reduce surface tension in the terminal bronchioles and alveoli. The majority of the lipid component is phosphatidylcholine, 50% of which is the phospholipid, Dipalmitoylphosphatidylcholine (DPPC). DPPC enables the surfactant layer to change its configuration during inspiration and expiration, reducing surface tension of the alveoli [12]. There are four surfactant proteins, SP-A, SP-B, SP-C and SP-D. The hydrophobic surfactant proteins SP-B and SP-C promote adsorption of the surfactant layer to the alveolar air-liquid interface and reduce surface tension and improve compliance of the lung, the major difference between animal derived vs. synthetic surfactants without surfactant proteins or surfactant protein analogs. The relative proportions of phospholipids and surfactant proteins may be important when comparing surfactants (Table 1 and 2). Current research in synthetic surfactants focuses on developing replacements for animal derived SP-B and SP-C.

Synthetic surfactants without surfactant proteins or surfactant protein analogs are inferior to the animal derived surfactant preparations with SP-B and SP-C [8]. Adverse outcomes, such as pneumothorax, were more frequent with synthetic surfactants without surfactant proteins vs. animal derived surfactants. Higher mortality rates were observed when non-protein containing synthetic surfactant (pumactant) vs. the animal derived surfactant, causing early termination of the study and withdrawal from the market [19]. Colfosceril palmitate is no longer marketed in the United States.

The most recent developments in surfactant therapy are two synthetic surfactants that contain either polypeptide protein analogs or recombinant human surfactant protein C. Lucinactant contains DPPC, PG, palmitic acid, and the addition of a protein analog KL-4 (Sinapultide) that mimics the activity of SP-B. Venticute, contains DPPC, PG, palmitic acid and recombinant SP-C. Of these, only lucinactant is available in the United States.

Animal Derived Surfactants

Commercially available animal derived surfactants from bovine or porcine extracts or lung lavage are beractant (Survanta®), calfactant (Infasurf®), poractant alfa (Curosurf®), and bovactant (Alveofact®)[16-30]. These surfactants differ in their concentration of phospholipids, plasmalogens and the surfactant-proteins, SP-B and SP-C (Table 2). Beractant, a bovine minced lung extract, has added DPPC. Calfactant, a lavaged calf lung extract, has a higher concentration of SP-B than beractant. Poractant alfa, a porcine minced lung extract, has the highest concentration of phospholipids and plasmalogens. Poractant alfa has more SP-B than beractant or calfactant.

Clinical Comparison of Animal Derived Surfactants

Beractant is the surfactant with the longest duration of use in the United States. Comparisons of the animal derived surfactants, calfactant vs. poractant alfa vs. beractant is incomplete and consensus regarding the best preparation has yet to be determined. A summary of these comparison studies are presented in Table 3 (Included as suplementary data). Bovactant and BLES® (Bovine Lipid Extract Surfactant, BLES Biochemicals, Inc, London, ON, Canada) are not available in the United States.

Beractant vs. Calfactant

Bloom and colleagues [31] compared calfactant vs. beractant in infants ≤ 29 weeks, <1250 g birth weight. Early, prophylactic use of calfactant vs. beractant showed benefits over the rescue treatment strategy. Prophylactic calfactant increased the dosing interval, decreased the duration of mechanical ventilation (20 ± 22 vs. 27 ± 26 days, mean ± SD, p=0.01) and decreased the duration of supplemental oxygen (36 ± 39 vs. 46 ± 48 days, p=0.02). Frequency of air leaks, pulmonary hemorrhage, severe grade 3 or 4 Intraventricular Hemorrhage (IVH), Necrotizing Enterocolitis (NEC), Retinopathy of Prematurity (ROP), and sepsis were similar between groups. The mortality rate, however, was slightly higher in the calfactant vs. beractant treated infants (14% vs. 8%, p=0.06), due to higher mortality rates in infants <600 g birth weight. For infants <600 g, mortality was 63% (19 out of 30) of infants treated with calfactant vs. 26% (6 of 19) of infants treated with prophylactic beractant (p=0.007). The findings were considered to reflect an unprecedented survival rate in the subset of beractant

treated infants <600 g (13 out of 19, 74%). Thus, while calfactant induced a sustained improvement in respiratory support, there was no improvement in survival and a potentially unexplained mortality difference in extremely premature infants.

