**REVIEW ARTICLE**

**Surfactant replacement therapy**

Milton Harumi Miyoshi*

**Abstract**

**Objective:** to analyze and update information about surfactant therapy replacement in newborns with lung diseases.

**Sources:** literature review, including textbooks, meta-analyses, prospective, randomized controlled trials, retrospective assessments and case studies. Literature was reviewed based on the author’s clinical and scientific experience regarding surfactant replacement therapy in neonatal lung diseases.

**Summary of the findings:** surfactant replacement therapy for the neonatal respiratory distress syndrome improves respiratory function, and reduces the need for oxygen supplementation and pressure support ventilation, in addition to minimizing the air leak syndrome. However, the use of surfactant did not prevent the occurrence of other intercurrent diseases such as patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia. The surfactant treatment decreased neonatal mortality up to 40%. The effectiveness of exogenous surfactant on other respiratory diseases with surface film dysfunction, such as meconium aspiration syndrome, pneumonia, acute respiratory distress syndrome and congenital diaphragmatic hernia has not yet been widely accepted.

**Conclusions:** surfactant replacement is now considered the standard treatment for newborns with respiratory distress syndrome. We hope that, in the future, new synthetic surfactant preparations will be more effective in treating other infant respiratory diseases.


**Introduction**

The first attempts of replacing exogenous surfactant in human neonates were made in the 1960s, following the report that deficiency of surface-active substance would be the main factor in the pathogeny of Respiratory Distress Syndrome (RDS) or hyaline membrane disease. The referred studies used aerosolized saturated phosphatidylcoline and were not able to demonstrate positive effects in patient outcome. After the unsuccessful results of these early experiments, other research studies were aimed at better understanding the various aspects of endogenous surfactant metabolism and of establishing experimental models of deficiency of surface-active substance. These studies were carried out with the objective of allowing for the inclusion, in routine clinical practice, of surfactant replacement therapy in newborn babies with RDS. In 1980, Fujiwara et al. were the first to report positive results with the use of exogenous surfactant in humans. Based on that study, a series of non-controlled studies, using various
types of preparations, indicated an improvement in pulmonary function with the replacement of the surface-active substance in RDS neonates. These results, together with those of research using animal models, presented promising positive results that helped convincing researchers on the reasons for, and efficacy of, using exogenous surfactant in newborns with RDS. However, the conclusive demonstration that surfactant therapy would be safe and could be used to change the course of the disease was only possible thanks to multicenter, prospective, randomized studies financed by the pharmaceutical industry. Currently, the efficacy of tracheal instillation of artificial surface-active substance is already well-established; and its administration is already part of the medical routine in the treatment of neonates with respiratory failure due to lung immaturity. In Brazil, this fact has been recognized by the Ministry of Health (portaria 139; Diário Oficial da União in November 12, 1997) with the inclusion of the surfactant in the listing of special procedures covered by the Brazilian public healthcare system (Sistema Único de Saúde).

Presently, studies are being aimed at establishing a treatment strategy with exogenous surfactant in order to optimize effects in RDS newborns, and evaluate its actual efficacy in the control of respiratory failure resulting from other pulmonary conditions of the neonatal period, such as meconium aspiration syndrome (MAS), congenital pneumonia, bronchopulmonary dysplasia (BPD), pulmonary hypoplasia, and so on. In addition, these studies are aimed at investigating the therapeutic potential of new preparations made of phospholipids and synthetic apoproteins.

Classification and composition of the exogenous surfactant

The types of surfactant used in the different controlled clinical trials with humans and with experimental models can be divided into two larger groups: one with preparations of endogenous surfactants of animal lungs; and the other with synthetic preparations. This classification includes both the surfactants already being used in clinical practice and others still being investigated.

I. Preparations containing endogenous surfactant of animals

Surfactant extracted with organic solvent from bronchoalveolar lavage:
- lipid-extracted bovine surfactant* (Alveofact™)
- bLES** (bovine Lipid Extract Surfactant)
- Calf Lung Surfactant Extract* (Infasurf™)

Surfactant extracted with organic solvent from minced animal lung:
- lipid-extracted porcine surfactant* (Curosurf™)

Surfactant extracted with organic solvent from minced animal lung and supplemented with phospholipids or recombinant apoproteins:
- Surfactant TA* (Surfacten™)
- Modified bovine surfactant* (Survanta™)
- Modified bovine surfactant + recombinant SP-C***

II. Synthetic or recombinant preparations

Synthetic surfactant without apoproteins:
- ALEC* (Artificial Lung Expanding Compound)
- Colfosceril palmitate* (Exosurf™)

Surfactant with synthetic peptides:
- KL4**: hydrophobic, synthetic peptide with 21 amino acids and composed of sub-units containing 1 residue of lysine (K) and 4 leucines (L). It has characteristics similar to those of SP-B apoprotein. The peptide is associated with the saturated phospholipids.

Surfactant with recombinant apoproteins:
- Surfactant with recombinant SP-C****

Out of the above referred products, some are commercially available (*), while others are still being evaluated in their use with human newborn babies (**). Others, still, are currently being submitted to investigation with animal models (***). In the Brazilian market it is possible to find the following products:

- Bovine lipid extract surfactant (Alveofact™): natural surfactant extracted from bronchoalveolar lavage of intact bovine lung. The final product, in water suspension at 45 mg of phospholipids per ml concentration contains approximately 99% phospholipids and neutral fats and 1% apoproteins SP-B and SP-C. It is available in 1.2-ml flasks (50 mg of phospholipids). This preparation must be stored between 2 and 8 degrees Celsius. The suggested dosage is 1.2 ml/kg.

- Porcine lipid extract surfactant (Curosurf™): natural surfactant extracted from minced porcine lung. The final product, in water suspension at 80 mg of phospholipids per ml concentration contains approximately 99% lipids, especially phospholipids, and 1% apoproteins SP-B and SP-C. In relation to the bronchoalveolar lavage-extracted products, this preparation contains the largest amount of phospholipidic
tissue (phosphatidylethanolamine and sphingomyelin) and the smallest of apoproteins. It is available in 1.5- and 3.0-ml flasks (120 and 240 mg of phospholipids, respectively) and should be stored between 2 and 8 degrees Celsius. The suggested dosage is 1.25 to 2.5 ml/kg.

