Exogenous surfactant therapy –
What is established and what still needs to be determined

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Abstract

Objective: to review well-known aspects of exogenous surfactant therapy, and to discuss controversial points regarding the current state of research.

Sources: review of the literature, using Medline and Cochrane Database Library, in association with the authors’ experience in relation to exogenous surfactant replacement therapy.

Summary of the findings: the main aspects of surfactant characteristics: composition, pool, metabolism, inactivation and immediate effects after its administration are well established. However, there are some doubts related to the use of exogenous surfactants that need to be cleared up: choice of surfactant type, most appropriate length of treatment, adequate dose and number of doses, best administration route and complications associated with its use. Currently, the research about exogenous surfactant therapy focuses on two aspects: the use of surfactant in other pathologies besides the respiratory distress syndrome of the newborn, and the development of new surfactants through the addition of proteins or analogous proteins, with the aim of improving its action and reducing its inactivation.

Conclusions: the use of exogenous surfactant has become a routine in neonatal intensive care units, but both clinical and experimental research is still necessary.


Introduction

The history of exogenous surfactant therapy dates back to 1929, when German physiologist Neergaard wrote the article entitled “New notions about an essential principle of respiratory mechanics: the retractive force of the lungs, dependent on alveolar surface tension”.¹ He showed that a lung inflated with air had a greater transpulmonary pressure than a lung inflated with the same volume of water, inferring that atelectasis of the newborn could be caused by remarkable retractive forces of the surface tension of the lungs.

In the 1940s, Gruenwald investigated autopsied lungs in newborns and described hypoventilation, which caused the lungs to resemble a solid organ that could be inflated with fluid but would lose its normal architecture when inflated with air.²

In the late 1950s, Avery and Mead stated that pulmonary surfactant deficiency observed in preterm newborns caused repetitive collapse and reexpansion of alveoli, and was therefore crucial to the pathogenesis of the hyaline membrane.³
Fugiwara, in 1980, went a step further. In a non-controlled study, surfactant was given intratracheally to preterm newborns with respiratory distress syndrome (RDS), with evident improvement of oxygenation; thus showing the efficacy of the new technique.4

In 1980s, several researchers investigated surfactants of different origins (human, porcine, bovine, synthetic) against placebos, culminating in the availability of surfactants for clinical use on a regular basis in the late 1980s and in the early 1990s.

In the last 12 years, several studies have been carried out with the aim of determining the best therapeutic scheme, taking into consideration the moment of treatment (prophylactic x therapeutic), the type of surfactant (synthetic x natural), and the dose of surfactant, among other aspects. These studies have been recently reviewed by Roger Soll in a series of meta-analyses.5-7

In recent years, research about surfactant therapy has focused on three major aspects: the first one is concerned with the use of surfactant in pathologies other than RDS, including meconium aspiration syndrome (MAS), pneumonia, acute respiratory distress syndrome (ARDS), congenital diaphragmatic hernia, among others; the second aspect deals with the investigation of the effects of alveolar recruitment with increase in the peak inspiratory pressure during surfactant administration; and the last one is concerned with the development of new surfactants by the addition of synthetic or analogous proteins, with the aim of improving their action and reducing their inactivation by plasma proteins.

The present article aims at reviewing exogenous surfactant therapy and discussing the current state of research, in which no consensus on the use of exogenous surfactant has been reached yet.

**Surfactant characteristics**

*Surfactant composition and pool*

The chemical composition of pulmonary surfactant is known to be quite similar among several mammalian species,8 with no differences that justify the use of a specific animal species for the extraction of pulmonary surfactant, for therapeutic purpose.

Surfactants usually consist of lipids and proteins. Approximately 80 to 90% of their mass consists of lipids, including neutral lipids and phospholipids.

About 70 to 80% of phospholipids consist of phosphatidylcholine, usually in saturated form (45% of the surfactant mass). Phosphatidylglycerol represents 5 to 10% (in mass), whereas phosphatidylinositol, phosphatidylethanolamine and phosphatidylserine account for less than 10% of total lipids. Cholesterol and cholesterol esters represent less than 5% of the surfactant mass, and their role is not perfectly known yet, although they change the flow and organization of lipid membranes.

