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Editorial Review

Surfactant Replacement Therapy In Respiratory Distress Syndrome

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BACKGROUND

For years, one of the most significant causes of morbidity and mortality associated with premature delivery was the so-called idiopathic respiratory distress syndrome[1]. As surfactant deficiency became known to be the main cause of this lung disease, B.G. Avery put forward the idea of surfactant replacement but it was not until 1980 that the first successful surfactant replacement therapy in humans was reported by Fujiwara and colleagues. When surfactant became available it was of animal origin initially, bovine and porcine. Since then synthetic and semi-synthetic surfactant have also become available. Traditionally, surfactant has been used for treatment of respiratory distress syndrome but now it is also being tested for therapy of other lung diseases.

LUNG DEVELOPMENT

As respiratory distress syndrome is a developmental disorder rather than a disease process per-se, which is usually associated with premature birth, an appreciation of lung development is basic to understanding the pathophysiology of respiratory distress syndrome.

The lungs develop from an out-pouching of the embryonic gut at 24 days of gestation. By 12 week, the trachea, bronchi, lobes, pulmonary artery and pleura are present but at this time, there are no air spaces and the lung appears "glandular". The airways become cannulized, the terminal respiratory air spaces develop and by 26-28 weeks of gestation, the alveoli appear and the capillary network has proliferated. The number of alveoli continues to increase until early childhood, resulting in an 11-fold increase in the air tissue interface. The lining of the alveolus consists of 90% type 1 cells and 10% types II cells[2]. After 20 weeks of gestation, the type II cells contain vacuolated, osmophilic, lamellar inclusion bodies, which are packages of surface-active material.

The timing of surfactant (lecithin) production in quantities sufficient to prevent atelectasis depends on an increase in fetal cortisol levels that begins between 32-34 weeks of gestation. Between 34-36 weeks, sufficient surface active material is produced by type II cells in the lungs, is secreted into the alveolar lumen, and is excreted into the amniotic fluid. Thus the concentration of lecithin in amniotic fluid indicates fetal lung maturity.

PHYSIOLOGY OF SURFACTANT

The lipoprotein surfactant is 90% lipid and is composed predominantly of saturated phosphatidyl-choline but also phoshatjdylglycerol, other phosholipids and neutral lipids. (Table 1). The surfactant proteins are packaged into lamellar body and contribute to surface-active properties and recycling of surfactant[3].

Table 1: Composition of Pulmonary Surfactant (% by wt)

Phospholipids			**85%**
	PC	80%	
	PG	7%	
	PI + PS	5%	
	PE	4%	
	Sph	2%	
	Other	2%	
		100%	
Neutral lipids			**7%**
	(Cholesterol, FFA)		
Surfactant associated protein			**8%**
	SP-A, SP-B, SP-C	100%	

PC, Phosphatidylcholine; PG, Phosphatidylglycerol; PI, Phosphatidyl-linositol; PS, Phosphatidyl serine; PE, Phosphatidyl ethanolamine; Sph, Sphingomyelin; SP-A, B & C - Surfactant proteins A, B, C

Synthesis, transport, secretion & uptake

Surfactant phospholipids are synthesised in the

endoplasmic reticulum. The glucose/glycerol precursor may be derived from lung glycogen or circulatory glucose. Once synthesized it is transported through the golgi apparatus to multivesicular bodies, and ultimately packaged in lamellar bodies before secretion. After exocytosis of the lamellar bodies surfactant phospholipids are organised into a complex lattice called tubular myelin phospholipid that provides material for a monolayer at the air-fluid interface in the alveolus.

Surfactant phospholipids and proteins are taken up by type II cells, probably transported by endosomal multivesicular bodies, and then catabolized or transported to lamellar bodies for recycling (Fig. 1).

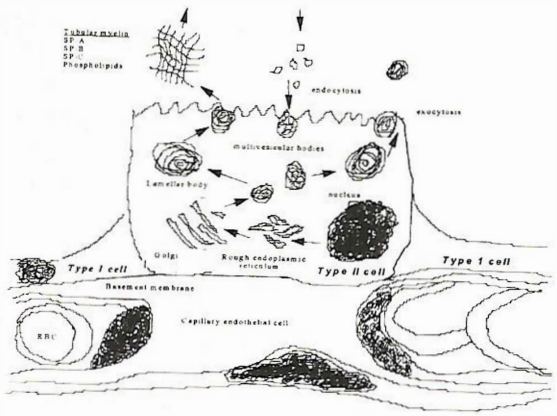


Fig. 1: Surfactant synthesis, transport & secretion[4].