- *Colfosceril palmitate (Exosurf™)*: synthetic surfactant without apoproteins and composed of the phospholipid dipalmitoylphosphatidylcholine, emulsifying agents, a non-ionic detergent (tyloxapol), and alcohol (hexadecanol). The final product contains 108 mg of dipalmitoylphosphatidylcholine, 8 mg of tyloxapol, and 12 mg of hexadecanol. It is available in lyophilized powder and can be stored at room temperature. If diluted with 8.0 ml of distilled water, the preparation contains 13.5 mg of phospholipids per ml. The suggested dosage is 5.0 ml/kg.

- *Modified bovine surfactant (Survanta™)*: natural surfactant extracted from minced bovine lung and supplemented with dipalmitoylphosphatidylcholine, palmitic acid, and tripalmitin. The final product, in water suspension at 25 mg of phospholipids per ml concentration contains 88 to 90% phospholipids, out of which 50% are in desaturated form and in which there is less than 1% apoproteins SP-B and SP-C. In relation to the bronchoalveolar lavage-extracted products, this preparation contains less apoproteins. It is available in 8.0-ml flasks (200 mg of phospholipids). It should be stored between 2 and 8 degrees Celsius. The suggested dosage is 4.0 ml/kg.

**Pulmonary surfactant functions**

The most well-known function of the pulmonary surfactant is that of stabilizing the alveoli and the bronchioli during the expiration stage, in order to prevent collapse of distal airways and loss of lung volume. During inspiration, the surfactant promotes a uniform recruitment of alveoli, consequently reducing the pressure gradient between the interstitium and the alveolus and the formation of alveolar edema. In addition, it is also understood that the surfactant presents immunologic, antibacterial, and anti-inflammatory properties, possibly related to apoproteins SP-A and SP-D.

**Physiological basis for the replacement of exogenous surfactant in neonatal pulmonary diseases**

In order for surfactant surface-active properties to remain constant on the alveolar surface, there have to be control mechanisms that regulate, in a strict manner, the various steps of its metabolism. This is a complex system that includes synthesis, storing, and secretion of the surfactant by type 2 pneumocytes. On the alveolar surface, a series of structural alterations of the recently secreted surfactant take place leading to formation of the tubular myelin and of the membrane rich in dipalmitoylphosphatidylcholine. Finally, during the neonatal period, it is possible to observe surfactant uptake in terminal airways through type 2 pneumocyte. The surfactant is then reincorporated, without deleterious effects, into the lamellar bodies and next secreted again to the alveolar surface (Figure 1).

---

**Figure 1** - Pulmonary surfactant metabolism
Any factor that may disturb one of the multiple steps involved in forming, and maintaining the surface-active film rich in saturated phospholipids may reduce the quantity of active surfactant in the air-liquid interface of the alveolar surface. Abnormalities of the surfactant system may occur starting at the processes of synthesis, intracellular processing, secretion and adsorption, up to that of uptake and recycling. Alterations can be divided into two large categories:

- Quantitative surfactant deficiency due to low reserves as a result of insufficient production of the surfactant, as in immature lungs (RDS), malformed lungs (pulmonary hypoplasia), and acute respiratory distress syndrome (ARDS).

- Qualitative surfactant deficiency due to dysfunction of the alveolar surfactant - this group includes the factors that interfere in the alveolar cycle of surfactant metabolism, the more important being inactivation of the surface-active film. The mechanisms involved in this process are still not well-understood. It is known, however, that surfactant inactivation can occur due to alteration, destruction, or removal of the film of phospholipids of the alveolar surface; or, still, due to addition of other substances with surface-active properties that replace or compete with the original film. The main agents involved in surfactant inactivation are proteins (albumin, fibrinogen, and hemoglobin), fluids (pulmonary edema), markers of tissue lesion (cytokine and protease), and the oxidizing (high-concentration oxygen) and physical (barotrauma and volutrauma) agents. The overflow of these substances into the alveoli occurs basically due to the increase in vascular permeability observed in immature lungs; this situation is deteriorated by ventilator-induced lesions and by infectious and asphyxial processes. Moreover, a series of studies have shown that the components found in meconium (cholesterol, fatty acids, and bilirubin) interfere with surfactant function.

The deficiency in the surface-active film results in an increase in surface tension forces and elastic recoil of the lungs, leading to instability and progressive alveolar atelectasis with reduction of lung compliance and of functional residual capacity. These factors can alter the relation ventilation-perfusion, causing hypoxemia, hypercapnia, and acidosis. In the past few years, a better understanding of the various aspects of surfactant metabolism has directed research towards evaluating the efficacy of exogenous surfactant replacement therapy in lung pathologies, other than RDS, that alter the function of the surface-active substance. Among the potential treatment uses of exogenous surfactant there are meconium aspiration syndrome, pneumonias, bronchopulmonary dysplasia, and ARDS.

Clinical effects of exogenous surfactant replacement therapy in RDS

The short and long-term effects of exogenous surfactant replacement in preterm newborns who develop RDS, and in those who present risk for developing the disease, have been extensively evaluated in a series of multicentered, controlled, randomized studies.

- Effects on lung function: the clinical efficacy directly related to surfactant activity was evaluated through parameters of respiratory function and severity of the course of RDS. Essentially, all controlled studies on exogenous surfactant therapy indicated an improvement in one or more variables of lung function, such as arterial oxygenation, need for oxygen supplementation or for pressure support ventilation. In addition, the prophylactic or early use of the surfactant has been reported efficacious in reducing the severity of the course of the disease. After instillation of the exogenous surfactant it is possible to observe a rapid improvement in arterial oxygenation and, at a slower pace, in lung compliance. Others have reported that immediately after the administration of exogenous surfactant, it is possible to observe an increase in functional residual capacity (FRC) resulting from recruitment of atelectatic alveoli and of stabilization of open alveoli. The increase in FRC allows for a greater surface for gas exchanges, improving ventilation-perfusion, reducing intrapulmonary shunt, and, consequently, correcting hypoxemia. Subsequently, with the recruitment of new alveolar units and reduction of distortion of thoracic cavity shape due to the decrease in ventilation support, it is possible to observe an increase in lung compliance. Thus, improvement in arterial oxygenation occurs before, and it does not seem related to, an increase in lung distensibility.