The key function of phospholipids is acting as a molecule that reduces surface tension in the air/fluid ratio inside the alveolus. This unique characteristic allows preventing the repetitive collapse and reexpansion of alveoli at the end of expiration, when the forces that cause alveolar collapse are maximized and inversely proportional to the average alveolar radius. However, phosphatidylcholine alone is not able to explain the main surfactant characteristics: stability during compression, quick adsorption from subphase to the alveolar surface and the capacity to reorganize the monolayer when dispersed into an aqueous medium. In fact, at 37º C phosphatidylcholine takes the gel form, changing to the “liquid” and dispersed form at 41º C.9 Therefore, it depends on other surfactant components to form a stable layer on the alveolar surface when at physiological temperature.

Proteins, which include SP-A, SP-B, SP-C and SP-D, represent approximately 10% of the surfactant mass.

SP-A is a water-soluble protein, and the most abundant in the surfactant, accounting for 5% of its mass. It consists of a group of 26-KD monomers strongly linked together by covalent bonds, resulting in a 650-KD molecule. Among the functions of SP-A are pulmonary immune defense, since it is able to bind to carbohydrates and to interact with lung immune cells. The absence of SP-A hinders the elimination of both bacteria and viruses from the lungs, favoring the systemic dissemination of infections.10 The major roles of SP-A include protection of surfactant against the inhibition of its functions by proteins found in the alveolar edema.11

SP-A seems to influence the surfactant metabolism only in *in vitro* studies, since in transgenic animals with deficiency of this protein no influence exists on the metabolism or function of surfactant.

SP-B is a small 18-KD hydrophobic protein, which is essential to the pulmonary surfactant function; its congenital absence is incompatible with life.12,13

Among the functions of SP-B are formation and organization of tubular myelin inside the alveolus,14 in addition to facilitating the adsorption of phosphatidylcholine at physiological temperature.

SP-C is also a hydrophobic peptide that forms as rigid helical structure of 4.2 KD. Although its functions are similar to those of SP-B, allowing the adsorption of phosphatidylcholine at physiological temperature, its congenital deficiency does not result in death from respiratory insufficiency, although it might evolve into familial interstitial pulmonary disease.15

We may say that, of all its components, lipids, SP-B and SP-C are chiefly involved in the biophysical and functional properties of pulmonary surfactant.
SP-D is a water-soluble glycoprotein formed by 43-KD monomer aggregates, resulting in 560-KD multimers. Just like SP-A, it is not present in surfactant preparations of animal origin obtained through lipid extraction and does not reduce surface tension, seemingly having an important role in protecting the lungs from infection by binding to a variety of carbohydrate and glycolipid complexes, interacting with the surface of bacteria and other microorganisms.16

The amount of surfactant found in the lungs correlates logarithmically with the alveolar surface in several animal species.17 In human beings, a report based on five subsegmental washings in volunteering adults allowed an estimate of alveolar pool of 3mg of surfactant/kg.18 This estimate was confirmed in a study involving 24 dead subjects, aged between 13 months and 80 years, in which the estimated alveolar pool of surfactant was a 4mg/kg and that for total lung was approximately 56mg/kg.19

The amount of pulmonary surfactant decreases with age, but not remarkably. Interestingly enough, preterm newborns with RDS have an amount of surfactant between 1 and 5 mg/kg,20 similar to that observed in adults and approximately tenfold as high as that observed in full-term newborns, which is way below the dose used in the treatment of RDS in newborn infants, showing that the structure of a newborn’s lung and maybe the presence of proteins in the alveolar lumen determine the necessity for a greater pool at birth, as found in the lung of full-term newborns, in order to guarantee proper function.

**Surfactant metabolism**

The surfactant is produced in pneumocyte II. Phospholipids and proteins SP-B and SP-C are synthesized in the rough endoplasmic reticulum, from where they are initially stored in Golgi complex and, later, in the lamellar bodies (Figure 1). Periodically, the latter are expelled from pneumocyte II when the surfactant is released to the alveolar lumen, thus organizing the tubular myelin.

The kinetics of synthesis and secretion into the alveolus is quite slow, and takes from 30 to 48 hours in newborn animals;21 in general, this time is greater in newborns if compared to adults.

