Abstract

In preterm infants, RDS is primarily caused by deficiency of pulmonary surfactant in an immature lung. For the past 50 years, related research and experiments with regards to surfactant replacement therapy have been encouraging and inspiring.

Numerous trials have been conducted to demonstrate that surfactant plays an important role in the management of respiratory distress syndrome in preterm babies, whether it is synthetic, natural or recombinant. The use of surfactant regarding aspects of other disease has been explored as well, including meconium aspiration syndrome, congenital pneumonia and acute respiratory distress syndrome.

With the advance of science, the molecular structure and function of most surfactant components has been well understood and well established. Pulmonary surfactant associated proteins (SPs) consist of a heterogeneous composition of lipids and proteins and it has been identified as SP-A, SP-B, SP-C, and SP-D.

Recently, US FDA approved the first synthetic peptide-containing surfactant (Lucinactant) to treat RDS in preterm newborns. Surfactant replacement therapy has been one of the greatest achievements in the management of preterm newborns in the past few decades. (J Pediatr Resp Dis 2013;9:31-39)

Key words: surfactant, respiratory distress syndrome (RDS)

INTRODUCTION

In 1959, Avery and Mead first reported on the finding that the deficiency of surface active material may be significant in the pathogenesis of hyaline membrane disease. The association of surfactant deficiency between respiratory distress syndrome (RDS), formerly known as hyaline membrane disease (HMD), was then established and better understood. In the 1960s, attempts to replace artificial surface-active materials were made, but the aerosolized saturated phosphatidylcholine were unsuccessful. The following aggressive studies and research led to the first positive-result report in 1980 of exogenous surfactant replacement therapy in preterm infants. Fujiwara et al reported eight of ten preterm infants with RDS survived after receiving artificial surfactant endotracheally. Currently, the efficacy of tracheal instillation of surfactant has been well-established for both prophylaxis and treatment of RDS in preterm newborns. This article will review and update the use of surfactant.

Structure and Function of Surfactant

With the advance of science, the molecular structure and function of most surfactant components has been understood and established. Surfactant lipids are mainly phospholipids which are essential for reducing surface tension within the lung. The most abundant surfactant phospholipid is desaturated dipalmitoylphosphatidyl-choline (DPPC), which is a phospholipid (and a lecithin) consisting of two palmitic acids and it plays an essential role in decreasing surface tension. The DPPC has both a hydrophilic region and a hydrophobic region. Pulmonary surfactant associated proteins (SPs) consist of a heterogeneous composition of lipids and proteins and it has been identified as SP-A, SP-B, SP-C, and SP-D. The hydrophobic surfactant proteins, SP-B and SP-C, compose the mobile liquid region covering the large surface area of the alveolar epithelium. They lower the alveolar surface tension and maintain minimal surface tension within the lungs in order to avoid lung collapse during respiration.
While the hydrophilic surfactant proteins, SP-A and SP-D, primarily pose as an immune mediator in lung host-defense mechanisms and presents immunologic, antibacterial, and anti-inflammatory properties,\(^7,8\) In 1999, Dr. Griese, had reviewed and recapitulate all the biophysical and immunological functions of pulmonary surfactant\(^5\) as presented in Table 1.

### New Generation of Pulmonary Surfactant Preparation

A number of pulmonary surfactant preparations are available worldwide at this time, including synthetic surfactants and natural surfactants derived from animal sources (Table 2). The first two exogenous surfactant preparations, Beractant (Survanta) and Poractant alfa (Curosurf), contain surfactant proteins B and C, but SP-A and -D are eliminated during the preparation process due to their hydrophilic characteristic. In March 2012, the US FDA approved the first synthetic peptide-containing surfactant (Lucinactant) to treat RDS in preterm newborns. Latest researches and studies of the new generation of synthetic surfactant are reviewed and summarized in Table 3.