- Effects on clinical entities associated with prematurity and RDS: the therapy with exogenous surfactant significantly reduces the incidence of air leaks (pneumothorax and of pulmonary interstitial emphysema). This is probably due to its stabilizing effect on terminal airways. The replacement of the surface-active substance, however, has not been effective in reducing complications observed during the course of the disease, such as patent ductus arteriosus, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, and retinopathy of prematurity. In relation to BPD or to chronic lung disease, both separate and group assessment of the various controlled studies indicated that the use of the surfactant did not reduce this complication. An increase in newborns who survived without chronic lung disease was, however, observed. In addition, a series of evidence indicates that exogenous surfactant replacement therapy reduced the severity of the disease. Consequently, incidence and severity of the main complications related basically to prematurity did not increase despite the increase in survival of these patients.

As to what concerns neonatal mortality, others have observed a 30 to 40% decrease in deaths of newborns with RDS. In developed countries, this result occurred more markedly in the more immature patients. In Brazil, where neonatal mortality rates of premature babies with birthweight
greater than 1,000 grams are still high, the use of surfactant presented a greater impact on the reduction of mortality of more mature neonates (Figure 2). Extremely low-birthweight babies, whose lung immaturity is only part of an overall systemic immaturity, require not only surfactant replacement therapy, but also a sophisticated infrastructure for the effective reduction of their mortality.

Clinical effects of exogenous surfactant therapy in other neonatal lung diseases

– Meconium aspiration syndrome (MAS): the use of surfactant in MAS is still very controversial. It is based on the fact that fatty acids, cholesterol, and bilirubins present in the meconium are capable of inactivating and displacing the surface-active film that covers the alveolar air-tissue interface causing atelectasis and reduction of lung compliance. Despite the physiological basis that justifies the use of surfactant in aspirative pneumonia, there are disagreements in the experimental results. Studies with newborn pigs showed that high doses of modified bovine surfactant did not improve arterial oxygenation, did not lower surface tension in the alveoli, and did not result in improvement of histologic alterations of the lung caused by meconium aspiration. Other studies with rabbit and rat models with meconium in the respiratory tree demonstrated that the use of surfactant allows for discrete improvements on lung compliance and alveolar volume, thus reducing hypercapnia. Prospective and randomized studies with newborn babies\(^{10,11}\) indicated an improvement in oxygenation and in pulmonary mechanics; these studies also indicated a reduction of the need for extracorporeal membrane oxygenation (ECMO) in patients who received modified bovine surfactant in multiple doses of 100 to 150 mg/kg. Yet, the use of surfactant did not change the incidence of pneumothorax or of chronic lung disease, nor the mortality rate.

In order to facilitate removal of the meconium and, possibly, of inflammatory markers - in addition to lowering surface tension with the improvement of lung mechanics - others have investigated the use of bronchoalveolar lavage with surfactant. Pilot studies\(^{12}\) were carried out with newborns with MAS and severe hypoxemia, during the first hours of life and with modified natural surfactant at a concentration of 5 mg/ml at 15 ml/kg. Though results have corroborated the safety and the efficacy of the method, it is still necessary to carry out multi-centered, controlled and randomized studies before this strategy is included into the regular clinical practice. Because inactivation of the surfactant is one of the main factors that limit the success of exogenous replacement of the surface-active substance, there are indications that the new generation of surfactants, with synthetic peptides (KL4) or recombinant SP-C or, still, supplemented with non-ionic polymers (dextran) would be more resistant to inactivation caused by meconium.\(^4\) Initial studies with models of acute pulmonary lesion, including of MAS, have presented promising results.

It is possible that surfactant replacement at high dosages, together with apoproteins B and C, could improve the relation ventilation-perfusion, present in cases of MAS. In this sense, this would also reduce the need for more aggressive therapeutic strategies.

– Congenital Pneumonia: the course of respiratory failure in cases of neonatal, bacterial, or viral pneumonia depends, partially, on dysfunction of the surfactant system caused by the inflammatory exudate. Research studies with animal models of pneumonia caused by group B streptococcal (GBS) infection have shown improvement of pulmonary function after tracheal instillation of phospholipidic fraction of porcine lung. There have been no prospective, controlled studies in human newborns in this sense. Recently, in a non-randomized study, the effect of exogenous surfactant replacement was evaluated in newborns with clinical and laboratory signs of acute inflammatory disease and GBS infection proven by culture results. The study indicated that, in comparison to neonates with RDS, patients with GBS infection required higher initial doses and repeated treatment for the correction of hypoxemia. In addition, the improvement in gas exchange was slower in GBS than in RDS infants.\(^{13}\) It is expected that advancements in genetic engineering will allow for new surfactants supplemented with apoproteins A and D. In this sense, these surfactants would stimulate alveolar macrophage
and, consequently, be more effective than the preparations available at the present time.4

- Pulmonary hypoplasia: research in the field of pulmonary hypoplasias has been aimed at better understanding the alterations that occur in congenital diaphragmatic hernia (CDH). Experimental studies have shown that, in CDH, structural immaturity of the parenchyma occurs together with biochemical immaturity.14 This indicates that gestations with affected fetuses present immaturity of the relation lecithin/sphingomyelins and absence of phosphatidylylycerol in amniotic fluid. Studies with animal models have indicated a reduction in the amount of saturated phosphatidylcoline, more markedly in the ipsilateral lung. These facts corroborate the use of exogenous surfactant in CDH patients. Clinical experimentation is limited to studies with a reduced number of patients15 and that have presented variable results; responses were always inferior to those observed in RDS, MAS, or congenital pneumonia neonates. Despite the poor results, it is possible that the use of exogenous surfactant in newborns with lung hypoplasia could reduce ventilator-induced lesions and, consequently, reduce the need for more aggressive therapies such as ECMO.