After being secreted into the alveolus, the surfactant goes through a complex cycle (Figure 1). Initially, the fat molecules organize themselves (with the help from proteins) so as to form the monolayer that lines the alveolar surface - the tubular myelin. With successive movements of contraction and stretching that occur at each respiratory cycle, part of the tubular myelin disorganizes itself and loosens itself from the main film in the form of small vesicles, which are reabsorbed into pneumocyte II. In the cell, a small part is catabolized, while the largest part of the reabsorbed surfactant is mixed with the lamellar bodies, where it is reorganized in a recycling process. Therefore, in preterm newborns, about 50% of the alveolar pool consists of surfactant, with great capacity to reduce surface tension, and another 50% is formed by inactive vesicles to be recycled. This relation is more unfavorable in situations of lung injury.22

This recycling process minimizes the necessity for surfactant synthesis, whereas it maintains an adequate alveolar pool and, at the same time, activates the surfactant components reabsorbed into pneumocyte II, by the addition of new elements (especially proteins) and by the structural reorganization of lipids and proteins. The latter process is particularly important to the treatment with exogenous surfactant, to which SP-A and SP-D (absent in commercial preparations) are added by means of recycling.

The exogenous surfactant used for the treatment of RDS is quickly incorporated to the lung tissue, and only 40% is retrieved in the alveolar space immediately after administration.23

The treatment with exogenous surfactant does not interfere with the metabolic pathways of the endogenous surfactant; consequently, its production is not inhibited by feedback.

Water-soluble proteins SP-A and SP-D are synthesized and released independently of phospholipids and fat-soluble proteins SP-B and SP-C.

**Surfactant inactivation**

The surfactant’s function of reduction of alveolar surface tension may be inhibited by plasma proteins, which invade the alveolar space in acute lung injuries. This inactivation is a reversible phenomenon and basically occurs due to interference in the formation of the surfactant monolayer, caused by the presence of proteins, through a competition mechanism at the air-fluid interface.

The inactivation phenomenon depends on several factors, including the amount of surfactant and proteins that compete for the air-fluid interface;24 the type of protein found in the alveolar lumen (fibrin monomers are located between the proteins with higher capacity of surfactant inactivation);25 and the amount of specific surfactant proteins (SP-A, SP-B and SP-C), which reduce inactivation.26 This phenomenon is mitigated with the prenatal use of corticosteroids, presumably by a better recycling mechanism, resulting in larger concentrations of specific proteins in the end product.27

**Immediate effects of surfactant treatment**

The first response to surfactant treatment is a rapid and intense increase in oxygenation, which occurs some minutes after administration, allowing a fast reduction in the concentrations of inspired oxygen.
Lung compliance improves more slowly, allowing a gradual reduction in the maximum peak inspiratory pressure in order to maintain an appropriate tidal volume.

This effect can be better understood by observing the reduction in opening pressure (pressure through which the lung is filled above the volume of the dead space) at the inspiratory stage of the pressure-volume curve of animals treated with surfactant in comparison with control animals. The greater alveolar recruitment results in increase of maximum pulmonary volume and higher stability of expiration, when alveoli remain open, resulting in larger residual functional capacity. The sum of these effects explains the dramatic improvement in oxygenation observed after surfactant treatment.

Microscopically, surfactant treatment leads to greater uniformity in alveolar expansion, reducing areas of atelectasis/hyperdistension, with a more important effect on the reduction of lung injury obtained with surfactant treatment. The effects on pulmonary blood flow are controversial, with the report of an increase or unaltered flow in the pulmonary artery.

Available surfactants and administration techniques

**Types of surfactants**

There are two basic choices for exogenous surfactant therapy: “natural” surfactants obtained from animals by lipid extraction by means of pulmonary washings or homogenate, which preserves the composition of SP-B and SP-C, with or without the addition of phospholipids to the end product; and synthetic surfactants, produced in laboratory. The major available surfactants are described in Table 1.

Although both types of surfactants change the course of RDS, the responses, especially in the short run, are different.

Natural surfactants produce an immediate response as to the improvement of oxygenation and of pulmonary function, demanding a close and constant monitoring of...
newborns soon after treatment, in order to avoid undesirable complications. Synthetic surfactants take some hours to show the same effects. The explanation for this phenomenon is probably related to the fact that synthetic surfactants have the main role of increasing the alveolar and tissue pool, which will be recycled inside pneumocyte II, being added to specific proteins, which are not present in the commercial product.

A meta-analysis has recently compared the studies conducted with extracts of natural surfactants against synthetic surfactants for the treatment of RDS; however, none of them used the new synthetic surfactants (KL-4 and rSP-C). The review of results obtained from the 11 studies revealed that both types of surfactants proved effective in the treatment of RDS, but with a lower risk of pneumothorax and lower mortality associated with the treatment using natural surfactant, as well as a tendency towards a lower risk of evolution into bronchopulmonary dysplasia or death.