A follow up study of extremely premature infants by Bloom and Clark [32] showed no difference between groups treated with calfactant vs. beractant for any parameter in either the rescue treatment (23 0/7 to 29 6/7 weeks) or the prophylaxis protocols. The study was closed early due to slow enrollment and changes in practice among the study centers. The authors were unable to reject or accept the null hypothesis, due to insufficient power. Clark and colleagues [33], conducted a retrospective study comparing calfactant (n=1115) vs. beractant (n=4054) and found no differences in weight-specific mortality or morbidity. In infants <601 g, the mortality rates were similar (44% vs. 43%, respectively; p=0.94). Study interpretation was complicated by a slightly higher percentage of in-born infants in the calfactant than beractant group (988/1115, 89% vs. 3436/4054, 85%; p=0.01). These data did not support a clinical benefit of one drug over the other. Ramanathan and colleagues [34] in a three way retrospective study comparing infants treated with poractant alfa vs. calfactant vs. beractant found higher mortality rates in infants with birth weights 1000-1249 g treated with calfacant vs. in those treated with beractant. There were significant differences in mortality in the group treated with poractant alfa (see below).

Poractant alfa vs. Beractant

There is extensive experience with poractant alfa in Europe, where it has long been the most used surfactant for the treatment of RDS in premature infants [35-44]. The European data, however, are complicated by the trend against aggressive management of extremely premature infants <25 weeks gestation, the population with the highest morbidity and mortality [44]. Speer and colleagues [42] compared poractant alfa (200 mg/kg, 2.5 ml/kg initial dose followed by subsequent doses of 100 mg/kg, 1.25 ml/kg every 24 hours as clinically indicated) vs. beractant (100 mg/kg, 4 ml/kg for the initial and subsequent doses every 12 hours as indicated) in 73 infants with RDS and birth weight 700-1500 g. Infants treated with poractant alfa required slightly less respiratory support during the first day of life vs. infants treated with beractant. There were no differences in air leak, pulmonary hemorrhage, BPD or death between groups. Ramanathan and colleagues [45], studied 293 ventilated infants with RDS, (birth weights 750-1750 g) and compared poractant alfa 100 mg/kg initial dose, poractant alfa 200 mg/kg initial dose and beractant 100 mg/kg initial dose. The mean FiO_2 area under the curve for the first 6 hours after surfactant administration for poractant alfa (100 and 200 mg/kg initial dose) was less (p<0.003) vs. in infants treated with beractant. While neonatal mortality rate in the groups at large were not significantly different, in the subgroup of infants ≤32 weeks, there was a significantly lower mortality at 36 weeks in the poractant alfa 200 mg/kg initial dose (3%) vs. either poractant alfa 100 mg/kg initial dose (11%) or beractant 100 mg/kg (11%, p=0.03). Baroutis and colleagues [46] studied infants <32 weeks, <2000g with RDS requiring mechanical ventilation, treated with bovactant vs. poractant alfa vs, beractant. Each surfactant was administered intratracheally (100 mg/kg) within the first 4 hours of life and the second dose was given 12 hours later. This differed from the recommended initial dose of bovactant (50 mg/kg) and poractant alfa (200 mg/kg). They found that infants treated with poractant alfa had shorter ventilator courses, needed fewer days of oxygen, and had shorter hospital stays vs. infants treated with beractant. Malloy and colleagues [47] compared 58 infants <37 weeks gestational age, mechanically ventilated for RDS who were treated with poractant alfa vs. beractant. In the first 48 hours, infants who received poractant alfa had a lower FiO_2 than infants who received beractant (p=0.018). In addition, the prevalence of PDA was lower in the infants treated with poractant alfa vs. the group treated with beractant (17% vs. 45%, p=0.02). There was a trend suggesting a lower mortality in the infants treated with poractant alfa (0%) vs. those treated with beractant (10%, p=0.08). Fujii and colleagues [48] compared 52 infants <30 weeks gestation with RDS requiring mechanical ventilation, treated with poractant alfa (n=25, birth weight of 930 ± 231 g, 27.1 ± 1.6 wks) vs. beractant (n=27, birth weight 900 ± 271 g, 26.7 ± 1.7 wks) and found mean airway pressure (p=0.003) and respiratory index (MAP x FiO_2, p=0.032) for the first 72 hours of life was lower in the poractant alfa vs. beractant group. There were a greater number of infants extubated at 48 hours (13/25 vs. 6/27, P=0.027) and 72 hours (15/25 vs. 8/27, P=0.029) in the poractant alfa group. There were fewer PDAs in the group treated with poractant alfa vs. in those treated with beractant. Singh et al. [49] performed a meta-analysis of the completed randomized controlled trials comparing animal surfactants and concluded that mortality is significantly lower and need for re-dosing was less in poractant alfa (200 mg/kg) treated infants vs. in infant treated with low dose poractant alfa (100 mg/kg) or beractant treated infants. Ramanathan and colleagues [50], in a retrospective study, examined 14,173 preterm infants treated with poractant alfa vs. calfactant vs. beractant, surfactant preparations available in the United States. Overall mortality was lowest in infants treated with poractant alfa (3.61%) as compared to beractant (4.58%, p=0.053) and calfactant (5.95%, p=0.043). In infants with birth weight 500-749 g, mortality rate in poractant alfa treated infants was significantly lower (11.72%) vs. in infants treated with calfactant (20.67%, p<0.001), or beractant (17.39%, p< 0.011). Dizdar and colleagues [51], in a smaller randomized control study, showed a similar trend in reduced mortality and reduced chronic lung disease rates in infants treated with poractant alfa vs. beractant.