Surfactant proteins are synthesized in polyribosomes and extensively modified in the endoplasmic reticulum, golgi apparatus and multivesicular bodies. Surfactant proteins are detected within lamellar bodies or in secretory vesicles closely associated with lamellar bodies, before secretion into the alveolus. Reuptake by endocytosis forms multivesicular bodies (MVB) which recycle surfactant. The enzymes, receptors, transporters and surfactant proteins are controlled by regulatory processes at the transcriptional level in the nucleus (N). Corticosteriods and thyroid hormones are regulatory ligands that may accelerate surfactant synthesis.

Various tests can be performed to assess the fetal lung maturity, the most commonly used is the L:S ratio. If the L/S ratio is < 1.5, the incidence of RDS may be upto 70% but if it is between 1.5 - 2.0 the incidence may be reduced to 40% while an L/S ratio > 2.1 indicates that RDS is unlikely. The presence of minor phospholipids such as phosphatidylglycerol also is indicative of fetal lung maturity and may be useful in situations in which the L/S ratio is borderline or possibly affected by maternal diabetes which reduces lung maturity. Alternatively "shake test" may be performed on the amniotic fluid or on the gastric aspirate obtained within the first hour of life[5]. Generation of stable foam in a test tube, 15 minutes after shaking at 1:2 dilution with ethanol indicates adequate pulmonary surfactant activity.

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome is caused by surfactant deficiency and affects mainly preterm infants.

Incidence

Respiratory distress syndrome can effect all the preterm infants to varying degree and severity but the incidence and severity generally increases with decreasing gestational age at birth and is usually worse in male infants. Although the incidence is 1% of all births yet it is important as it is responsible for 25% of deaths in this age group each year.

Apart from pre-maturity certain other factors are known to affect the incidence of respiratory distress syndrome (Table 2).

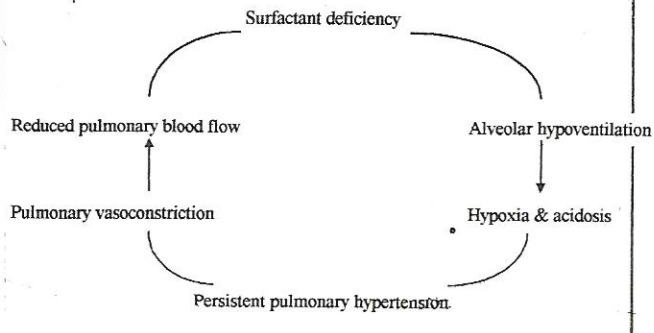
Pathogenesis of RDS

Quantitative & qualitative abnormalities of pulmonary surfactant contributes to the pathogenesis of lung disease in the newborn infant6. In premature infants, deficiency of surfactant production and secretion decreases intracellular and extra-cellular pools of surfactant, leading to alveolar surfactant insufficiency and atelactasis. Qualitative abnormalities of surfactant are also associated with many types of lung injuries. Alveolar capillary leak, haemorrhage, pulmonary oedema and alveolar cell injury fill the alveolus with proteinaceous material that inactivates surfactant. Serum and non-serum proteins, including albumin, fibrinogen, haemoglobin and meconium are potent inactivators of pulmonary surfactant in vivo and vitro[7].

Table 2: Factors affecting the incidence of RDS

Increased
* perinatal asphyxia
* maternal diabetes
* caesarean section without labour
* second twin
* after a previous infant had respiratory distress syndrome
* antepartum haemorrhage
* erythroblastosis
* male infants

Reduced
* stressful pregnancy (PIH, hypertension, infection)
* maternal drug addiction
* intra-uterine growth retardation
* maternal steroid therapy
* girls.



(R--- L shunt: through foramen ovale and ductus arteriosus)

Fig. 2: The pathogenesis of RDS

The deficiency or dysfunction of surfactant leads to alveolar collapse, reduced lung volume, decreased lung compliance and ventilation perfusion abnormalities. Right to left shunting of up to 70% or more occurs through collapsed lung (intrapulmonary) or across the ductus arteriosus and foramen ovale (extra-pulmonary) if pulmonary hypertension is severe. Persistent hypoxaemia causes metabolic acidosis and respiratory acidosis will also be present because of alveolar hypoventilation. This further reduces surfactant production and affects pulmonary vascular resistance, myocardial contractility, cardiac output and arterial blood pressure. The perfusion of the kidneys, gastrointestinal tract, muscles and skin is reduced leading to oedema and electrolyte disorders (Fig. 2).