**Time of treatment**

Classically, the prophylactic use of surfactant for the treatment of RDS was compared with the therapeutic use. The term “prophylactic” may create some confusion; however, in most studies, it was used with the meaning of treatment within a time interval preset by researchers, usually in the resuscitation room.

The logic of prophylactic use is based on the better distribution of surfactant, when administered before the first breath and on reduced lung injury, resulting in less alveolar edema and less inactivation by proteins.

The logic of therapeutic use is based exclusively on the treatment of newborns who evolved into RDS and developed possible unnecessary complications.

Other studies comparing prophylactic and therapeutic use were reviewed in a meta-analysis that has been updated recently. All the studies used natural surfactants.

### Table 1 - Main surfactants available for clinical and experimental use

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Preparation</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfacten</td>
<td>Surfactant-TA</td>
<td>Bovine lung extract plus DPPC, tripalmitoylglycerol and palmitic acid</td>
<td>Tokyo Tanabe (Japan)</td>
</tr>
<tr>
<td>Survanta</td>
<td>Beractant</td>
<td>Bovine lung extract plus DPPC, tripalmitoylglycerol and palmitic acid</td>
<td>Ross Products Division of Abott Laboratories (USA)</td>
</tr>
<tr>
<td>Curosurf</td>
<td>Poractant</td>
<td>Pig lung submitted to extraction with chloroform-methanol; purified by liquid-gel chromatography</td>
<td>Chiesi Pharmaceuticals (Italy)</td>
</tr>
<tr>
<td>Infasurf</td>
<td>Calf lung surfactant extract</td>
<td>Extract of calf lung fluid submitted to extraction with chloroform-methanol</td>
<td>Forrest Laboratories (USA)</td>
</tr>
<tr>
<td>BLES</td>
<td>Bovine lipid extract surfactant</td>
<td>Extract of cow lung fluid submitted to extraction with chloroform-methanol</td>
<td>BLES Biochemical (Canada)</td>
</tr>
<tr>
<td>Alveofact</td>
<td>SF-RI 1</td>
<td>Extract of cow lung fluid submitted to extraction with chloroform-methanol</td>
<td>Boehringer Inglheim (Germany)</td>
</tr>
<tr>
<td>Exosurf</td>
<td>Colfosceril plamitate, hexadecanol, tyloxapol</td>
<td>DPPC with 9% of hexadecanol and 6% of tyloxapol</td>
<td>Burroughs-Wellcome Co. (USA and England)</td>
</tr>
<tr>
<td>Pneumactant*</td>
<td>Artificial Lung Expanded Compound (ALEC)</td>
<td>DPPC and PG at 7:3 ratio</td>
<td>Britannia Pharmaceuticals (England)</td>
</tr>
<tr>
<td>Surfaxin</td>
<td>Lucinactant</td>
<td>Chemically synthesized peptide combined with phospholipids and palmitic acid</td>
<td>Discovery Laboratories (EUA)</td>
</tr>
<tr>
<td>Venticute</td>
<td>rSP-C Surfactant</td>
<td>Recombinant SP-C combined with phospholipids and palmitic acid</td>
<td>Byk Gulden (Germany)</td>
</tr>
</tbody>
</table>

DPPC = dipalmitoylphosphatidylcholine, PG = phosphatidylglycerol, SP-C = Surfactant protein C, rSP-C = recombinant surfactant protein C
This meta-analysis showed a reduction in the risk of pneumothorax, interstitial emphysema, mortality, bronchopulmonary dysplasia or mortality associated with the prophylactic treatment. The study suggests that for every 100 newborns prophylactically treated, there will be a reduction of pneumothorax in two newborns and five deaths. On the other hand, the possible attenuating role of the prenatal use of corticoids in the results was not clarified.

Also, early treatment (within the first two hours of life) or late treatment (after the second hour of life) of RDS has been studied as well. A meta-analysis including four studies (two with synthetic surfactant and two with natural surfactant) showed a reduction in the risk of pneumothorax, interstitial emphysema, prenatal mortality, chronic pulmonary disease and death at 36 weeks’ corrected gestational age. With treatment within the first two hours of life, there is a tendency towards the reduction in the risk of bronchopulmonary dysplasia or death after 28 days of life.\(^6\)

The analysis of the results of two approaches showed the advantages of prophylactic or therapeutic treatment up to the second hour of life. It is therefore evident that the earlier the treatment, the better the results.

