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Surfactant Replacement Therapy: An Overview

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ABSTRACT

Pulmonary surfactant is a soap-like chemical synthesized by type II alveolar pneumocytes and is a mixture of phospholipids (predominantly dipalmitoylphosphatidylcholine), some other lipids and proteins. Its main functions include lowering the surface tension and maintaining the stability of alveoli. The first documented trial involving exogenous use of surfactants as a therapy was recorded in early 1970s using synthetically produced phospholipid mixtures once the chemical composition of surfactants was deciphered. Gradually there was a transition to the use of more natural sources. And animal derived surfactants like Surfactant TA, Beractant, Bovactant, Poractant Alfa etc. were then introduced. Recent works have highlighted the physiological importance of the surfactant-proteins and present day exogenous surfactants are mostly synthetic combinations incorporating the protein-part, either the whole surfactant proteins or peptides that act like surfactant proteins. Examples of this group include lucinactant, rSP-C surfactant, CHF 5633 etc. The commonest therapeutic indication of surfactants is in preterm infants suffering from Infant Respiratory Distress Syndrome (IRDS) or Hyaline Membrane Disease. Present guidelines recommend the use of early rescue therapy rather than prophylactic use of surfactant as it reduces acute pulmonary injury and the need for mechanical ventilation. Multiple-dose regimen has been found to be more effective than single dose surfactant therapy and minimum 100 mg/kg of surfactant is recommended. LISA is preferred method of delivering surfactant when baby is breathing spontaneously, on nasal CPAP or when intubation is not required for treatment. Exogenous surfactants form the mainstay of therapy in these infants born with deficiency of pulmonary surfactants which predisposes their lungs to collapse.

Key words: Pulmonary surfactants, Respiratory Distress Syndrome, RDS, LISA, multiple-dose regimen, rescue therapy

INTRODUCTION

The word surfactant means a surface acting agent that lowers surface tension. Pulmonary surfactant is a thin liquid film synthesized by type II pneumocytes of the alveolar lining. [1] It decreases surface tension at the gas-liquid interface of alveoli and also maintains the stability of the alveolar lattice apart from also preventing transudation of interstitial fluid into the alveoli. [2,3] Pulmonary surfactant is a mixture of 90% lipids (Dipalmitoylphos-phatidylcholine -DPPC 62%, Phosphatidylglycerol, other phospholipids, neutral lipids), 8% Protein (Albumin, IgA and Surfactant protein A,B,C & D) and 2% Carbohydrates. [1,4] Once the chemical composition of surfactants was discovered, initial trials began in early 1970s with a mixture of chemically synthesized mixture of phospholipids. The use of surfactant as a therapeutic agent gained momentum during the 1970 and 80s. [5] Later on, there was a gradual transition to more natural sources like different type of animal-derived lung extracts which also had the proteins. These protein-containing combinations were demonstrated to be more effective in studies on immature rabbit models. Subsequently it was tried in immature lamb models eventually paving the way for their use in

preterm infants who are born with a deficiency of pulmonary surfactants. [6,7] Today it is known that, exogenous surfactant therapy increases the pool size rapidly and improves pulmonary gas exchange until endogenous surfactant is released [8] and surfactant replacement therapy is a well-established treatment strategy in respiratory distress of newborn infants. It reduces both neonatal mortality and pulmonary air leaks by about 50%. [5] Even with its obvious benefits, surfactant therapy still remains a point of debate regarding aspects like which surfactant is to be used, when to be administered, what is the ideal dosing regimen and what is the best mode of delivery, etc. Yet another contentious issue is the possibility of potential antigenic reactions to animal-derived extracts. This article is intended to provide a holistic overview of the existing knowledge about the different aspects of surfactant replacement therapy.

Types of Exogenous Surfactants:

Exogenous surfactants are classified as natural (purified and extracted from either lung minces or lung lavages) or synthetic as shown in Table 1.