Beractant vs. Lucinactant

Moya and colleagues [52] studied 1295 premature infants 24-32 weeks gestation and birth weights 600–1250 g treated with lucinactant (175 mg/kg, 5.8 ml/kg/dose, n=527) vs. colfosceril palmitate (67.4 mg/kg, 5 ml/kg/dose, n=509) vs. beractant (100 mg/kg, 4.0 ml/kg/dose, n=258) in the SELECT trial (Safety and Effectiveness of Lucinactant Versus Exosurf in a Clinical Trial of RDS in Premature Infants). Infants treated with lucinactant had a lower mortality rate from RDS at 14 days vs. infants treated with either colfosceril palmitate (4.7 vs. 9.4%, p=0.002) or beractant (10.5%, p=0.001). Death or BPD at 36 weeks was lower in the infants treated with lucinactant (40.6%) vs. in infants treated with colfosceril palmitate (46.2%, p=0.021), but similar to beractant (43.8%, p=0.32). Frequencies of other morbidities of prematurity were similar in all three groups. The difference in mortality rates between lucinactant vs. beractant deserves some comment. The concentration of sinapultide (synthetic peptide KL-4) in lucinactant is consistently higher than the SP-B concentration in beractant. In addition, the lucinactant phospholipid dose was 75% greater than for beractant. The authors speculate that lucinactant may be superior to beractant in reducing mortality rate associated with RDS by improved rapid adsorption to the air-liquid interface. One of the difficulties with the use of lucinactant is its high viscosity at room temperature and the need for warming in a 44°F cradle for 15 minutes prior to use. In conclusion, Lucinactant is a new synthetic surfactant with clinical efficacy equivalent to that achieved with available animal derived surfactant preparations.

Poractant alfa vs. Lucinactant

Lucinactant was approved for prophylactic use in the United States in 2012, and is the first synthetic surfactant with a surfactant protein

