Review Article
Surfactant therapy: the current practice and the future trends

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ABSTRACT

The efficacy of surfactant preparations used in the prevention and treatment of respiratory distress syndrome (RDS) is a well known fact; however, many controversies remain. The debate over which surfactant to be used, when and what is the best mode of delivery is still raging.

Currently, animal-derived surfactants are preferred and clearly recommended by various practice guidelines, but new synthetic surfactants containing peptides that mimic the action of surfactant proteins are emerging and they seem to have a comparable efficacy profile to the natural surfactants. It is hoped that with further improvements, they will outperform their natural counterparts in terms of reliability and cost-effectiveness.

Early surfactant administration was shown to further reduce the risk of RDS and its complications. However, as nasal continuous positive airway pressure (nCPAP) is becoming increasingly the preferred first-line therapy for RDS, the less invasive approaches of respiratory support along with early selective surfactant administration (e.g. INSURE) appears to provide a better option.

Although neonatal RDS is still the main indication of surfactant therapy, other pathological processes received considerable attention and major research has been dedicated to explore the role of surfactant in their management, Meconium aspiration syndrome (MAS) and congenital pneumonia are two worthy examples.

The most updated practice guidelines do recommend the use of endotracheal instillation as the preferred mode of surfactant delivery. However, aerosolization and other non-invasive methods are being investigated with some success; nonetheless, further improvements are very much in need.

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INTRODUCTION

The extensive research which led to the identification of pulmonary surfactant and its therapeutic roles is one of the greatest human triumphs against disease. The many milestones in this fascinating story are worth telling.

The beginning of this success story can be traced back to Kurt von Neergaard who was the first to suggest that surface tension plays a role in lung elasticity [1]. In the mid 1950s, Pattle and others described a thin layer of material lining the alveolar surface of the lungs, this material was capable of reducing surface tension to a low level during the respiratory cycle [2,3]. In 1959, Avery and Mead published a seminal article demonstrating that hyaline membrane disease (HMD) was due to lack of surfactant [4]. In a decade or so the first synthetic surfactant trials were conducted using a nebulized di-palmitoyl phosphatidylcholine (DPPC) preparation. These trials were largely negative; with no discernible beneficial clinical effects [5]. This led some investigators to believe that neonatal RDS is caused by pulmonary ischemia [6]. Acceptance that surfactant deficiency was responsible for RDS did not occur until 1973 when Enhorning and colleagues demonstrated that tracheal instillation of whole surfactant taken from adult animals into pre-term rabbits could restore normal lung function [7]. Few years later Adams et al. demonstrated the benefits of the natural bovine surfactant on the lungs of preterm lambs [8]. Several more years of supportive animal studies were needed before Fujiwara et al in 1980 were able to demonstrate the therapeutic value of exogenous surfactant in human infants suffering from RDS. He administered a modified bovine surfactant (Surfactant-TA) to 10 preterm infants and clearly demonstrated the acute beneficial effects of natural surfactant [9].

What is Surfactant?

Pulmonary surfactant is a complex mixture of lipids and proteins; it is synthesized by alveolar pneumocytes type II. Phospholipids comprise approximately 90% of pulmonary surfactant, of which almost 80% is phosphatidylcholine, 10% is phosphatidylglycerol, and the remainder is made of small amounts of other phospholipids and neutral lipids including cholesterol. The principal surface-active material in surfactant is di-palmatoyl phosphatidylcholine (DPPC). It represents 60% of surfactant by weight and accounts for 80% of the phospholipids [10,11].

Surfactant lipids are synthesized primarily in the endoplasmic reticulum of the alveolar pneumocytes type II cells and are transferred via the Golgi system to the lamellar bodies. Intracelulraly, the lamellar body is the storage compartment for surfactant-associated lipids and for the hydrophobic SP-B and SP-C. Lamellar bodies are secreted into the alveolar space in response to stretch, β-adrenergic, and purinergic agonists. Transport of lamellar bodies is regulated by the ABCA3 transporter molecule, which is found in the limiting membrane of these organelles. After exocytosis, lamellar bodies unravel and undergo a morphological change producing the tubular myelin that represents the major extracellular pool of surfactant lipids from which mono- and multilayered films are formed.