Table 1: Classification of surfactants [8-10]

Type	Source	Prepared from	Name of Surfactant
Natural	Animal	Minced Lung Extracts	Surfactant TA (Surfacten)
			Beractant (Survanta)
			Poractantalfa (Curosurf)
		Lung lavage extracts	CLSE (bLES)
			Calfactant (Infasurf)
			SF-RI1 (Alveofact)
	Human	Amniotic Fluid extracts	Human surfactant
Synthetic	First generation	Synthetic protein free	Pumactant (ALEC)
			Colfoscerilpalmitate (Exosurf)
			Turfsurf (Belfast surfactant)
	Second generation	SP-B analogues (Sinapultide)	lucinactant (Surfaxin)
		SP-C analogues (Lusupultide)	rSP-C surfactant(Venticute)
	Third generation	SP-B &SP-C enriched	CHF 5633

What to use: Natural or Synthetic Surfactants?

Synthetic surfactants are theoretically less immunogenic than animal derived surfactants as they lack foreign proteins. But, a lot of randomized controlled trials conducted recently have found that infants with established RDS who receive animal derived surfactant extracts as treatment have a decreased risk of pneumothorax, pulmonary interstitial emphysema, bronchopulmonary dysplasia and had an overall a reduced risk of mortality as compared to protein-free synthetic surfactants, clearly emphasizing the beneficial effect of surfactant proteins outweighing the antigenicity plausibility. [11] Hence, natural surfactants are now recommended for use. [12-14] In a meta-analysis of the Cochrane database, protein-containing new generation synthetic surfactants were compared to animal derived surfactant extracts. Animal derived surfactant preparations did not seem to have a markedly different effect than the synthetic surfactants in terms of mortality and chronic lung disease but demonstrated a trend towards decreasing rates of bowel disease. [15] Further studies need to be done to demonstrate a clearly perceptible benefit prior to routine recommendation of synthetic surfactants.

Composition & Dosage of Exogenous Surfactants:

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. [16] The entirely synthetically processed surfactant preparations are composed mainly of DPPC and are free of surfactant-associated proteins. Some differences in their composition do exist among animal-derived surfactants. [17] Term neonates usually have a surfactant storage pool of approximately

100 mg/kg, whereas preterm neonates have an estimated pool of only 4–5 mg/kg at birth. So a minimum of 100 mg/kg of surfactant should be administered to preterm neonates with RDS. [8] Composition and dosage schedule of various commonly available surfactants are summarized below. (Table 2).

Table 2: Composition and recommended dosage of various surfactants [5,8,10,13,18-20]

Generic Name	Trade Name	Source	Major Phospholipids	Proteins	Dose	Company
Animal Derived						
Beractant	Survanta	Bovine	DPPC and PG	<0.1% SP-B and 1% SP-C	100 mg/kg/dose (4 mL/kg)	Abbott Laboratories
Beractant	Neosurf	Bovine	DPPC and PG	<0.1% SP-B and 1% SP-C	135mg/kg/dose (5ml/kg)	Cipla
Poractant alfa	Curosurf	Porcine	DPPC and PG	0.6% SP-B and 1% SP-C	100–200 mg/kg/dose (1.25–2.5 mL/kg)	ChiesiFarmaceutici
Calfactant	Infasurf	Bovine	DPPC and PG	0.7% SP-B and 1% SP-C	105 mg/kg/dose (3 mL/kg)	Ony
Bovactant	Alveofact	Bovine	-	-	50 mg/kg/dose (1.2 mL/kg)	Lyomark
Synthetic						
Colfosceril	Exosurf	Synthetic	DPPC (100%)	none	67.5 mg/kg /dose (5 mL/kg)	GlaxoWellcome
Lucinactant	Surfaxin	Synthetic	DPPC and POPG	KL4 peptide as SP-B	175 mg/kg/dose (5.8 mL/kg)	Discovery laboratories

Ideal dosage schedule: Single vs Multiple Dose?

Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements 30% or more within the first 72 h of life should be administered repeated doses of surfactant and it may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose. [12] UK guidelines also support that second and sometimes a third dose of surfactant can be considered in ongoing RDS. [14] Clinical trials have also been conducted for a comparative evaluation of multiple-dose regimen vis-à-vis single-dose regimen. The former has been found to be effective in improving oxygenation and ventilatory requirements in both groups of infants: those at high risk of respiratory distress and those with established respiratory distress and was also not associated with significant complications. So, the multiple-doses strategy was concluded to be the most effective treatment policy. [21]

Indications of Surfactant Therapy:

1. Prophylactic Therapy: [8,12,18,22]

A prophylactic or preventive surfactant strategy is defined as surfactant administration to infants at high risk of developing RDS for the primary purpose of preventing the development of RDS. It is indicated in :

- Babies who require intubation for stabilization.
- Premature infants at high risk of developing RDS secondary to surfactant deficiency (eg<32 weeks or low birth weight <1,300 g)
- Infants in whom there is laboratory evidence of surfactant deficiency such as lecithin/sphingomyelin ratio <2:1, bubble stability test indicating lung immaturity or the absence of phosphatidylglycerol.
- Infants delivered <28 weeks where mother received no/incomplete antenatal steroids.