**Beractant (Survanta):** natural and modified surfactant extracted from minced bovine lung and containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The final product, in water suspension at 25 mg of phospholipids per ml concentration contains 88 to 90% phospholipids, 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL apoproteins SP-B and SP-C. It is available in 8 mL flasks (200 mg phospholipids) containing a white to light brown liquid which should be stored between 2 and 8 degrees Celsius. The suggested dosage is 4 ml/ kg.

**Poractant alfa (Curosurf):** natural surfactant extracted from minced porcine lung. The final product in water suspension contains approximately 99% polar lipids (mainly phospholipids) and 1 % hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). Each milliliter of suspension contains 80 mg of surfactant (extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.2 mg is SP-B. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylethanolamine and sphingomyelin) and the smallest of apoproteins. It is

### Table 1. The biophysical and immunological functions of pulmonary surfactant

<table>
<thead>
<tr>
<th>Functions of surfactant</th>
<th>Biophysical functions</th>
<th>Immunological functions</th>
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<tbody>
<tr>
<td>Prevents collapse of the alveoli during expiration.</td>
<td>Prevents lung edema formation by balancing hydrostatic filtration forces.</td>
<td>Phospholipids suppress the proliferation, immunoglobulin production and cytotoxicity of lymphocytes.</td>
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<tr>
<td>Supports lungs during inspiration.</td>
<td>Stabilizes and keeps small airways patent.</td>
<td>Phospholipids inhibit cytokine (TNF, IL-1, IL-6) release from macrophages.</td>
</tr>
<tr>
<td>Prevents lung edema formation by balancing hydrostatic filtration forces.</td>
<td>Facilitates removal of particles and cellular debris from the alveoli into the large airways.</td>
<td>SP-A and SP-D modulate the phagocytosis, chemotaxis and oxidative bursts of macrophages.</td>
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<tr>
<td>Stabilizes and keeps small airways patent.</td>
<td>Transports particles &lt;6 mm into the epithelial lining fluid.</td>
<td>Neutralization of endogenous mediators like radicals and reactive oxygen species.</td>
</tr>
<tr>
<td>Facilitates removal of particles and cellular debris from the alveoli into the large airways.</td>
<td>Improves mucociliary transport.</td>
<td>Neutralization of endogenous mediators like radicals and reactive oxygen species.</td>
</tr>
<tr>
<td>Transports particles &lt;6 mm into the epithelial lining fluid.</td>
<td></td>
<td>SP-A and SP-D can also bind and capture of bacterial toxins.</td>
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available in 1.5-and 3.0-ml flasks (120 and 240 mg of phospholipids, respectively) containing a white to creamy white suspension which be stored between 2 and 8 degrees Celsius. The suggested dosage is 1.25 to 2.5 ml/kg for intratracheal use only.

**Lucinactant (Surfaxin):** synthetic pulmonary surfactant formulation consisting of phospholipids, a fatty acid, and sinapultide (KL4 peptide), a 21-amino acid hydrophobic synthetic peptide and composed of sub-units consisting of a repetitive sequence of four lysine molecules and one leucine molecule with the characteristics similar to those of SP-B and its physical structure was believed to resemble that of one of the amphipathic domains of human SP-B. Each mL of SURFAXIN provides 30 mg phospholipids (22.50 mg DPPC and 7.50 mg POPG, Na), 4.05 mg PA, and 0.862 mg sinapultide in tromethamine and sodium chloride. It is a white to off-white opaque gel-like suspension at