Surfactant is inactivated by mechanical and biological processes and converted into the surface-inactive, small aggregate which is taken up by alveolar pneumocytes type II cells, and reutilized or catabolized [12]. Alveolar macrophages internalize and degrade small surfactant aggregate under control of the signaling of granulocyte-macrophage colony-stimulating factor (GM-CSF). Indeed, deletion of the genes encoding GM-CSF or its receptor, or presence of autoantibodies that block GM-CSF activity cause an accumulation of surfactant that is characteristic of pulmonary alveolar proteinosis in mice and humans [13,14].

Surfactant-associated proteins

Surfactant protein component constitutes about 8% -10% of its bulk. Four proteins are identified and designated as surfactant protein [SP], A through D. In contrast to the hydrophilic SP-A and SP-D, the hydrophobic SP-B and SP-C directly affect the biophysical properties of surfactant lipids both in vivo and in vitro, and are critically important for surfactant function. SP-B and SP-C work cooperatively to optimize rapid absorption and spreading of phospholipids on a surface and to facilitate the development of low surface tensions on surface area compression. Surfactants prepared by organic solvent extraction of natural surfactants or from lung tissue contain SP-B and SP-C, but lack SP-A and SP-D [15]. Surfactant proteins A and D belong to a family of proteins named "collectins" because it has collagenous and lectin-binding domains. SP-A is the most abundant surfactant-associated protein and was the first to be described. SP-A has a central role in tubular myelin formation and metabolism and function of surfactant, as well as in host defense. Genetic studies show that certain SP-A polymorphisms are clearly associated with an increased severity of RDS and the subsequent development of chronic lung disease in premature infants. SP-A is not contained in surfactants used for treatment of RDS [16].

SP-B is a small, polypeptide encoded by a single gene located on chromosome 2. Extracellular SP-B plays a critical part in surfactant homeostasis by promoting adsorption of lipid molecules into the expanding surface film and enhancing their stability during the compression and expansion that occur during the respiratory cycle. It is an active component of surfactant-replacement preparations used in the treatment of RDS in preterm infants. The level of SP-B is low in preterm infants who are at risk for RDS. In contrast to SP-A, genetic disruption of SP-B expression causes an unambiguous neonatal respiratory phenotype in both human infants and mice [17].

Surfactant protein C, like SP-B, is a small hydrophobic protein. The human SP-C gene has been localized to the short arm of chromosome 8. Unlike SP-B gene mutations, which lead to respiratory distress soon after birth, SP-C deficiency usually presents at a few months of age as interstitial lung disease. Disorders in SP-C metabolism are generally inherited as autosomal-dominant genes with variable penetrance [18].

The functions of SP-D include carbohydrate-domain recognition on the surface of pathogens. In vitro experiments suggest that SP-D is involved in the first line of defense against inhaled pathogens. Unlike the case with SP-A, there are no reports of SP-D polymorphisms conferring a higher risk of RDS or neonatal bronchopulmonary dysplasia (BPD). However, certain SP-D polymorphisms have been linked to increased susceptibility to chronic obstructive pulmonary disease in some populations and childhood infection with respiratory syncytial virus [19].

Exogenous surfactants

Exogenous surfactants (Table 1) are currently classified into natural and synthetic surfactants. The natural ones are purified and extracted from either lung minces or lung lavages. Their phospholipid concentration is above 80% and all contain the proteins SP-B and SP-C, but not SP-A. However, some differences in their composition do exist, for instance the porcine-minced-lung extract surfactant undergoes an additional purification step that removes neutral lipid, whereas free fatty acids and DPPC are added to the bovine-minced-lung extract surfactant. Moreover, SP-B concentration is lower in the lung minced preparation compared with lung lavage extracts. The entirely synthetic surfactant preparations are composed mainly of DPPC and are free of surfactant-associated proteins [20].

The majority of natural surfactants presently on the market contain low levels of SP-B relative to human

Table 1 - Types of surfactant used in clinical trials

Natural	Minced lung extracts	• Surfactant TA (Surfacten) • Beractant (Survanta) • Poractant alfa (Curosurf)
	Lung lavage extracts	• CLSE (bLES) • Calfactant (Infasurf) • SF-RI1 (Alveofact)
	Amniotic fluid extract	• Human surfactant
Synthetic	Old, protein-free	• Pumactant (ALEC) • Colfosceril palmitate (Exosurf) • Turfsurf (Belfast surfactant)
	New, contains protein analogues	• lucinactant (Surfaxin)

surfactant, and the concentration of this protein can vary between lots of the same brand. Moreover, animal-derived surfactants contain foreign proteins that are potentially immunogenic.