analog, sinapultide. Sinha and colleagues [53] studied infants 24-28 weeks gestation and birth weights 600 – 1250 g, receiving lucinactant (175 mg/kg, 5.8 ml/kg) vs. poractant alfa (175 mg/kg, 2.2 ml/kg/dose, less than the recommended initial dose of 200 mg/kg) in the STAR trial (Surfaxin Therapy Against Respiratory Distress Syndrome). In this non-inferiority taril, infants treated with lucinactant vs. poractant alfa at these doses had similar mortality rates at 28 days, BPD rates at 28 days (62.2% vs. 63.7%, respectively, p=NS) and survival rates without BPD at 36 weeks (64.7% vs. 66.9%, respectively, p=0.86). In the analysis comparing lucinactant vs. poractant alfa, the one-year fixed-time-point estimates of mortality rates were similar, 18.6% vs. 21.9%, respectively (NS) [54]. If those patients lost to follow up were included as mortalities, lucinactant (19.4%) had a lower mortality rate vs. poractant alfa (24.2%). The authors concluded that administration of lucinactant to infants at risk for RDS results in neonatal survival rates at least comparable with that of infants given animal derived surfactants beractant vs. poractant alfa. This study was stopped early due to slow recruitment, and the mortality rate used for comparison was from poractant alfa studies that were done 18 years before the start of this trial. Furthermore, there was no difference in the morbidity through one-year corrected age in infants given lucinactant versus other animal derived surfactants.

rSP-C surfactant

There are several studies comparing rSP-C (recombinant human SP-C) with various surfactants treating adult respiratory distress syndrome, but no published studies comparing efficacy of rSP-C surfactant with animal derived surfactant in neonates with RDS. Clinical trials in neonates are ongoing. Like lucinactant, however, the phosopholipid concentration is substantially less than in the most concentrated animal derived surfactant and the volume of administration is greater. Recombinant SP-C surfactant holds promise for future use without potential infectious disease and immune implication.

More studies are needed to address relative efficacy of the various surfactant preparations, especially in premature infants <30-32 weeks. Focused studies on the very premature infants with the highest morbidity and mortality rates may be more revealing than more inclusive studies that include infants ≥30 weeks gestation, where the mortality and morbidities are relatively low and more difficult to influence with a neonatal treatment strategy. In addition, new variations in surfactant administration, consistent with a minimally invasive respiratory support strategy may change the relative efficacy of the available surfactant preparations.

Surfactant Therapy without Intubation

In premature infants with RDS, strategies to avoid intubation and invasive positive pressure mechanical ventilation are being used to reduce the incidence of chronic lung disease. The data support equivalence of early CPAP vs. rescue surfactant administration with strategies utilizing early prophylactic surfactant [55-59]. Nonetheless, there is a large body of evidence suggesting that early prophylactic surfactant use is better than rescue [60]. Thus, many clinical investigators are seeking to administer prophylactic surfactant without endotracheal intubation.

Novel strategies for non-invasive surfactant administration were recently reviewed by Gupta and Donn [61]. Intraamniotic surfactant administrations into the mouths of three fetuses using a fiberoptic endoscope were described [62]. Fetal, intrauterine, fiberoptic scope administration of surfactant is more invasive and requiring greater technical skill, than current management strategies for antenatal steroid administration, maintenance of the pregnancy and conventional management of RDS. Pharyngeal administration of surfactant to an infant following delivery of the head, after suctioning of the mouth and pharynx, to allow inhalation of surfactant with the first breath was described using calfactant in 23 infants 560-1804 g at birth [63]. The approach is limited to vertex vaginal deliveries, but is technically feasible. No additional data are available regarding efficacy. Surfactant administration (calfactant) through a Laryngeal Mask Airway (LMA) for rescue therapy in 11 preterm infants with RDS ≥1200 g birth weight, resulted in "an abrupt and sustained decrease in oxygen requirement" [64]. This pilot study shows potential feasibility of LMA for minimally invasive surfactant administration, but there is no comparison with standard management and availability of smaller LMA sizes will be needed for the more premature infants most likely to benefit from surfactant administration.