<table>
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<th>Table 2. Classification and composition of the exogenous surfactant</th>
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<tr>
<td><strong>Classification / Generic Name</strong></td>
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<tr>
<td>----------------------------------</td>
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<tr>
<td><strong>Synthetic or recombinant pulmonary surfactant</strong></td>
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<tr>
<td><strong>Synthetic surfactants without Protein-free</strong></td>
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<tr>
<td>Pumactant</td>
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<tr>
<td>Colfoscil palmitate</td>
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<tr>
<td><strong>Surfactants with recombinant proteins</strong></td>
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<tr>
<td>Recombinant SP-C (lusulptide)</td>
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<tr>
<td><strong>Surfactants with synthetic peptides</strong></td>
</tr>
<tr>
<td>Lucinactant (sinapultide) –KL4 **</td>
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<tr>
<td>Aerosolized form of Lucinactant</td>
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<tr>
<td><strong>Natural surfactants</strong></td>
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<tr>
<td><strong>Surfactant extracted from lung lavage</strong></td>
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<tr>
<td>Bovactant</td>
</tr>
<tr>
<td>CLSE***</td>
</tr>
<tr>
<td>Calfactant</td>
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<tr>
<td><strong>Surfactant extracted from minced animal lung</strong></td>
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<tr>
<td>Poractant alfa</td>
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<tr>
<td><strong>Supplemented and processed animal lung tissue</strong></td>
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<tr>
<td>Beractant</td>
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<td>Surfactant TA</td>
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* ALEC: artificial lung-expanding compound  
** KL-4: It is a synthetic peptide with 21 amino acids and composed of sub-units consisting of a repetitive sequence of four lysine molecules (L: 4 residuals) and one leucine molecule (K: 1 residual) with the characteristics similar to those of SP-B  
*** CLSE: calf lung surfactant extract
2° to 8°C, which becomes a free-flowing suspension upon warming for 15 minutes in a dry block heater set at 44°C.

Newer surfactants with synthetic bioengineered SP peptides may replace the natural surfactants and eliminate concerns about animal-derived products in the near future. Furthermore, the indication of exogenous surfactants replacement therapy will certainly expand to other types of neonatal respiratory disease, or even beyond the childhood. Additionally, the less invasive administering method also appears promising, such as the use of aerosolized surfactant.18-24

**Clinical Applications**

**RDS**

For the past several decades, clinical scientists and physicians have explicited and expanded the knowledge of surfactant in molecular biology and also advanced our understanding of the role that pulmonary surfactant replacement therapy may play in the treatment of diseases of neonates, children, and adults.

The lungs of preterm infants with RDS are both anatomically and biochemically immature; they neither synthesize nor secrete surfactant well. Administering exogenous surfactant to a preterm newborn with RDS could decrease the minimum pressure required to open the lung and increases the maximal lung volume. It helps to prevent lung collapse at low pressures and results in foam stability at the air–liquid interface, greatly enhancing gas diffusion. Surfactant replacement therapy of RDS, either as a rescue measure or a prophylactic
therapy, is of proven benefit. Numerous trials have shown that surfactant replacement therapy reduces mortality and several aspects of morbidity in babies with RDS. Several meta-analyses have been conducted and published which showed the promising effects on RDS. These morbidities include deficits in oxygenation, the incidence of pulmonary air leaks (pneumothorax and pulmonary interstitial emphysema) and the duration of ventilatory support use. Surfactant replacement also can increase of survival rate of very-low-birth-weight preterm infants without increasing incidence rate of bronchopulmonary dysplasia (BPD).

**MAS (Meconium Aspiration Syndrome)**

Although it is becoming less frequent, MAS is still a major cause of morbidity among term infants. Findlay et al. conducted a randomized study and reported better oxygenation, lower incidence of pneumothorax, faster control of persistent lung hypertension, and less need of extracorporeal membrane oxygenation (ECMO) in newborns that received up to four 15-mg/kg doses of surfactant administered in about 20 minutes every 6 hours. Lotze et al. conducted a multicenter study with a population of 328 term newborns (who have MAS more often than preterms) with severe respiratory failure. The pathology described was compatible with MAS in a high percentage of the patients, and no reduction in complications was observed after surfactant treatment, although the percentage of patients that needed ECMO was lower.

In a meta-analysis of 4 trials enrolling 326 treated infants, the relative risk of ECMO being required in a meta-analysis of two trials (n = 208) is reduced by up to one third (typical Relative Risk is 0.64 with 95% CI: 0.46 -0.91; NNT=6, with 95% CI: 3-25). One trial (n = 40) reported a statistically significant reduction in the length of hospital stay (mean difference - 8 days (95% CI: -14--3 days)).