Which surfactant to use?

Many surfactants have been tested in human newborns during the 1980s and 1990s (Table 1). The meta-analyses conducted have confirmed that both types of surfactant decrease the risk of air leaks and mortality. Synthetic surfactants, however, have shown reduction in risk of BPD, intraventricular hemorrhage (IVH), and patent ductus arteriosus (PDA). A more recent meta-analysis of studies compared natural and synthetic surfactants has shown improved outcomes if natural surfactants are used; there was fewer pneumothoraces (RR 0.63; 95% CI 0.53-0.75) and a reduction in mortality (RR 0.87; 95% CI 0.76-0.98) as well [21].

Several studies have compared natural surfactant to each other, infants treated with calf lung surfactant extract (calfactant) or porcine lavaged surfactant (poractant) have a swifter improvement in oxygenation and reduced ventilatory requirements compared with infants treated with bovine lung minced extract surfactant (beractant). This is probably due a higher concentration of phospholipids in some preparations in comparison to others [22, 23].

How much and how many?

The original dosing strategies were derived from animal studies of the 1980s. In 1993, Halliday and his colleagues reported that a higher dose (200 mg/kg) of Poractant alfa (Curosurf) when compared to a lower

dose (100 mg/kg) resulted in faster improvement of oxygenation and fewer needed second dosing but there was no difference in the primary outcome (combined increased oxygen need and death) [24]. However, in 2005 in another review he reported that the higher dose have resulted in a significant reduction in mortality (RR 0.29; 95% CI, 0.10-0.79) [25].

Soll et al, in a systematic review looking into the issue of multiple doses vs. a single dose, reported that the repeated dosing schedule showed further reduction in the risk of pneumothoraces (RR 0.51; 95% CI 0.30-0.88) with a trend toward reduction in mortality. However, there is no much additional benefit from repeating doses beyond two times [26].

Prophylaxis versus Rescue

In evaluating prophylactic versus rescue strategies, controlled studies have shown that prophylactic administration of surfactant results in a reduction in mortality (OR 0.61; 95% CI 0.48–0.77), and in the pneumothoraces (OR 0.62; 95% CI 0.42–0.89). But there was no reduction in the rate of BPD (RR 0.96; 95% CI0.82-1.12) suggesting that the process of intubation and surfactant administration may have been causing harm in some infants [27]. However, this approach of surfactant administration in the delivery room will, inevitably, result in a number of infants who will be subjected to this unnecessary and potentially harmful treatment especially in this era of widespread use of antenatal corticosteroids.

The benefits of an 'early rescue' strategy (i.e. to administer surfactant to symptomatic infants within two hours of life) have been explored by comparing the outcome of this novel approach with that of the classic rescue treatment. A meta-analyses of several trials demonstrate that early selective surfactant administration is associated with a decreased risk of neonatal mortality (OR 0.87; 95% CI 0.77–0.99), a significant reduction in the incidence of pneumothoraces (OR 0.70; 95% CI 0.59–0.82), chronic lung disease (RR 0.70; 95% CI 0.55-0.88),

and chronic lung disease or death at 36 weeks (RR 0.84; 95% CI 0.75-0.93) [28].

Going less invasive

The increased use of less invasive modes of respiratory support such as nCPAP and the wide use of antenatal corticosteroids shifted the grounds towards less use of surfactant; many trials were conducted trying to further delineate the role of surfactant. In such an environment the INSURE technique came to life [29]. Keeping in mind that an optimal distribution of surfactant can be achieved only when it is given as a bolus, the INSURE technique (INtubate — SURfactant —Extubate to nCPAP) has been evaluated extensively. In 2007 a systematic review reported that infants with RDS managed with INSURE have less mechanical ventilation (RR 0.67; 95% CI 0.57- 0.79), fewer pneumothoraces (RR 0.52; 95% CI 0.28-0.96), and less BPD (RR 0.51; 95% CI 0.26-0.99) [30].