2. Rescue Therapy: [12, 18, 23-25]

A rescue or therapeutic surfactant administration is one in which surfactant is given to preterm infants with established RDS. It can be of two types depending on the time of administration.

Early Rescue: Surfactant is administered in preterm neonates with RDS within 2 hours of birth.

Late rescue: Surfactant is administered after 2 hours. It is done usually in out-born

neonates who are transported late to referral centers.

- Intubated infant with RDS should receive exogenous surfactant therapy
- Infants treated with non-invasive ventilation with one the following circumstances:

a) FiO_2>0.5 to maintain SpO_2>88% or a PaO_2>45 mmHg
b) $PaCO_2$>55 mmHg to 60 mmHg with a pH <7.25
c) Apnea requiring bag and mask ventilation
d) >6 apneas/6 h
e) Evidence of significant work of breathing (retractions, grunting and chest wall distortion in infants presenting with increases in oxygen needs)

- Babies with a clinical diagnosis of RDS on CPAP (Continuous Positive Airway Pressure), FiO2 > 0.30 in the first hours after birth (predictor of subsequent CPAP failure).
- Intubated infant with meconium aspiration syndrome requiring more than 50% O_2
- Intubated newborn infants with pulmonary hemorrhage with clinical deterioration
- Sick newborn infants with pneumonia and an oxygenation index [FiO_2 x MAP (mean airway pressure)x100/PaO_2] greater than 15.
- Lung ultrasound having an appearance specific of RDS.

In developed countries which have an overall better infrastructure for critical neonatal care in terms of facilities and coverage, there are clear guidelines and protocols for Surfactant Replacement Therapy (SRT). Developing nations are trying to scale up neonatal intervention strategies and are also widely using SRT, but they lack clear cut guidelines for administration. A clinical scoring system for this purpose known as "Clinical Respiratory Distress (RD)" score was introduced. This could be utilized for early decision making in treating preterm infants with respiratory distress between 26and 34weeks. [26]

Rescue Therapy or Prophylactic Therapy?

Recent analysis of the Cochrane database revealed that stabilization using surfactant therapy was more effective among those infants who developed breathing problems as compared to those who were at risk of developing RDS and given surfactants as prophylaxis. It concluded that using surfactants in infants with established RDS could yield better results against a more aggressive approach by prophylactic use. [22] Some studies have also reported that prophylactic use of surfactant in babies may further increase the risk of lung injury or death. [22] Hence, CPAP with early rescue surfactant is considered as the optimal management for babies with RDS rather than prophylaxis. [13-14] European guidelines also recommend that outcomes are best if surfactant is reserved for infants showing clinical signs of RDS. [13]

Early rescue or Delayed rescue?

Naidu JT concluded that early surfactant administration within 2 hours of life as compared to late administration significantly reduced the need mechanical ventilation and mortality among preterm infants with respiratory distress syndrome. [27] Studies analyzed in a Cochrane review also revealed that strategy of early surfactant administration with extubation to nasal CPAP was associated with significant reductions in the need for mechanical ventilation, fewer air leak syndromes (such as pneumothorax) and lower incidence of bronchopulmonary dysplasia as compared to a strategy of later selective surfactant administration and continued mechanical ventilation in infants with RDS. [28] Similar conclusion was also arrived by another study. [29]

Methods of Surfactant Delivery:

Several techniques have been described and used in clinical trials (Table 3) for administering surfactants.