- Acute Respiratory Distress Syndrome: lung alterations in ARDS occur due to acute, diffuse lung lesion brought on by a variety of factors such as infection, asphyxia, shock, and oxygentherapy. Despite the fact that this syndrome has been more widely studied in adult patients, it is possible that it occurs in all age ranges, including that of neonates. In ARDS, it is also possible to observe a reduction in the production of endogenous surfactant as a result of type 2 pneumocyte lesion. However, the principal point in the pathogeny of the disease is the sequestration and activation of leukocytes at alveolar capillaries. These inflammatory cells release cytokines, proteases, free radicals and a series of other markers that cause tissue lesion, thus increasing vascular permeability with overflow of fluids and proteins. The presence of these substances in the air space inactivates the surface-active film of the alveolar surface. Results of controlled, randomized studies with replacement of exogenous surfactant in ARDS are controversial and restricted to adult patients. Endotracheal instillation of modified bovine surfactant, at a total dosage of 400 mg/kg (divided into 4 doses at every 6 hours) reduced the need for oxygen and the mortality rate.16 The same effect, however, was not observed with the use of aerosolized synthetic surfactant (colfosceril palmitate).17 It is possible that the disagreement between these two studies was a result of the type of surfactant used (natural as opposed to synthetic) and/or of the instillation technique (endotracheal instillation as opposed to nebulization). The studies with pediatric patients were carried out with small population groups of patients in which the use of varied dosages and types of surfactants promoted some type of improvement of clinical status. In the actual clinical practice, the most important restriction to the use of exogenous surfactant in ARDS is the dosage required for treating a “large” lung in repeated doses to overcome the phenomenon of inactivation. The development of new surfactants with high surface properties and great resistance to inactivation may be useful for this type of patients.

Impact of the universal use of exogenous surfactant

The controlled studies carried out during the second half of the 1980s clearly demonstrated that exogenous surfactant replacement therapy increased the survival of premature patients that developed RDS.3 In addition, epidemiological analyses on neonatal mortality have shown a significant reduction in the death rate resulting from RDS with non-controlled use of the medication, after the beginning of its commercial availability in 1990.18 Thus, in developed countries, the widespread use of exogenous surfactant has proven important for the reduction in neonatal mortality rates, especially that of premature babies.

In Brazil, information on the impact of the use of exogenous surfactant on neonatal mortality after its commercial availability are scarce. At the Neonatal Unit of the Teaching Hospital at UNIFESP/EPM, the comparison of neonatal mortality during the pre-surfactant availability period (1990-1992) and after its inclusion in routine clinical practices (1996-1998) indicated a reduction in death rates, especially among very low birthweight newborns (Figure 3). These results were corroborated by those observed at a private hospital, the Santa Joana Hospital and Maternity, in São Paulo (Figure 4).

![Figure 3 - Neonatal mortality considering birthweight in the presurfactant and postsurfactant periods. Neonatal Unit - UNIFESP/EPM](image-url)
Figure 4 - Neonatal mortality considering birthweight in the presurfactant and postsurfactant periods. Hospital and Maternidade Santa Joana, São Paulo, Brazil

At the institutional level, apparently, the introduction of the surfactant into the daily medical practice has shown positive effects. At the population level, however, the availability of the medication at public hospitals, after its inclusion in the listing of special procedures covered by the Brazilian public healthcare system, does not seem to have promoted, up until now, the same results observed at the institutional level. By examining data of the Mortality Information System (Sistema de Informações sobre Mortalidade - SIM) and the Livebirths Information System (Sistema de Informações sobre Nascidos Vivos - SINASC) for the years of 1996 to 1998, in Brazil (Table 1), it is possible to observe that, in this period, there were no changes in the characteristics of the population of newborns regarding the proportion of low birthweight neonates, very low birthweight neonates, and extremely low birthweight neonates. Aside from that, the assessment of early neonatal mortality (up to seven days of life) caused by respiratory or cardiovascular disorders did not indicate significant reduction of the death rate in the year following the commercial availability of the exogenous surfactant.

Despite the fact that the provided information was not very specific in relation to deaths due to RDS, it is possible to infer that, in Brazil, the availability of the surfactant apparently did not alter the prognosis of preterm neonates that develop respiratory failure. This may be a consequence of the exogenous surfactant being used in situations of inadequate infrastructure for the care of newborns with multiple organ dysfunction. It is important to emphasize, thus, that the surfactant therapy will only be effective with pediatric patients if carried out together with the appropriate allocation of human resources, and adequate equipment, for the treatment of critically-ill newborns. In this sense, the recommendations of the American Academy of Pediatrics Committee on Fetus and Newborn were re-published after approximately 10 years, indicating the minimal conditions under which the exogenous surfactant is to be administered (Table 2).

Table 1 - Characteristics of the population of newborns considering the number of low birthweight, very low birthweight, and extremely low birthweight infants born between 1996 and 1998, in Brazil, and early neonatal mortality rate (up to seven days of life) due to respiratory or cardiovascular problems per 1,000 live births

<table>
<thead>
<tr>
<th>Year</th>
<th>Total live births</th>
<th>&lt;1,000g (%)</th>
<th>1,000-1,500g (%)</th>
<th>1,500-2,500g (%)</th>
<th>&gt;2,500g (%)</th>
<th>Early neonatal mortality (&lt;1 week) due to respiratory or cardiovascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>2,929,041</td>
<td>0.32%</td>
<td>0.93%</td>
<td>7.7%</td>
<td></td>
<td>6.7%</td>
</tr>
<tr>
<td>1997</td>
<td>3,022,619</td>
<td>0.33%</td>
<td>0.94%</td>
<td>7.6%</td>
<td></td>
<td>6.5%</td>
</tr>
<tr>
<td>1998</td>
<td>3,144,547</td>
<td>0.34%</td>
<td>0.96%</td>
<td>7.8%</td>
<td></td>
<td>5.9%</td>
</tr>
</tbody>
</table>

Sources: Mortality Information System (SIM) and Livebirths Information System (SINASC), based, respectively, on the information obtained from the death certificate and statement of live birth. http://www.datasus.gov.br/
Table 2 - Minimal requirements for the administration of exogenous surfactant, according to the American Academy of Pediatrics, 1999 \(^\text{19}\)

- Presence of medical and nursing professionals especially qualified in the treatment of low birthweight newborns, including expertise in mechanical ventilation
- Availability of adequate equipment for monitoring and treating critically ill low birthweight newborns with multiple organ failure
- Availability of laboratory and radiological infrastructure
- If these minimal requirements are not met, the administration of surfactant can be performed providing that the newborn is immediately transferred to a reference nursery

Optimal effects with the exogenous surfactant will only be possible if the hospital or institution has implemented minimal conditions for the care of newborns with different levels of multiple organ failure, in addition to respiratory failure.