A sensible therapeutic proposal is the treatment of the cases with established diagnosis of RDS, as soon as possible, preferably within the first two hours of life.

Studies comparing prophylactic and therapeutic use within the first two hours may help to clarify the approach at the time of treatment.

**Dose and administration technique**

Given the fact that the alveolar pool of surfactant in newborns with RDS does not differ remarkably from the alveolar pool in adults without respiratory disorder,\(^19\) showing the crucial role of the “quality of the surfactant” (protein contents), of the pulmonary structural immaturity of newborns and the inactivation of protein release into the alveolar lumen, which occurs in the premature lung immediately after birth,\(^33\) the need to determine the adequate dose of exogenous surfactant is clear if the situation is to be reverted or minimized in premature lungs.

One of the first studies to address this issue was carried out by Ikegami et al, in 1980 (34). By using premature lambs with natural sheep surfactant (containing SP-A, SP-B, SP-C and SP-D) in doses ranging from 19, 53, 64 to 173 mg/kg and by means of an *in vitro* analysis by determination of the surface tension of the surfactant, using a Wilhelmy scales, the authors observed that the dose of 64mg/kg of surfactant produced worse results if compared to a higher dose.

These results are in agreement with the proposal made by Clements and King, who suggest that the theoretical amount of surfactant necessary to cover the alveolar surface would be 1mg (by mass) per gram of lung, which would correspond approximately to a dose of surfactant of at least 36.4 mg (total lipids) per kilo or 40mg of surfactant/kg.\(^35\)

Most clinical studies used the dose of 100mg/kg, except for the studies with Curosurf\textsuperscript{TM} (surfactant obtained through pig’s lung extract), in which the dose consisted of 200 mg/kg and most part of studies with human surfactant used the dose of 60mg/kg.

Fujiwara, compared the dose of 120mg/kg with the dose of 60mg/kg, and found better results (less need for ventilatory support and reduction in the incidence of intracranial hemorrhage and of bronchopulmonary dysplasia) with the dose of 120mg/kg.\(^36\)

It is reasonable to suppose that the initial dose of 100mg/kg (which was empirically used in the initial phase) may be held as adequate for most clinical situations, based on the technical considerations regarding the minimum amount of surfactant necessary to line the alveolar surface, along with studies that compare different doses of surfactant, and given the currently available information that the inactivation of the alveolar surfactant (even in adequate amounts of surfactant) is a highly dose-dependent phenomenon. An exception would be the situation in which inhibition of the exogenous surfactant function is expected (late treatment, where alveolar edema is already present and is intense, SAM, pulmonary hemorrhage, etc.). In view of the dose-dependent effect of inactivation, the initial dose of 200mg/kg may be more appropriate.

A second approach would be to use multiple doses of surfactant, in relation to treatment with a single dose, with the aim of reverting inactivation.

In this sense, a meta-analysis including the results of two studies that compared single dose with multiple doses of natural surfactant (100mg/kg) showed that the latter approach resulted in improved oxygenation with less need for mechanical ventilation, a reduction in the incidence of pneumothorax and a tendency towards reduced mortality.\(^7\)

The author did not observe an increase in the incidence of complications associated with the use of surfactant in multiple doses.

In general, considering the metabolic cycle within pneumocyte type II, especially if an initial lung injury is avoided, it is not necessary to apply more than one dose of surfactant.

**Administration technique**

Several administration techniques have been used, yielding different results.

The use of nebulized surfactant was put aside after several attempts, since even using ultrasonic nebulization, the amount of surfactant that reaches the alveoli is quite low; about 7.6% of the dose of surfactant reaches the lungs.\(^32\) However, this approach allows a more homogenous distribution than conventional instillation. The efficiency of nebulization is directly correlated with compliance and the rate of ventilatory efficiency after the treatment. This inefficiency of the technique is probably related to the
particle size created by the nebulizer, loss of surfactant to the circuit, and location of the nebulizer in the ventilator circuit.

The use of the bolus administration technique was based on experimental studies, where it proved efficient. Instillation right after birth and prior to the first breath results in a uniform distribution of the surfactant, with excellent clinical response, while the administration after a short period of ventilation results in a less uniform distribution. On the other hand, due to the obvious interference of the treatment at birth with resuscitation maneuvers, the treatment should be implemented after stabilization of the newborn, preferably at the neonatal ICU.

Newborns treated with stable thorax in the horizontal position have a comparable distribution of surfactant in both lungs, with no difference in efficacy when the administration technique in two or four aliquots is compared with positioning maneuvers of the chest.