A technique for minimally invasive surfactant administration was developed by Kribs and colleagues [65], using Magill forceps to advance a soft catheter into the trachea of infants receiving CPAP support for moderate RDS. Multicenter studies were reported in 2010 and 2011 [66,67]. There were significantly fewer infants on invasive mechanical ventilation at 3 days of life and early surfactant therapy reduced the frequency of chronic lung disease in both studies without affecting mortality. It was uncertain whether these results will be replicated when means other than a gas jet induced CPAP are used. Dargaville et al. [68] described use of a stiff vascular catheter to provide Minimally Invasive Surfactant Therapy (MIST). In a feasibility study, 11 preterm infants 25-28 weeks gestational age, using a 16 gauge vascular catheter without intubation, Magill forceps or sedation. Dargaville et al [69] reported their experience in 61 infants 25-28 weeks and 29-32 weeks gestation, compared with historical controls. In infants 25-28 weeks, the need for invasive mechanical ventilation at 72 hours was less (32% vs. 68%), and duration of oxygen therapy was less in the MIST group than in historical controls. They concluded that MIST is a technique worthy of further study. Both of the tracheal administration techniques require some skill in direct larnygoscopic visualization of the larynx and placement of the feeding tube or catheters.

In a recent study by Kanmaz and colleagues [70], a soft catheter trimmed to 3 cm was inserted into the trachea using a Millar 00 laryngoscope, without need for Magill forceps. They called their technique the Take-Care procedure to instill 1.25 ml/kg (100 mg/kg phosopholipid) of poractant alfa. While this is less than the recommended dose, they were quick (6 hours later) to give a second dose if the baby had significant RDS with impending respiratory failue. The Take-Care administration of surfactant (n=100) was compared with the INSURE (Intubated Surfactant and Extubate) strategy of surfactant administration (n=100). Take-Care strategy was associated with a lower rate of mechanical ventilation at 72 hours of life (30% vs. 45%, p=0.02), shorter duration of nCPAP and mechanical ventilation (p=0.006 and p=0.002, respectively), and lower rates of bronchopulmonary dysplasia. (relative risk -0.27, 95% confidence interval -0.1to -0.72). For infants ≤28 weeks, BPD was lower in patients in the Take-Care group vs. in the InSurE group (13.6% vs. 26.2%, p=0.008). This represents one of the most compelling articles demonstrating that our use of positive pressure mechanical ventilation may be more harmful than we previously recognized. It remains to be determined whether the Take-Care strategy is different from CPAP with rescue surfactant.

Finally, a nebulized or aerosolized surfactant may provide a non-invasive, atraumatic mode of delivery requiring modest technical experience. Efficacy is dependent upon aerosolization without denaturing surfactant protein and with particle size that reaches the

terminal airways. Surfactant cannot adsorb to the delivery device or upper airway and must provide a sufficient dose to the terminal airways to be effective therapy. Development of an aerosolized technology has been challenging [71-73]. Aerosolized surfactant administration to premature infants with RDS has been studied in several pilot studies: bovactant by Jorch and colleagues [74] (n=20), Colfosceril palmitate by Arroe and colleagues [75] (n=22), poractant by Berggren and colleagues [76] (n=34), and lucinactant by Finer and colleagues [77] (n=17). In these studies, surfactant has been aerosolized using various nebulizers and delivered through various CPAP devices. Aerosolized surfactant administration appears well-tolerated, but only modest, at best, respiratory improvements are reported. Per kg dosing was used in one study [74], using bovactant, resulting in a slight improvement of the alveolar-arterial O_2 gradient. The largest aerosolized dose, 480 mg of poractant alfa, resulted in no clinical improvement. There were no randomized studies comparing aerosolized vs. conventional endotracheal surfactant administration. Phase 2 studies with lucinactant (Aerosurf®) are on-going. This intriguing therapy shows some promise, but further clinical research regarding dosing, surfactant delivery, and comparison with conventional therapies needs to be conducted before it is used clinically.