- **Stimulating lung maturation**: the beneficial effects of antenatal corticosteroid administration, in the sense of reducing the mortality of premature babies, were demonstrated over three decades ago. Data from randomized and controlled studies \(^\text{22}\) show that corticosteroids administered to the mother reduce the mortality and occurrence of respiratory distress syndrome in approximately 50% of risk-group premature newborns. More recently, the effects of antenatal corticosteroid therapy combined with the use of postnatal exogenous surfactant were retrospectively evaluated in a database of multicentered studies. The use of antenatal corticosteroid administration alone reduced RDS mortality from 20% to 6%; the combined use of corticosteroids and postnatal surfactant, in turn, reduced mortality from 7% to 0%. \(^\text{23}\) These data show that antenatal administration of corticosteroids can change many aspects of neonatal RDS, independently of the surfactant system; optimal therapy effects are obtained with postnatal administration of artificial surface-active substance. Moreover, recent data show that corticosteroids can accelerate the maturation of extrapulmonary organs, reducing some of the complications associated with RDS, such as HPIV, which often limit the prognosis of extremely premature newborns. In 1994, following a Consensus Development Panel, the National Institute of Child Health and Human Development published the following recommendations for antenatal corticosteroid therapy in RDS prevention \(^\text{24}\):
  - All fetuses between 24 and 34 weeks’ gestation at risk for preterm delivery should be considered candidates for antenatal treatment with corticosteroids.
  - The decision to use antenatal corticosteroids should not be altered by fetal race or gender or by the availability of surfactant replacement therapy.
  - Patients eligible for therapy with tocolytics should also be eligible for treatment with antenatal corticosteroids.
  - Treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart. Optimal benefit begins 24 hours after initiation of therapy and lasts 7 days.
  - Because treatment with corticosteroids for less than 24 hours is still associated with significant reductions in neonatal mortality, of RDS, and IVH, antenatal corticosteroids should be given unless immediate delivery is anticipated.
  - In preterm premature rupture of membranes at less than 30 to 32 weeks’ gestation in the absence of clinical chorioamnionitis, antenatal corticosteroid use is recommended because of the high risk of IVH at these early gestational ages.
  - In complicated pregnancies where delivery prior to 34 weeks’ gestation is likely, antenatal corticosteroid use is recommended unless there is evidence that corticosteroids will have an adverse effect on the mother or delivery is imminent.

Table 3 - Strategies to optimize surfactant replacement therapy

<table>
<thead>
<tr>
<th>1. Stimulate pulmonary maturity</th>
<th>Prenatal corticosteroid use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Reduce or avoid barotrauma/volutrauma</td>
<td>Resuscitation maneuvers in the delivery room; Adequate ventilatory support: Optimization of conventional ventilation; High-frequency ventilation (HFV)</td>
</tr>
<tr>
<td>3. Promote a more homogeneous distribution of surfactant</td>
<td>Improvement of the instillation technique; Timing adequacy of surfactant administration</td>
</tr>
<tr>
<td>4. Improve the function of exogenous surfactant</td>
<td>Fortification with synthetic apoproteins; New formulations with phospholipids and synthetic apoproteins</td>
</tr>
</tbody>
</table>

Reducing or preventing barotrauma and volutrauma: currently, the studies being carried out with mechanical ventilation are aimed at searching for ventilatory strategies with reduced negative effects on airways, especially in immature, developing lungs. \(^\text{25}\) It is known that positive
pressure ventilation, even if carried out short-term, can cause the production of various inflammatory markers that, in turn, cause local and distant tissue lesions. This process increases the influx of substances to the alveolar surface that, in turn, alter the function of the surface-active film, thus reducing the action of both the native and exogenous surfactant. Studies with experimental models have shown that the process of ventilation can be initiated in the delivery room concurrently with positive pressure ventilation procedures of resuscitation maneuvers. It is understood that tidal volumes, which are probably harmless to mature lungs, can cause tissular lesions on immature lungs and, also, compromise the effect of the exogenous surfactant which is later administered. Consequently, during positive pressure ventilation in the delivery room, it is always important to monitor airway pressure levels; it is also important to administer the smallest tidal volume possible considering adequate ventilation of the patient.

The ventilation strategies used in handling RDS respiratory failure can vary from multiple combinations of conventional intermittent mandatory ventilation (IMV) parameters to the use of non-conventional techniques, such as high frequency oscillatory ventilation (HFOV). Up until now, there is no consensus regarding the best practice for improving the response to exogenous surfactant. A series of controlled clinical trials were carried out to determine whether the elective use of high frequency oscillatory ventilation (HFOV) as compared to conventional ventilation in preterm infants who are mechanically ventilated for the respiratory distress syndrome decreases the incidence of chronic lung disease (CLD). The review of these studies indicated that there are trends towards decrease in CLD in the HFOV group. The HFOV did not, however, change the mortality rates and, in addition, the authors observed that there are trends towards increases in intraventricular hemorrhage and in periventricular leukomalacia in the HFOV group. Based on the lack of evidence to support that HFOV is superior to conventional ventilation as a primary method of respiratory assistance, and on the possible association of HFOV with neurological complications, at the present time we understand that HFOV should only be used in cases of failure of the conventional ventilation method.