Not just for RDS; the other indications

Meconium aspiration syndrome (MAS) results from acute deposition of a noxious material (mecomium) in previously healthy and normally developed airways. The deleterious effects of this event evolve over many hours as inhaled meconium migrates distally. Lavage therapy has been used in MAS management for several decades. Many solutions were tried and were found to have suboptimal results [31,32]. However, dilute surfactant was a more effective agent than saline or perfluorocarbon.

The non-randomized studies of dilute surfactant lavage in MAS were inconclusive, whereas the randomized controlled trial, "lessMAS" trial, reported reduced mortality or need for ECMO (10% vs. 31%) (OR 0.24; 95% CI: 0.06–0.97) and a trend to reduce mortality in centers where ECMO is not available (5.3% vs. 29%) (OR 0.14; 95% CI: 0.02–1.3) but no difference on duration of ventilation, oxygen therapy or hospital stay was noted [33]. A meta-analysis of controlled trials of dilute surfactant lavage reported a significant reduction of mortality or need for ECMO

in infants treated with surfactant lavage form 29% to 9% (RR 0.34 (95% CI 0.11-0.99) [34].

Another approach to this problem was to administer a bolus dose of surfactant with or without preceding dilute surfactant lavage. To date, two randomized controlled trials could not demonstrate any beneficial effect on reducing mortality or any major pulmonary outcomes in MAS patients [35,36].

Although surfactant-saline dilute is the most commonly used mixture in these trials, several combinations of polymers and synthetic surfactants are currently in trial [37]. Surfactant-dextran combination was shown to produce a better recovery of meconium particulate matter in the lavage compared to surfactant/saline mix and it led to improved lung compliance and oxygenation at 60 minutes of age [38].

The use of surfactant in infants with group B Streptococcus pneumoniae (GBS) has been tried in several small studies. The rationale behind its use is the expected compromise of surfactant functions by bacterial pneumonia via various mechanisms, including inactivation of surfactant and damage to the epithelial cells that synthesize it. Herting et al, reported that using surfactant in an experimental neonatal GBS pneumonia as a vehicle for specific GBS immunoglobulin resulted in a greater reduction in GBS proliferation than with using either surfactant or antibody therapy alone [39]. However, in 2000, the Collaborative European Multicenter Study Group reported that the response to surfactant in neonatal pneumonia was slower than in infants with RDS and that repeated doses were needed more often [40]. Apparently, there is insufficient evidence at present that surfactant treatment improves the long-term outcome of septic newborns with respiratory failure.

Surfactant replacement therapy has also been used to treat massive pulmonary hemorrhage, considering the inactivating role of blood presence in the alveolar space. The supporting evidence for this strategy comes mainly from observational studies as randomized controlled trials are difficult to perform due to the unpredictable nature of the problem [41,42]. Aziz and Ohlsso in a systematic review published in 2008 were unable to identify any randomized or quasi-randomized trials that evaluated the effect of surfactant in neonatal pulmonary hemorrhage. Therefore, no conclusions from such trials could be drawn [43].

In a lamb model of congenital diaphragmatic hernia (CDH), administering surfactant prophylactically resulted in an improvement of gas exchange with both a significant increase in PaO2 and a fall in PaCO2, in addition to improved lung volumes and compliance [44]. Nonetheless, no beneficial effects have been observed with rescue surfactant in this model of CDH [45]. On the other hand, there have been reports of small series of human infants with CDH who have some improvement with surfactant treatment and prophylaxis [46,47]. However, larger series have not confirmed these results [48].

Newer ways of administration

The continued refinement of neonatal intensive care is rapidly changing the place of surfactant therapy. The more widespread use of nasal CPAP (nCPAP) as the initial mode of respiratory support means many preterm infants can now avoid intubation altogether in early post-natal life. Indeed, several studies demonstrated that treatment with nCPAP from birth without administration of surfactant results in fewer ventilator days and trends towards a lower risk of BPD [49 -51]. However, many preterm infants starting on nCPAP ultimately require intubation and extra oxygen supplementation suggesting that further improvement in their outcome may be possible with early and selective surfactant treatment. In this setting, INSURE approach seems a reasonable option. The literature currently available is yielding conflicting results which should lead us to look for some other alternatives [52 -55].