It is recommendable that the administration be made in a single aliquot with the stable newborn in the horizontal position, after proper positioning of the tracheal tube. The ventilator circuit should be closed at the time of administration in order to prevent loss of airway pressure, which could cause pulmonary collapse. The use of adapters with side opening or tracheal tube with injector port at the extremity allows the administration of surfactant without the need of opening the ventilator circuit. Larger volumes of surfactant (usually 4 ml/kg of preparations at 25 mg/ml) have a better distribution than that obtained with more concentrate surfactants.

Treatment complications

A series of less important events without major repercussions in the long run may be associated with the bolus administration of surfactant, especially in larger volumes. These events, which include transient cyanosis, increase in PaCO₂, tachycardia, bradycardia, and reflow of surfactant to the ventilator circuit, among others, may be avoided or are corrected easily with the administration of surfactant by qualified personnel. The elevation of FiO₂ 10% above the necessity of the newborn at the moment of treatment, the use of a lateral injector port or a tube with an infusion device, combined with a relatively slow (but not extremely slow) infusion speed with continuous control of oxygen saturation, can avoid or minimize these events, which perhaps should not be named “complications” associated with the use of surfactant.

A major complication with surfactant treatment, although rare, and more severe as it is associated with high morbidity and mortality, is pulmonary hemorrhage.

Several authors have reported an increase in the incidence of pulmonary hemorrhage, both after treatment with synthetic and natural surfactant, of which the latter showed a higher incidence of hemorrhage. The hemorrhage occurs several hours after treatment, and an association between its occurrence and the increase of left-right flow through the ductus arteriosus has been made.

What is still unclear

The role of new surfactants

Although the composition of pulmonary surfactants is quite complex, the major elements in charge of their function can be summarized in four components: phosphatidylcholine (the key element in surface tension), phosphatidylylglycerol, and fat-soluble proteins SP-B and SP-C. The latter two have specific functions in the surfactant, and their absence causes considerable function loss, indicating that they should be present in the end product. Both proteins are found in commercial surfactants obtained by lipid extraction from mammalian lungs, although in lower amounts than that found in the natural surfactant.

Given the crucial importance that these proteins have to the function of the pulmonary surfactant, new products have been developed, although they are not commercially available, with the aim of developing surfactant proteins synthetically without the need for animal extraction. A concern regarding the use of natural SP-C is with its purity level and its tendency towards aggregation at the moment of extraction.

A surfactant based on a recombinant form of modified human SP-C (rSP-C) has been recently developed and tested (Venticute™, BYK Gulden Kenstanz, Germany). Human SP-C consists of dipalmitoyl cystine in positions 4 and 5, which in the rSP-C molecule were replaced with phenylalanine. This change in the molecular structure did not interfere with the final function assessed in vivo. In a premature animal model, the function of this new surfactant was similar to the natural sheep surfactant (which contains SP-B and SP-C) in the dose of 100 mg/kg, assessed by respiratory mechanical parameters (necessary ventilatory pressure to obtain a tidal volume of 6 to 8 ml/kg, dynamic compliance and functional residual capacity), and gas analysis.

The new surfactant was very effective in two well-established models of pulmonary immaturity, namely rabbits and premature lambs. The pulmonary function in premature lambs after treatment with SP-C or sheep surfactant was equivalent, except for a slight difference in oxygenation. In premature rabbits the response to treatment with both surfactants was similar, when the animals were ventilated with positive end-expiratory pressure (PEEP) of 3 cm/H₂O.

Also using animal models, it has been observed that both dexamethasone and phosphodiesterase inhibitors maximize surfactant action with rSP-C, and that their
use in a hypersensitive animal model did not result in increased risk for anaphylaxis.59

Recently, adults with ARDS have been treated with rSP-C and have shown improved gas exchange, less necessity for ventilatory support and better survival rates.50

Phase III clinical studies, including adults with ARDS, are being carried out.

Another synthetic surfactant recently developed is KL-4 (Surfaxin™, Discovery Laboratories, Daylestown, United States), which contains a 21-unit peptide (KLLLLKKLLLLKKLLK, where K = lysine and L = leucine) that emulates the properties of SP-B, and phospholipids (phosphatidylcholine and phosphatidylglycerol). This new surfactant showed to be efficient in improving gas exchange in experimental models51 and in newborns with RDS treated up to four hours after birth.52

Further randomized, phase III studies are necessary before the regular clinical use of these new surfactants.