Consequently, up until this date, there is no concrete evidence of the superiority of a ventilatory technique specific for making exogenous surfactant replacement therapy more effective. In Brazil, the recommended strategy should be the conventional ventilation method in order to minimize lung lesions (Table 4).

-- Promoting homogeneous distribution of the surfactant: among the variables that influence the distribution of the surfactant, it is possible to underscore instillation technique and presence of previous lung lesion.

<table>
<thead>
<tr>
<th>Table 4 - Ventilatory strategies for pulmonary protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personalize the ventilatory support</td>
</tr>
<tr>
<td>• Always use the lowest peak pressure</td>
</tr>
<tr>
<td>• Restrict the time of FiO₂ use to a value greater than 0.60</td>
</tr>
<tr>
<td>• Always use and optimize PEEP</td>
</tr>
<tr>
<td>• Avoid auto-PEEP</td>
</tr>
<tr>
<td>• Accept respiratory acidosis in the acute phase of the disease (“permissive hypercapnia”)</td>
</tr>
<tr>
<td>• Never delay the withdrawal from mechanical ventilation</td>
</tr>
</tbody>
</table>

Investigations related to exogenous surfactant instillation technique (volume of the medication, speed of administration, and position of the baby) are aimed basically at the improvement of pulmonary surfactant distribution. Studies with animal models demonstrated that the distribution becomes more uniform as the volume of surfactant instillation increases. The administration of large volumes of surfactant, however, is not possible in clinical practice due to the risks of obstructing the patient’s airways. As a result, most protocols recommend the administration of volumes of surfactant between 3 and 5 ml/kg. As in any other drug administered through inhalation, the surfactant deposits especially in the better ventilated regions of the lung. According to this principle, instillation of total surfactant volume in various aliquots would lead to nonuniform distribution of the medication. That occurs because the administration of an aliquot allows for the improvement of ventilation in a specific region of the lung and, consequently, the surfactant in the next aliquot will go directly into this same area, resulting in a nonhomogeneous distribution. It is recommended, thus, that surfactant instillation be carried out using the smallest number possible of aliquots while observing the total volume to be given.

The speed of surfactant administration can also affect its distribution. The literature describes two techniques for instillation of the drug: rapid bollus instillation or slow infusion. Bolus instillation has been reported to cause greater oscillations in arterial blood pressure (BP) than slow infusion. However, the distribution of exogenous surfactant and its effect on gas exchange are superior when using bolus instillation. In practice, it is recommended that the total volume be administered in 30 to 60 seconds time. Moreover, studies have reported that gravity determines the distribution of the surfactant to the dependent lungs. Studies with animal models demonstrated that the distribution of surfactant volume in various aliquots would lead to nonuniform distribution of the medication. That occurs because the administration of an aliquot allows for the improvement of ventilation in a specific region of the lung and, consequently, the surfactant in the next aliquot will go directly into this same area, resulting in a nonhomogeneous distribution. It is recommended, thus, that surfactant instillation be carried out using the smallest number possible of aliquots while observing the total volume to be given.

The speed of surfactant administration can also affect its distribution. The literature describes two techniques for instillation of the drug: rapid bolus instillation or slow infusion. Bolus instillation has been reported to cause greater oscillations in arterial blood pressure (BP) than slow infusion. However, the distribution of exogenous surfactant and its effect on gas exchange are superior when using bolus instillation. In practice, it is recommended that the total volume be administered in 30 to 60 seconds time. Moreover, studies have reported that gravity determines the distribution of the surfactant to the dependent lungs. In following this principle, the most widely used technique in controlled studies was of administering the total dose of surfactant in 4 aliquots with the patient in prone position (1st and 2nd aliquot) and then right side down and left side down (3rd and 4th aliquot, respectively). Alternatively, the total dosage can be instilled in two aliquots with the patient in prone position with right side down and left side down. The
latter strategy is similar to the earlier in relation to effects on gas exchange, but it presents the advantage of requiring less handling of the newborn.

Outside these concerns, the surfactant can be administered with or without interrupting the mechanical ventilation. In the earlier case, the surfactant is delivered directly into the airways through an endotracheal or gastric tube placed in the tracheal cannula. After the instillation of the drug, the newborn is ventilated with a balloon and oxygen at 100% for 30 seconds. Interruption of ventilation during surfactant instillation has been associated with variations in cerebral blood volume increasing, thus, the risk for intraventricular hemorrhage and cerebral ischemic lesion. In the latter case, the surfactant is divided into two aliquots and instilled via a lateral port of the cannula connector (Exosurf™ protocol) in a slow fashion in order to avoid reflux and cannula obstruction. Another way of administering the surfactant without interrupting ventilation is by using a dual-lumen endotracheal tube. The advantage of this technique is that it allows depositing the drug at the distal end of the cannula, keeping it permeable.

According to the evidence available, our assessment is that surfactant instillation should be carried out without interruption of ventilation and with dual-lumen endotracheal tube. Moreover, the total dosage should be divided into a maximum of two aliquots and administered with bolus instillation, at a speed between 30 and 60 seconds.

Another factor that limits the distribution of exogenous surfactant is the intensity of lung lesion, either due to inactivation or to the fact that the lung is not always homogeneously compromised. Since lesion grade is directly related with duration and intensity of ventilatory parameters, it is understood that early surfactant instillation may prevent these lesions since it will require less ventilatory support during the course of the disease. Depending on the time of treatment, the surfactant can be administered prophylactically or therapeutically. In the prophylactic strategy, the surfactant is administered to all newborns who are at risk for developing RDS. Administration is carried out right after birth and with the objective of preventing onset of the disease and/or lessening the effects of clinical evolution of the disease. Moreover, the presence of residual fetal lung fluid during the first minutes of life allows for a better distribution of the exogenous surfactant. Most authors consider that the patients at risk for RDS are those with birthweight less than 1,250 grams. In the therapeutic strategy, in turn, the surfactant is administered only after RDS is diagnosed, during the first hours of life, and with the objective of lessening the effects of clinical evolution of RDS.