Minimally invasive surfactant therapy

Surfactants generally have been administered via intratracheal instillation. Clinical experience and the results of animal studies show that rapid instillation is more effective than slow instillation and it results in a better distribution of surfactant dose. However, the difficulty in intubation and the serious side effects drove the efforts to devise new methods for surfactant administration; these methods collectively are referred to as minimally invasive surfactant therapy (MIST).

Intra-amniotic instillation of surfactant in the vicinity of the fetus's mouth and nose via an ultrasound-guided needle has been described. Two non-randomized studies evaluating this method have been published; in the first study the investigators reported success in a series of six babies with no RDS in four and only mild RDS in the other two [56]. In the second study the treated women had proportionately more babies with biochemically defined lung maturity and milder RDS [57].

Nasopharyngeal administration of surfactant has also been described in a study of 23 infants. Surfactant was given after delivery of the head but before delivery of the body. 10 of the 23 infants treated this way (43%) required intubation before 72 hours of life [58]. In another study, Trevisanuto et al reported the successful instillation of surfactant via a laryngeal mask airway (LMA) without sedation in a group of 8 preterm infants. Improvement in oxygenation was noted in all of them. The applicability of this technique seems limited, however, due to the lack of familiarity and the difficulty with placement of the device in infants lesser than 28 weeks' gestation [59].

Bolus surfactant therapy by tracheal catheterization, another method of administering surfactant while avoiding ventilation, has been developed in German neonatal units [60]. The technique involves placement of a fine intra-tracheal catheter while babies keep spontaneously breathing on nCPAP. Pilot studies reported that the procedure was tolerated well with good outcomes in comparison with historical controls [61,62]. A multicenter study comparing 319 infants with 1222 historical controls suggested a reduced need for mechanical ventilation and a lower incidence of BPD [63].

In 2011, Göpel et al [64] in a randomized controlled trial (the AMV trial) enrolled 220 infants with gestational age of 26-28 weeks, who were managed by nCPAP and oxygen supplementation (FiO2 >0.30-0.60) in the first 12 h of life, the intervention group (108 infants) requiring subsequently a less positive pressure ventilation support (28 vs. 45%). Nevertheless, no clear difference in the rate of adverse events between both groups was observed [64]. On the other hand, Kanmaz et al [65], in a recently published randomized controlled trial comparing this technique with the INSURE approach, concluded that it significantly reduces both the need and duration of mechanical ventilation (OR -0.52, 95% CI -0.94 to -0.29), and thus the rate of BPD in preterm infants (RR -0.27, 95% CI -0.1 to -0.72).

This approach was used with some modification in the 'Hobart method' utilizing a narrow bore semi-rigid vascular catheter inserted through the vocal cords under direct vision. An initial evaluation of this method was conducted in 25 preterm infants of 25–34 weeks' gestation. The procedure was well tolerated and oxygenation improved significantly after surfactant administration, suggesting adequate surfactant delivery, and treated infants showed a trend towards a reduction in need for intubation < 72 hours compared to historical controls [66]. On the basis of these encouraging findings two large-scale studies are in progress (Collaborative Paired Trials Investigating Minimally-Invasive Surfactant Therapy - OPTIMIST). The primary outcomes are death or BPD in infants < 28 weeks gestation (OPTIMIST-A) and duration of mechanical respiratory support in infants > 28 weeks gestation (OPTIMIST-B) with multiple secondary endpoints. These trials are designed to have sufficient

power to give definitive information about the place of surfactant delivery by brief tracheal catheterization in preterm infants on nCPAP [67].

Aerosolized surfactant

The recent trends favoring utilization of noninvasive respiratory support for preterm infants with surfactant deficiency have created a demand for a similarly noninvasive means of administering exogenous surfactant. Administering drugs via nebulization, if successful, could become The truly non-invasive approach of all time. Nonetheless, the past experience with nebulized surfactant therapy was disappointing and thus was abandoned for decades until recently when new technologies resurrected the hopes of an efficient surfactant delivery via nebulization; a method that facilitates effective surfactant administration while on nCPAP and avoids clinical instabilities associated with bolus fluid instillation [68].