Table 3: Methods and techniques of surfactant administration [8-10,30-32]

Type	Methods	Device used	Instruments
LISA (Less Invasive Surfactant Administration)	Cologne	Flexible suction catheter	Laryngoscope & Magill forceps
	SONSURE	Flexible nasogastric tube	Laryngoscope& Magill forceps
	Take Care	Flexible nasogastric tube	Laryngoscope No forceps
MISA (Minimally invasive surfactant administration)	Hobart	Semi-rigid vascular catheter Device name: for example, Lisacath	Laryngoscope No forceps
	QuickSF	Soft catheter Device name: Neofact	Laryngoscope&intra-pharyngeal guidance device
	Laryngeal Mask	Special device placed in hypopharynx	No Laryngoscope No forceps
Invasive	INSURE	Endotracheal tube	Laryngoscope No forceps
Non-invasive	Aerosol Nebulization	Nebuliser with mask/prongues	NoLaryngoscope No forceps
Intra-partum	Pharyngeal Surfactant	Injection into the pharynx Flexible short tube and syringe	No Laryngoscope No forceps
	Intra-amniotic Surfactant instillation	in vicinity of the fetus's mouth and nose via an ultrasound-guided needle	No Laryngoscope No forceps

Which is the appropriate method?

Choosing the appropriate method for administration still remains a point of continuing contention in the medical community.

1. "INSURE" is a method comprising of intubation, surfactant administration, brief period of ventilation (usually < 1 hour) and rapid extubation to nasal CPAP.
2. Less Invasive Surfactant Administration (LISA) is a modern and different approach which allows surfactant administration through a feeding tube or 4-5 Fr suction catheter inserted into trachea without intubation. LISA also does not obstruct larynx as occurs with a larger diameter endo-tracheal tube while intubation. [30] Further during LISA, CPAP is used to promote alveolar recruitment that helps in the distribution of surfactant. LISA also avoids long time positive pressure ventilation that is given after intubation and thus prevents acute lung injury. A systematic review and meta-analysis also opined that LISA is more effective than intubation for surfactant delivery in preterm infants with respiratory distress syndrome. [33] Another trial comparing LISA with the INSURE approach, concluded that LISA significantly reduces both the need and duration of mechanical ventilation and thus the rate of BPD in preterm infants. [34] But on the contrary, LISA can only be practiced infants who are breathing spontaneously or in CPAP, but don't need intubation.
3. Minimally invasive surfactant therapy (MIST)is a technique where surfactant is delivered using a slightly stiff catheter like angiocath 16 G without using Magill forceps for surfactant administration. [8] Its efficacy was assessed in a study with preterm infants of 25–34 weeks gestation and it showed a trend towards a reduction in need for intubation < 72 hours. [35] Two other large scale studies are on progress regarding MIST. [36]
4. The scope of Laryngeal Mask Airway (LMA) seems limited with high frequency of surfactant reflux and coughing, difficulty in placing the Laryngeal Mask Airway (LMA) device in infants lesser than 28 weeks gestation. [37]
5. Nebulization has its own demerits like denaturation of the proteins and loss of surfactant in upper airway/esophagus before it actually reaches the lungs, inactivation of surfactant and non-homogenous distribution. [38] So, these issues clearly indicate that it is not an appropriate method of delivery as the

surfactant might not reach its intended site of action.

CONCLUSION

The importance of exogenous surfactants in restoring normal ventilatory mechanics of the lungs and the subsequent reduction in neonatal mortality has been acknowledged beyond doubt. With the advent of newer and less invasive techniques of administration, the use of surfactant replacement therapy is increasing in the low and middle income countries. However, in the absence of state-of-the-art critical care infrastructure in most regions and ambiguity over protocols and guidelines, decision-making is still a tough call for the treating doctor. As various scientific and technical aspects of surfactant replacement therapy continue to be explored, from the existing body of medical literature a broad consensus appears on the following points.

I. Use of natural surfactants over synthetic surfactants
II. A minimum of 100 mg/kg of surfactant to be administered to preterm neonates with RDS and multiple doses better than using a single dose.
III. Early rescue therapy is recommended rather than prophylactic use of surfactant as early treatment reduces the acute pulmonary injury and also the need of mechanical ventilation. Early selective treatment also reduces burden of overuse of surfactant prophylaxis.
IV. LISA is the preferred method of delivering surfactant when baby is breathing spontaneously, on nasal CPAP or when intubation is not required for treatment.

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