Histology

Microscopic examination shows generalised collapse of alveoli with eosinophilic hyaline membrane formation in infants surviving more than a few hours. (hyaline membrane is also found in pneumonia and cardiac failure). The membranes begin to break up by the third day and are removed by macrophages. Sometimes there is frank pulmonary haemorrhage and interstitial emphysema. The muscle layer of the walls of the pulmonary arterioles are thickened and pulmonary lymphatics are dilated8.

CLINICAL EVALUATION

The disease has a wide spectrum of severity from mild respiratory distress lasting 2 or 3 days to a rapidly fatal illness causing death within a few hours. The onset is usually within the first 4 hours of birth with cyanosis in room air, tachypnoea, tachycardia, expiratory grunting, reduced air entry, sternal and intercostal recessions as the early clinical signs[9]. Hypotonia, oedema, ileus, decreased urine output and delay in passing meconium are the other non-respiratory clinical signs which may be present depending upon the severity of respiratory distress syndrome.

Although the development of respiratory distress in the first 12 hours in a preterm infant should alert the neonatologist to the possibility of surfactant deficiency, other pulmonary and non-pulmonary disorders presenting in the same way should also be kept in mind. History of pregnancy, labour and delivery are sometimes helpful to distinguish these disorders but often a chest radiograph is needed to make a definite diagnosis (Table 3).

The initial radiographic signs are a diffuse reticulogranular pattern of mottling of the lung fields and an air bronchogram appearance due to air in the major bronchi being highlighted against the white opacified lung. With increasing severity the

granular areas increase and become confluent so that the lung has a homogenous ground glass appearance and the heart borders are obscured.

Table 3: Differential diagnosis of RDS

* Congenital pneumonia
* Aspiration pneumonia
* Meconium aspiration syndrome
* Air leak------pnemothorax, pulmonary interstitial emphysema and pnemo-mediastinum.
* Transient tachpnoea of newborn
* Lobar emphysema.
* Pulmonary hypoplasia
* Diaphragmatic hernia
* Heart failure
* Persistent pulmonary hypertension
* Asphyxia and raised intracranial pressure
* Metabolic acidosis
* Congenital neuromuscular disorder
* Anaemia and hypovolaemia.

Serial analysis of pH and arterial blood gases are also essential for clinical evaluation.

MANAGEMENT

Since RDS affects mainly the preterm infants and as with any other problem the main effort should be directed towards prevention of prematurity by providing good antenatal care, improving the maternal nutritional status and controlling chronic illnesses. But sometimes it is not possible to prevent premature delivery and in those circumstances certain medications can be used to accelerate surfactant production. Antenatal glucocorticoid administration reduces the incidence and severity of RDS provided 48 hours of treatment is possible. It also results in fewer deaths, less intracranial haemorrhage and necrotising enterocolitis[10]. Combination treatment with glucocorticoids and thyroid releasing hormone may further reduce RDS by 50%[11].

RDS may also be prevented or atleast ameliorated if care is taken to prevent hypoxaemia, acidosis and hypothermia in preterm babies. Good resuscitation at birth with early expansion of the alveoli or terminal airways in the preterm baby is very important and for babies < 30 weeks gestation endotracheal intubation may lead to improved outcome[12]. In addition, great care should be taken to prevent or correct hypoglycaemia and fluid and electrolyte imbalance.

The specific treatment of RDS includes maintenance of normoxaemia with oxygen, CPAP[13], IPPV and surfactant replacement therapy.

SURFACTANT REPLACEMENT THERAPY

The availability of surfactant treatment has dramatically changed the care of infants with respiratory distress syndrome. All surfactant preparations are intended to replace the missing or inactivated natural surfactant of the infant[14]. Surface tension reduction and stabilisation of alveolar air-water interface is the basic function of surfactant compounds. Air-water interface stability imparts lower alveolar surface tension and prevents atelectasis or alternating areas of atelectasis and emphysema[15]. Surfactant replacement also contributes to the pool size of surfactant phospholipids, providing substrate for surfactant synthesis by means of recycling pathways[16].

Of the various surfactant preparations (Table 3), only two are available in Pakistan (Table 4).

Table 3: Surfactant preparations.

Preparation	Composition
Survanta (Abbot)	Cow lung wash with added DPPC, palmitic acid and triglyceride.
Exosurf (Welcome)	Synthetic: 85% DPPC + tyloxapol and hexadecanol.
Alec	Synthetic: 70% DPPC + 30% PG.
Curosurf[17]	Pig lung wash

INDICATIONS

Traditionally surfactant has been used as rescue therapy for established respiratory distress syndrome[18] but it is thought that prophylactic administration of surfactant in preterm babies[19,20] (< 30 weeks gestation), given within few moments of birth may be more beneficial and should be used provided there are no financial restraints. Surfactant therapy is also being tested for treatment of other lung conditions[21] and encouraging preliminary reports have been noted in cases of meconium

aspiration syndrome, pneumonia, persistent pulmonary hypertension, pulmonary haemorrhage[22], chronic lung disease[23] and adult respiratory distress syndrome (ARDS), but no protocols for treatment are available at the present time.