The prospect of efficacy and cost-effectiveness along with the improved uniformity of surfactant delivered to the alveoli will, certainly, determine the future and the acceptance of this modality especially in the population of infants more than 32 weeks' gestation, due to the higher potential of significant cost reduction. However, many factors pertaining to the patient variables, the nebulizer device, and the physical characteristics of the surfactant used will ultimately determine the utility and feasibility of therapy. Among patient-related factors are those associated with prematurity (small collapsible airways, small tidal volumes, low inspiratory flows, and irregular breathing patterns). Hence, positioning of the patient to promote open airways is vital to optimize alveolar surfactant deposition.

Device considerations

Many nebulizer devices are currently available and have been trialed for surfactant aerosolization. The Ultrasonic nebulizers produce large quantities of small-diameter particles (0.8–3.1 micrometer) and achieve more efficient aerosol deposition than Jet nebulizers [69], but they are not fit for surfactant aerosolization as they cause denaturation of the proteins and loss of phospholipids [70]. Whereas Jet nebulizers are of lower cost but poorer efficiency; they generate flows and volumes that significantly exceed the breathing pattern of the preterm infants, which reduces the drug concentration and actual dose delivered to the patient (< 1% deposition of aerosolized dose) [71]. The vibrating membrane nebulizers generate low flows that reduce drug delivery time, and highly uniform particle size. They markedly increase the proportion of aerosolized drug delivered (> 14% of the dose) [72]. The recently described type of nebulizer is based on the capillary aerosol generating (CAG) technology. It can generate low flow, high output rate and customizable particle size. The device is supplied with a special airway interface that reduces aerosol dilution and dead-space [73].

Drug's considerations

The mass median aerodynamic diameter (MMAD) of particles is the major factor to be considered when decision is made for using an aerosolized drug. Particles should be < 5 micrometer to bypass the upper airway. Smaller particle sizes improve deposition and penetration of the distal air spaces [74]. However, the use of submicron particles may result in less deposition of the drug especially in spontaneously breathing very low birth weight infant due to the short inspiratory times and low inspiratory flows [75]. Nonetheless, aerosolized surfactants may behave differently even with larger droplet size and achieve better intrapulmonary deposition than liquid bolus surfactant possibly due to enhanced surface area dispersion of the aerosol after deposition [76].

Newer Synthetic surfactants, why?

Despite the fact that animal-derived surfactants are preferred for treatment and prevention of RDS, they collectively have some concerning issues; the low

levels of SP-B relative to human surfactant and the varying concentration of SP-B between lots are well known in addition to the presence of many potentially immunogenic foreign proteins in these preparations. The efforts to address these problems led to many advances in terms of developing newer surfactants. Surfactant combined with recombinant SP-C (rSP-C) is currently being developed, but has not reached clinical trials in neonates [77]. Similarly, SPA containing surfactant is another possibility. Studies on SPA knockout mice seem encouraging [78]. Lucinactant, recently receiving FDA-approval, is a new synthetic surfactant containing an SP-B analogue, Sinapultide, which replicates SP-B action. This new preparation has demonstrated a greater resistance to oxidation and protein inhibition in comparison to animal-derived surfactants. Furthermore, it seems that aerosolization does not significantly alter the physical properties of this product [79].

CONCLUSION

The efficacy of various surfactant preparations in the prevention and treatment of RDS is an established fact, however, many controversies remain. These include among others, which surfactant type to be used, as well as the mode and timing of administration. Currently, natural surfactants are the drug of choice but the new synthetic surfactants containing peptides that mimic the action of surfactant proteins may change the landscape soon, since they have demonstrated a similar, if not superior, efficacy to natural surfactant. It is hoped that they will outperform the natural ones in terms of reliability and cost-effectiveness.

Early surfactant administration seems to be more beneficial in reducing the risk of RDS and its complications. However, as nCPAP is becoming increasingly the preferred first-line therapy for RDS, the less invasive approaches of respiratory support along with early selective surfactant administration (e.g. INSURE) appears to provide a better option.

Although instilling surfactant through an endotracheal tube is currently the recommended mode of drug delivery, the noninvasive methods such as nebulized surfactant are being trialed with some success, nonetheless, further improvements in surfactant therapy are dearly needed.

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