Alveolar recruitment and exogenous surfactant treatment

Several recent studies have suggested that alveolar recruitment obtained through the increase in peak inspiratory pressure (PIP) during surfactant administration improves the results of the treatment.53-55

Considering that a preterm newborn with surfactant deficiency has a tendency towards repetitive collapse and reexpansion of alveoli with a reduction of functional residual capacity, recruitment maneuvers before surfactant instillation allow the aeration of the collapsed and reexpanded parts of the lung, resulting in better distribution and better results with the administered surfactant.

In rabbits with surfactant deficiency, caused by bronchoalveolar lavage, submitted to mechanical ventilation with PEEP = 1 cmH2 O, the increase in inspiratory pressure by 8 to 9 cmH2 O two minutes before and maintained up to four minutes after treatment, resulted in improvement of functional residual capacity, tidal volume, dynamic compliance and gasometric parameters.53

On the other hand, by using a higher PEEP (3 cmH2 O), recruitment maneuvers did not produce a better performance in terms of respiratory or gasometric mechanics.

By also using an experimental model with surfactant deficiency caused by pulmonary lavage, recruitment maneuvers resulted in a more homogeneous distribution of surfactant with improvement of alveolar ventilation and oxygenation.55

On the other hand, it has been well established that the use of higher expiratory pressure at the moment of surfactant treatment brings, at least theoretically, a better alveolar recruitment, improving pulmonary function and maintaining the surfactant in its active form, when compared to the absence or low levels of PEEP.56,57 It has also been established that the use of elevated tidal volumes causes greater conversion of surfactant to inactive forms22 and increased lung injury, which could predispose the premature lung to bronchopulmonary dysplasia.

Finally, in the physiopathology of RDS, hypoventilated areas might not necessarily present atelectasis, but might be filled with fluid and proteins, which would cancel out the effect of recruitment maneuvers.

This way, at present, it is not possible to recommend alveolar recruitment strategies based on the increase of tidal volume secondary to elevated peaks of inspiratory pressure, because of the unwanted long-term effects secondary to a possible lung injury induced by this type of strategy, which would counteract any positive effect of surfactant distribution with immediate improvement of oxygenation and of respiratory mechanics.

It is also important to underscore that the moderate pulmonary recruitment obtained through the use of PEEP above physiological levels may improve the distribution and the response of surfactant treatment.

Use of surfactant in other diseases than RDS

Meconium aspiration syndrome (MAS)

Meconium is an inhibitor of the pulmonary surfactant activity. Aside from its obstructive and inflammatory characteristics, meconium causes an increase in surface tension that results in repeated collapse and reexpansion of alveoli with deterioration of pulmonary function. This inhibitory effect of meconium on surfactant function may be reverted by increasing the concentration of surfactant. This is the principle of surfactant treatment in meconium aspiration syndrome.

Sun et al. have assessed pulmonary function in full-term newborn rabbits after meconium aspiration, after treatment with porcine surfactant in the dose of 200 mg/kg, and observed improvement of dynamic compliance and better pulmonary aeration in the treated group.58 In a subsequent study, the same author compared the effects of early or late administration of exogenous surfactant (ES), and found improvement of gas exchange, lung compliance, alveolar expansion and reduced lung injury in treated animals, regardless of the time of ES administration. The author also observed reduced necessity for oxygenation and mean airway pressure, less formation of hyaline membranes, less intra-alveolar edema and less neutrophil inflow into intra-alveolar spaces.

There are few controlled studies that assess the use of ES in the treatment of MAS; in addition, the existing studies were carried out with a small number of patients and have conflicting results. Halliday treated 54 newborns with MAS...
with porcine surfactant and observed a slight improvement in oxygenation: 44 % of newborns did not have any improvement, 20 % had pneumothorax and 19 % died. Among survivors, 18% developed chronic lung disease. Lotze et al., in a multicenter study, assessed the use of bovine surfactant in a population of 328 full-term newborns with severe respiratory insufficiency, of which 21% had MAS. No difference was observed as to mortality, days of oxygen supplementation, length of mechanical ventilation or length of hospital stay, when compared to treated and untreated groups.

Only one controlled and randomized study was conducted to assess the use of ES in the treatment of MAS. Twenty newborns with MAS were treated with continually infused ES for 20 minutes. A significant improvement in oxygenation occurred after six to 12 hours, especially after additional surfactant doses. The author recommends further clinical studies before the routine use of ES for the treatment of MAS.