The literature has reported the advantages of prophylactic use of surfactant in premature newborns, especially in those with less than 28 weeks’ gestation. Considering the high cost of the drug (approximately US$ 400 per flask) and estimating that around 30 to 40% of newborns who receive the surfactant right after birth (prophylactic strategy) would not have needed the drug, it is understood that, until the present date, in Brazil it would be more recommended to adopt the therapeutic strategy. If the therapeutic strategy is adopted, it is important to remember to administer the surfactant as soon as RDS is diagnosed, and preferably during the first six hours of life. Alternatively to the prophylactic strategy, for extremely low birthweight newborns (less than 1,000 grams), there is the selective surfactant treatment. In this strategy, the surfactant is administered only to newborns endotracheally intubated during resuscitation maneuvers in the delivery room. It is important that the surfactant be administered within the first hour of life, soon after hemodynamic conditions are stabilized - independently of clinical or radiological status of the patient.

– Improving surfactant function: in vitro research with animal models have shown the advantages of natural over synthetic surfactant in relation to the surface-active properties, to the resistance to inactivation by proteins, and to the effects in pulmonary function. Large multi-centered studies on natural and synthetic surfactants, carried out with newborn babies during the 1980s and the beginning of the 1990s, indicated similar effects. Moreover, results of a multi-centered, randomized trial suggest that the modified bovine surfactant extract is more effective than the colfosceril palmitate in relation to gas exchange, pulmonary mechanics, incidence of pneumothorax, and increase in survival in babies without BPD. The advantages of natural surfactants over synthetic surfactants may be related to the presence of apoproteins (SP-B and SP-C), since these apoproteins allow for optimal surfactant function as to what concerns distribution, adsorption, and resistance to inactivation. Among commercially available natural preparations, it is understood that those of bronchoalveolar lavage contain more apoproteins than those prepared by mincing animal lungs. Despite the lack of clinical evidence comparing the various types of natural surfactants, in vitro investigations show the superiority of surfactant extracted from bronchoalveolar lavage in relation to surface properties and greater resistance to inactivation.

It is established that both natural and synthetic surfactant extracts change the clinical course of RDS, improving survival rates and reducing complications. The use of natural surfactants, however, seems to present more positive results in relation to immediate response (gas exchange and pulmonary mechanics) and some late effects (air leak syndrome) when compared to synthetic surfactants. In general practice, it is possible to use natural surfactant extracts as the drug of choice in situations of increase in intraalveolar proteins - as in cases of severe RDS in which surfactant administration was not possible during the first few hours, in congenital pneumonias, or in MAS.

The advancements in molecular biology in association with recombinant DNA technology have allowed for the
production of phospholipids and apoproteins analogous to those of endogenous human surfactant. 39 This has allowed for a positive outlook concerning the development of new preparations with composition similar to that of the native surfactant but with superior functions. From this vantage point, different approaches for the development of new surfactants are being investigated in experimental models and in human newborns:

- Combination of recombinant human apoproteins with synthetic phospholipids
- Preparations containing synthetic hydrophobic peptides combined with synthetic phospholipids
- Supplementation of commercially available products with recombinant apoproteins, synthetic hydrophobic peptides, or nonionic polymers.
- Preparations containing phospholipidic contents resistant to the process of inactivation.

The principal objective in the development of these new products is the possibility of developing new preparations with high surface-active properties, great resistance to the process of inactivation, and low toxicity. In addition, the production in vitro allows for better quality control than in processes of extraction from animal lungs. Finally, the potential large-scale production of the surfactant could reduce costs. Despite these theoretical advantages, investigations are still being carried out with experimental models; it is necessary to carry out more studies in the sense of evaluating the risks and benefits of these new preparations for humans.

**Protocol for surfactant administration during the neonatal period**

At the Neonatal Unit at UNIFESP/EPM, we try to follow the principles below in order to improve the effects of exogenous surfactant therapy.

1. Stimulate the use of antenatal corticosteroids.
2. Implement the minimum required resources (human, equipment, and laboratory) for the care of newborns with multiple organ failure. In addition, we implement a constant assessment of the quality of services being provided to these patients.
3. Administer preparations of endogenous animal surfactant extracts, especially in cases of extensive inflammatory lesions (severe RDS, pneumonias, MAS, and ARDS).
4. Posology:
   - Start with 100 mg/kg of phospholipids. If patient presents an improvement of pulmonary function, use the same dosage if retreatment is needed. Consider using greater dosages (approximately 150 mg/kg of phospholipids) in cases that develop with extensive inflammatory lesions (severe RDS, pneumonias, MAS, and ARDS).
   - Consider additional doses case by case. We recommend a minimum interval of six hours between doses; it is also important to remember that there are no evidence of advantages of the use of more than four doses.
5. Handling:
   - Warm up flasks (natural surfactant extracts) at room temperature (30 degrees Celsius) for 20 minutes or holding them in the hands for eight minutes. No other method for warming up the drug is recommended. After warm-up and when using natural surfactant extracts, if the drug is not used, it should be placed again in cold storage. The flask can be warmed-up for a second time. In the case of synthetic preparations, the product will remain stable for up to 24 hours at 2 to 30 degrees Celsius after it is diluted.
   - Homogenize the preparation turning it upside down twice. Do not shake the preparation in order to avoid the formation of foam.
   - Remove surfactant from the flask using a 3 or 5-ml syringe and 25 x 38 needle. Make sure to observe adequate asepsis techniques.
6. Indication:
   - RDS: as a rule, use the therapeutic strategy; in other words, the surfactant is to be administered as soon as the disease is diagnosed by clinical and radiological criteria. Moreover, the newborn should be receiving mechanical ventilation, intubated, and requiring FiO2 greater than or equal to 0.40 for a PaO2 between 50 and 70 mmHg or SatO2 between 89 and 93%. Reevaluate the need for additional doses at every six hours. Indicate retreatment if the patient remains mechanically ventilated and dependent of FiO2 greater than 0.30 for a PaO2 between 50 and 70 mmHg or SatO2 between 89 and 93%. If the newborn requires retreatment, first it is imperative to exclude the possibility of air leak syndrome, congenital pneumonia, patent ductus arteriosus, and persistent neonatal pulmonary hypertension.
   - Preterm newborns with birthweight less than 1,000 grams: consider administration of the surfactant after the hemodynamic condition is stabilized if the patient was endotracheally intubated in the delivery room as part of the resuscitation maneuvers. The surfactant should be instilled until one hour of life, independently of the respiratory or radiological status of the patient and only if the patient remains mechanically ventilated. Reevaluate the need for additional doses at every six hours. Indicate first retreatment if the patient requires FiO2 greater than or equal to 0.40 for a PaO2 between 50 and 70 mmHg or SatO2 between 89 and 93%. Indicate other retreatments if the patient remains mechanically ventilated and dependent of FiO2 greater than 0.30 for a PaO2 between 50 and 70 mmHg or SatO2 between 89 and 93%. If the newborn requires retreatment, first it is imperative to exclude the possibility of air leak syndrome,
congenital pneumonia, patent ductus arteriosus, and persistent neonatal pulmonary hypertension.