Table 4: Available preparations in Pakistan

	Exosurf	Survanta
Preparation:	Synthetic	Bovine (minced cow's lungs)
Composition:	Mixture of phospholipids No apoproteins	Phospholipids Apoproteins B & C not A
Vial:	8mls	8mls
Dose:	5mls/kg	4mls/kg
Instillation:	slow over 30 min manually or requiring use of syringe pump	rapid push via nasogastric feeding tube cut to the correct length of ETT
Onset of action:	delayed	Quick
No of doses	2 - 4	2 - 4
Cost/Vial	Rs. 23,500	Rs. 26,500

PROCEDURE

Surfactant replacement therapy carries with it possible risks as well as potential for benefit. It requires careful monitoring clinically by experienced doctors and nursing staff. There should be continuous SaO_2 monitoring and facilities for rapid, regular and accurate blood gas estimation to detect any complications of its use.

After establishing the diagnosis of respiratory distress syndrome, the infant's cardiovascular status is stabilised by giving plasma expander if needed since surfactant administration may be associated with hypotension and this is more likely if the infant is hypovolaemic[24]. ETT suction is performed if required and the infant is allowed to stabilise following suction. As the surfactant is refrigerated, it requires to be allowed to come to room temperature before instillation. Next the dose required by the baby is calculated and drawn in the syringe. The baby is placed in supine position (there is no need to change the positions of the baby while instilling the surfactant).

Exosurf is administered slowly over 30 minutes via the side port of the endotracheal tube adapter without interrupting mechanical ventilation while Survanta is administered rapidly through a catheter inserted into the endotracheal tube while the infant is disconnected from mechanical ventilation. The infant's colour and heart rate should be observed carefully during the procedure. If the infant deteriorates during the procedure, stop immediately and allow the infant to stabilise before continuing again. The blood pressure should be recorded continuously through the arterial line or every 5-10 minutes for the first half an hour after instillation, every ½ an hour for the next 1-2 hours and hourly thereafter if stable. If the blood pressure falls, volume expansion with a colloid 10-20 ml/kg over 10-15 minutes should be given, followed by dopamine if the blood pressure does not respond to the colloid.

ETT suction should not be performed for four hours after instillation.

If there is marked rapid improvement in chest expansion, the PIP may have to be reduced to prevent pneumothorax[25]. If the SaO_2 is over 97%, the FiO2 should be slowly reduced by 2-3% every 5-10 minutes until the SaO_2 stabilises around 95-97%. Hypoxia and hyperoxia must be carefully watched for and prevented[26]. Arterial blood gas estimation should be performed around ½ to 1 hour after administration of the surfactant and the IPPV should be adjusted according to the arterial blood gas result. Thereafter arterial blood gas estimation should be carried out after every 2-4 hours and the ventilation adjusted accordingly[27].

The 2nd dose is repeated after 6-12 hours.

SIDE EFFECTS

In occasional infants the endotracheal tube may get blocked or displaced during the procedure. Air leak (pneumothorax) may occur following bolus administration of surfactant. Rapid changes in tidal volume require immediate reduction of PIP. Failure to do so may lead to air leaks. Secondary pulmonary infections can also occur[28]. There is a

small risk for pulmonary haemorrhage, the incidence of which increases the more immature the infant.

There is a theoretical risk of development of antibodies to the surfactant especially the animal derived surfactants. In practice, however there are no reported instances of development of antibodies to surfactant following administration of exogenous surfactant.

EFFICACY OF SURFACTANT TREATMENT

Early effects include a reduction FiO2 need and improved PaO_2 and $PaCO_2$. Likewise, improved tidal volume and compliance should be noted with improved lung function and decreased ventilator PIP[29].

Long term effects include a decreased necessity for mechanical ventilation and less severe chronic lung disease of infancy[30]. There is decrease in mortality of 30-50%[31]. There is also some reduction in the incidence of air leaks, periventricular haemorrhage and broncho-pulmonary dysplasia[32,33]. Complications of PDA, NEC and ROP have not been significantly influenced by surfactant therapy to date[34].

With advancement of medical science and neonatology more and more of preterm infants are being saved therefore the incidence of respiratory distress syndrome is increasing and surfactant replacement has now become standard for prevention and treatment of respiratory distress syndrome.

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