Surfactant Cost-Benefit

Surfactant is clearly an effective drug for the treatment of RDS in premature infants, reducing mortality by 30% and air leak syndrome by 50% [78]. It has also been shown to reduce the overall cost of treatment for prematurity. In 1993, Soll and colleagues reported that in-hospital costs to 28 days were $3,300 less in infants receiving beractant compared to controls [79]. Thus, even with the high cost of surfactant and the paucity of Neonatal Intensive Care Unit beds, surfactant use is advocated by World Health Organization as an essential medicine in developing countries [80]. Furthermore, while early surfactant administration is more efficacious, late surfactant (administered at >2 hours) is still better than no surfactant. Which surfactant is the most cost-effective is controversial. Guardia and colleagues [81] performed a pharmacoeconomic analysis focusing on the cost of reintubation and mechanical ventilation in 1564 preterm infants who participated in published studies of lucinactant vs. beractant (SELECT Trial) or lucinactant vs. poractant alfa (STAR Trial). While extubation rates were similar between groups, the re-intubation rates were lower for infants treated with lucinactant (35% for lucinactant vs. 43% for beractant, p=0.021, SELECT Trial; 33% for lucinanctant vs. 47% for poractant alfa, STAR Trial). Since there were fewer reintubations in the lucinactant groups, and therefore fewer days of mechanical ventilation, they estimated an overall savings of about $1600 per patient treated with lucinactant compared to beractant and about $2500 per patient treated with lucinactant compared to poractant alfa, based upon the projected cost of a day of mechanical ventilation in the US from the Premiere Hospital Database dataset. There are several potential limitations of this analysis. Both the SELECT and the STAR Trials, and the pharmacoeconomic study by Guardia (2012) were sponsored by Discovery Laboratories, Inc. Warrington PA (distributors of lucinactant). The analysis only considered direct and indirect costs related to days of mechanical ventilation following reintubation. Other in-hospital costs, including the cost of surfactant, were excluded from the analysis. Furthermore, the SELECT and STAR Trials were conducted in 2001-2003 in many non-US NICU's at a time when early extubation and maintenance off the ventilator was not as high a priority as it is now. Thus, it is likely that the management strategies utilized in the analysis were substantially different than are currently practiced in the United States. The first dose of poractant alfa used in the STAR Trial was less than the recommended 200 mg/kg, and this study was terminated before reaching the prespecified endpoint. The SELECT study was primarily designed to compare lucinactant with cofosceril; beractant was used as a reference agent. As such, these comparisons fail to incorporate data showing that poractant alfa, with suggested dosing, facilitates earlier extubation when compared with beractant [45,47-49]. Thus, further studies are needed in order to demonstrate a true pharmacoeconomic comparison of lucinactant, beractant and poractant alfa.

Conclusions

Neonatology is now beginning a third decade employing exogenous surfactant to treat premature infants with RDS, with great success. The initial release of surfactant by the FDA in the United States in 1989 was associated with the largest yearly decrease in mortality for premature infants with RDS in decades. Since then, several surfactant preparations have been used in the United States and abroad. Data are clear that the synthetic surfactant preparations without surfactant proteins or protein analogs are inferior to the animal derived surfactant preparations. There is controversy regarding the relative efficacy of the various animal derived surfactants. The accumulating data suggests that there may be benefits to choosing one animal derived surfactant over another with regards to rapidity of action, volume of administration, and duration of action. Preliminary data suggested that poractant alfa may be associated with improved mortality and chronic lung disease rates in very premature infants <30-32 weeks gestational age at birth. More data are needed to make any conclusions regarding the differential effects on long-term outcome of the various animal derived surfactant preparations. The new synthetic surfactants with either SP-B analog or recombinant SP-C may have the advantage of the surfactant proteins found in animal derived surfactants, without the risk of animal derived infections or development of allergic reactions to animal proteins. Clinical comparisons of the newer synthetic surfactants with animal derived surfactants are incomplete. Lucinactant has been approved by the FDA for use in the United States and is being evaluated for its potential use as an aerosolized surfactant. Lucinatant efficacy appears at least equivalent to animal derived surfactants, although more cumbersome to administer. The area of prophylactic use of aerosolized surfactants is uncertain, but holds some promise. The development of new surfactants and surfactant administration strategies for treatment of RDS holds the promise of improving future outcomes for these very fragile patients.

Cost-benefit analysis support use of surfactant in premature infants with RDS, even in developing countries with limited medical resources. Including surfactant as an essential medicine, in spite of its cost, in developing countries may have greater health care implications than management of premature infants with RDS and may mandate regionalization of maternal-infant care. It is still unclear which surfactant and surfactant administration strategy is most efficacious, efficient, cost effective, and most applicable to global use. Global research on the use of surfactant to minimize chronic lung disease and reduce infant mortality in developing countries should be supported.

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