Other situations - MAS, congenital pneumonias, ARDS, and CDH: consider exogenous surfactant replacement therapy if the patient develops severe respiratory failure and requires mechanical ventilation via tracheal cannula. The same criteria for RDS can be applied, that is, if the patient requires FiO\textsubscript{2} greater than or equal to 0.40 for a PaO\textsubscript{2} between 50 and 70 mmHg or SatO\textsubscript{2} between 89 and 93%. Reevaluate the need for additional doses at every six hours. If the newborn requires retreatment, first it is imperative to exclude the possibility of air leak syndrome and persistent neonatal pulmonary hypertension.

7. Caring for the newborn before instillation:

- Verify the position of the end of the tracheal cannula by pulmonary auscultation or, preferably, by chest X-ray; the cannula should be located between the 1\textsuperscript{st} and 3\textsuperscript{rd} thoracic vertebrae.
- Try not to interrupt mechanical ventilation by using a dual-lumen endotracheal tube for administration of the surfactant.
- If necessary, aspirate the tracheal cannula approximately 10 to 15 minutes before surfactant instillation.
- Monitor cardiac frequency, pulse oximetry, peripheral perfusion, and systemic arterial pressure to check whether patient hemodynamic conditions are adequate. If patient goes into shock or presents hypertension, correct and stabilize the condition before instilling the surfactant.
- Adjust IMV parameters to:
  - FiO\textsubscript{2}: do not adjust unless interruption of mechanical ventilation is necessary; in which case FiO\textsubscript{2} should be increased 20%.
  - Inspiratory time: maintain between 0.3 and 0.5 seconds.
  - Expiratory time: maintain above 0.5 seconds.
  - Inspiratory pressure: adjust peak pressure in order to raise the thoracic cavity approximately 0.5 cm at the sternum. If it is possible to monitor respiratory mechanics, adjust for a tidal volume between 4 and 6 ml/kg.
  - PEEP: maintain between 4 to 6 cm H\textsubscript{2}O.
  - Note: if the ventilatory parameters are superior to those described above, it is not necessary to adjust them.

8. Precautions during instillation:

- Continuously monitor the cardiac frequency, the arterial pressure, and the arterial oxygenation through pulse oximetry; monitor also the reflux of the drug through the tracheal cannula or through the patient’s mouth.
- Administer the total dosage in two aliquots, at maximum. Carry out instillation of the drug at every 30 to 60 seconds.
- Interrupt administration of the drug in case of bradycardia (CF < 80 bpm) and/or hypoxemia (SatO\textsubscript{2} < 85%). Check the position of the tracheal cannula and stabilize the patient adjusting ventilatory parameters with balloon ventilation and oxygen at 100% before resuming surfactant instillation.

9. Precautions after instillation of the drug:

- Do not aspirate the tracheal cannula during the first hour following instillation of the exogenous surfactant unless there is clinical evidence of obstruction of the cannula.
- Monitor arterial oxygenation (pulse oximetry and arterial gasometry), cardiac frequency, and arterial pressure. The changes in pulmonary function occur rapidly after instillation of the surfactant; thus it is necessary to observe and monitor patients constantly.
- Adjust ventilatory parameters in order to maintain SatO\textsubscript{2} between 89 and 93%, PaCO\textsubscript{2} between 40 and 60 mmHg, cardiac frequency between 120 and 140 bpm, and average arterial pressure between 30 and 40 mmHg.

The following adjustments are suggested:
- FiO\textsubscript{2}: immediately after instillation of the exogenous surfactant, it is important to reduce oxygen supply. Reduce FiO\textsubscript{2} 5 to 10% at a time according to pulse oximetry (SatO\textsubscript{2}: 89 to 93%).
- Pressure support: adjust the pressure levels continuously according to improvements in lung compliance. Assess improvement in compliance according to degree of expandability (thoracic cavity raised approximately 0.5 cm at the sternum) and to tidal volume (maintain tidal volume between 4 and 6 ml/kg). Do not lower PEEP below 3 cmH\textsubscript{2}O.
- Maintain expiratory time above 0.5 seconds after surfactant instillation due to the risk for autoPEEP following improvement of lung compliance.

Conclusion

Surfactant replacement therapy represents, unquestionably, an advancement in the treatment of premature babies with RDS. It is proven that it presents benefits in the reduction of morbimortality of these patients. Moreover, under certain conditions, the use of exogenous surfactant seems to reduce the morbimortality of neonates with other pulmonary diseases whose course present dysfunction of the surface-active film. It is expected that the continuous advancements in the areas of molecular biology, of recombinant DNA technology, and of surface sciences will result in biologically compatible preparations, with significant surface properties and different compositions for every situation.
It is important to underscore, however, that understanding the phisiopathology of diseases, rigorously observing the overall healthcare of patients, and establishing notions of biochemistry, indications, and use of the surfactant are fundamental for the success of replacement therapy of the pulmonary surface-active substance.

References


Correspondence:
Dr. Milton Harumi Miyoshi
Rua Dr. Diogo de Faria, 764 – Vila Clementino
CEP 04037-002 – São Paulo, SP, Brazil
Phone: ++ 55 11 5579.1676 / 5579.4982
E-mail: dpn@osite.com.br