Pneumonia

Extensive pneumonia may lead to surfactant dysfunction by an inhibitory process secondary to extensive inflammatory process and edema that occurs along with the underlying process, or by abnormal phospholipid and protein fractions that have been described, associated with a variety of pathogens, including bacteria, viruses and fungi.

Reports of treatment of pneumonia with surfactant in humans are rare and controlled studies are not available. In preterm newborns with respiratory failure secondary to pneumonia, the surfactant proved to be safe, with improvement of hypoxemia in adults. Similarly, newborns infected by Streptococcus group B and treated with exogenous surfactant showed improvement in oxygenation one hour after treatment.

The immunogenicity and modulator activity of exogenous surfactants also needs to be further investigated before their routine use in severe pneumonia is allowed.

Congenital diaphragmatic hernia

There is some evidence regarding animal and human experiments that suggest improved pulmonary function and oxygenation with the use of exogenous surfactant in cases of congenital diaphragmatic hernia, with better survival rates. However, the lack of randomized, controlled studies with a larger number of patients does not allow us to affirm that the beneficial effects in the short run mean improvement of mortality or morbidity rates in the long run. This is mainly important if we take into consideration that congenital diaphragmatic hernia is a disease that maintains high mortality rates despite extreme interventions, such as nitric oxide therapy and extracorporeal membrane oxygenation.

Bronchiolitis

Bronchiolitis affects children younger than two years of age and those outside the neonatal period. It is an infection chiefly caused by the respiratory syncytial virus. The typical histopathological finding is injury to terminal alveoli and bronchioli, involving the alveolocapillary membrane and pneumocytes, with obstructive lesion on the small airways.

Lesion on pneumocytes type II causes a qualitative surfactant dysfunction that contributes to alveolar collapse and increased capillary permeability, deteriorating surfactant dysfunction by inactivation.

Surfactant treatment was proposed because of its stabilizing action on terminal bronchioli and alveoli and improvement of gas exchange. In a randomized study, the use of Curosurf™ showed improved oxygenation, reduction in the length of mechanical ventilation and reduction in the length of stay in the ICU.

Acute respiratory distress syndrome (ARDS)

In 1996, Anzueto et al. conducted a randomized clinical assay with 725 adult patients with sepsis-induced ARDS to assess the efficacy of aerosolized surfactant. No statistically significant difference was observed as to survival rate 30 days after treatment, length of stay in the ICU, length of mechanical ventilation or physiological outcome (oxygenation).

The article written by Anzueto et al. was commented in an editorial by Matthay. The possible explanations for aerosolized surfactant failure in ARDS are:

- The amount of surfactant that reached the peripheral alveoli was only 5% of the administered dose;
- The synthetic surfactant preparation, Exosurf, does not contain the protein component. Protein-containing surfactants may reduce surface tension more quickly and are more resistant to inhibitors, such as plasma proteins.
- Another possible reason for surfactant therapeutic failure is that, in spite of similarities, ARDS and RDS in infants are fundamentally different. The inflammatory injury caused by ARDS, which often results in fibrotic destruction of the lung, might not improve with surfactant treatment.
- Most patients in Anzueto’s study died of sepsis and multiple organ failure, not of respiratory insufficiency. With surfactant therapy, we could not expect deaths of patients with ARDS to be reduced, due to generalized infection or dysfunction of organs.

Final considerations

Exogenous surfactant therapy is very effective and considerably simplified the treatment of newborns with respiratory distress syndrome. The therapy is effective because it combines correction of quantitative primary...
deficiency of surfactant (the major cause of respiratory failure) with a favorable metabolism. In uninjured lungs, a single dose is sufficient to improve pulmonary function until the newborn is able to synthesize an adequate amount of endogenous surfactant. After the establishment of lung injury, surfactant function deteriorates and the ability of the premature lung to produce surfactant decreases. Although surfactant treatment does not seem to reduce the incidence of bronchopulmonary dysplasia, this finding results in greater survival of newborns, who would surely die without this treatment and who are at a greater risk for bronchopulmonary dysplasia. The interactions between surfactant functions and ventilator variables are important areas where general pulmonary response may be improved. The use of adequate PEEP, low tidal volume, and the avoidance of hyperventilation improve surfactant function and minimize lung injury. Although surfactants obtained from animal lungs are comparable in terms of efficacy, they are costly and nonstandardized. For the future, we should work towards the development of less expensive and more uniformly consistent surfactants.

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