**Pneumonia**

Bacterial pneumonia in preterm and term newborn infants can cause problems with the functioning of pulmonary surfactant. Pulmonary surfactant is an important part of the host defense against respiratory infections. Bacterial pneumonia in late preterm or term newborn infants often leads to surfactant deficiency or dysfunction, as surfactant is either inactivated or peroxidated.

Exogenous surfactants replacement therapy have also been shown to improve gas exchange in affected infants. Although mortality in this group of sick infants remains very high, the greatest improvement was seen in those given high dose treatments at frequent intervals. In a randomized trial in term infants with a mixture of meconium aspiration syndrome and pneumonia, treatment with Survanta significantly reduced the need for ECMO without increasing complications.

**ARDS (Acute Respiratory Distress Syndrome)**

ARDS is characterized by hypoxemia, decreased lung compliance, and pulmonary edema. ARDS results from a number of direct or indirect pulmonary insults including aspiration, trauma, near-drowning, and sepsis. Surfactant abnormalities in ARDS were first reported in 1979. Both infant respiratory distress syndrome and ARDS are characterized by a diminished amount of and defective biophysical activity of endogenous surfactant. Previously published meta-analyses of surfactant replacement therapy in ARDS patients showed no difference with regards to survival rate. The limitations of these reports are that they included the comparison of different surfactant preparations, modes of administration, and doses in patient populations with diverse protocol specific characteristics.

Taut et al. performed a pooled analysis of all five multicenter studies in which patients with ARDS due to various predisposing events were treated with rSP-C surfactant. Patients received either usual care (n= 266) or usual care plus up to four intratracheal doses (50 mg/kg) of rSP-C surfactant (n= 266). For the overall patient population, treatment with rSP-C surfactant significantly improved oxygenation (p= 0.002) but had no effect on mortality (32.6%). Therefore they suggested that rSP-C surfactant replacement therapy improved oxygenation and it was beneficial in patients with direct ARDS because more surfactant might be inactivated than in individuals with indirect ARDS. It has been demonstrated that the best strategy for the application of exogenous surfactant in ARDS patients would be the early and prolonged use of exogenous surfactant preparation.

There are only a few adverse effects related to surfactant replacement therapy including serious
transient bradycardia and hypoxemia during the administration of surfactant. There may also be possibility of acute blockage of the endotracheal tube after instillation. The risk of pulmonary hemorrhage following surfactant replacement treatment might increase, especially for extremely low birth weight neonates. Because of the rapid improvement in gas exchange after surfactant replacement therapy, the dramatic changes of lung compliance and ventilation/perfusion matching should be expected. Staff must be trained and aware of the nature and the speed of these changes, otherwise hyperventilation and overexpansion injury could also occur.

CONCLUSION

For the past 50 years, the research and experiments of regarding surfactant replacement therapy have been both encouraging and inspiring. Numerous trials have been conducted which demonstrate that surfactant plays an important role in the management of respiratory distress syndrome in preterm babies, whether it was is synthetic, natural or recombinant. The use of surfactant on the aspects of other diseases has been explored as well, including meconium aspiration syndrome, congenital pneumonia and acute respiratory distress syndrome. The further potential indications for pulmonary surfactant replacement should be extensively investigated, and so should the co-use of surfactant with other interventions, such as inhaled nitric oxide or CPAP. Future trials should concentrate on developing new synthetic surfactant that can possess all the functions and characteristics of natural surfactant at a lower cost, and also can also withstand resistance to any inactivating process with the aid of advanced genetic engineering and recombinant technology. Investigations should be encouraged focus on developing noninvasive means of deploying of surfactant, such as aerosolized form. In summary, surfactant replacement therapy has been one of the greatest achievements in the management of preterm newborns over the past few decades, and it has been established to decrease mortality in cases of very low birth weight infants without increasing any long-term morbidity.

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