REVIEW ARTICLE

Exogenous surfactant therapy in pediatrics

Norberto A. Freddi,[1] José Oliva Proença Filho,[2] Humberto H. Fiori[3]

Abstract

Objective: To review current knowledge about the use of exogenous surfactants in the treatment of different lung diseases causing acute respiratory failure in children.

Sources of data: This review is based on the authors' experience and on recent data retrieved from ONIA, Mdconsult, Medline and the Cochrane Database Library.

Summary of the findings: In spite of the success of the use of exogenous surfactants in Respiratory Distress Syndrome (RDS) of the newborn, some questions remain unanswered, such as the optimal administration timing - either very early (prophylactic), based on gestational age or on quick tests of lung maturity, or later, when the clinical picture becomes unequivocal. In other severe diseases requiring ventilatory support, the use of surfactants is still controversial, and data in the literature are limited and conflicting. However, successful use in several other diseases has been reported. Recent studies have focused on surfactant inactivation by substances that can be found in the airways. New surfactants with the addition of substances to control inhibition, such as polyethyleneglycol, are being tested for diseases in which inactivation seems to be a significant factor.

Conclusions: Therapy with exogenous surfactants, even as a treatment for RDS, has not been thoroughly investigated. Further studies should be conducted to improve surfactants - mainly their resistance to inhibition - and the treatment of diseases other than RDS.

J Pediatr (Rio J) 2003;79 (Suppl 2):S205-S12: Exogenous surfactant, respiratory failure, intensive care, respiratory distress syndrome.

Introduction

Pulmonary surfactant is a fundamental substance in the mechanics of the pulmonary system. It is found in all species that breathe through lungs and, when absent, the fluid found between alveoli and air increases surface tension, which exerts a collapsing force over the alveoli. Surfactant creates an interface between water molecules and the alveolar surface, reduces surface tension so that it approaches zero at the end of expiration when the alveolar surface is reduced, and, thus, avoids atelectasis.

In 1959, surfactant deficiency was shown to cause hyaline membrane disease, also called respiratory distress syndrome (RDS) of the newborn.[1] Many attempts, unsuccessful at first, were made to produce exogenous surfactants capable of replacing the endogenous production.

1. Coordinator of the PICU, Hospital Santa Catarina, São Paulo, SP, Brazil.
2. Coordinator of the PICU, Hospital e Maternidade Brasil, São Paulo, SP, Brazil.
3. Assistant professor, Department of Pediatrics, Pontifícia Universidade Católica do Rio Grande do Sul. PICU, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul.

In 1972, Enhorning and Robertson started working with surfactant extracts collected from adult rabbits and administered to premature rabbit offspring. They demonstrated that surfactant improved the pulmonary mechanical behavior of those animals.[2,3]

After Fujiwara et al.[4] published the first promising results of surfactant replacement in RDS, this therapy has become a routine practice in premature newborn units, and has completely changed the natural history of this syndrome. Concurrently, great interest was directed to a number of other potential uses of this therapy for other syndromes and diseases associated with surfactant dysfunction.

During the 1980s, several studies confirmed the efficacy of both natural and synthetic surfactants in the treatment and prevention of RDS.[5-12] The main case-control studies investigating the prophylactic or therapeutic use of surfactants were reviewed in two meta-analyses.[13,14] They summarized the evident beneficial effects of surfactant therapy on the natural clinical outcome of RDS. The most remarkable effects were a reduction in mortality and in the occurrence of pneumothorax and interstitial pulmonary emphysema.

Several commercial preparations became available for clinical use in the beginning of the 1990s. Administration of surfactant in RDS has become one of the main interventions conducted in neonatal units.

In the RDS of the newborn (NB), impairment of the surfactant system is primarily caused by lack of endogenous production due to lung immaturity. However, in other respiratory pathologies found in preterm or term newborns, as well as in older children and adults, there may be a reduction in surfactant function primarily caused by the presence of several inhibiting substances in the terminal airways. This reduction in surfactant function contributes to the respiratory failure associated with the primary disease. Several studies with experimental models or human subjects have attempted to define the role of exogenous surfactant therapy in these conditions, particularly in severe viral bronchiolitis, meconium aspiration syndrome, bronchopneumonia, and acute respiratory distress syndrome (ARDS). In spite of these attempts, precise indications, real benefits, costs and administration modes are still poorly defined.

Use of surfactant in the newborn

The indication of surfactant therapy is unquestionable when there is a diagnosis of hyaline membrane disease, or RDS of the newborn.[13,14] In such cases, the difficulty lies in identifying the patients that will require this therapy so that its use can be initiated as early as possible.

The drug is usually administered in one 100mg/kg dose, although a few studies recommend a different dosage. The administration of an initial 200mg/kg dose - the estimated pool of endogenous surfactant in the NB - of porcine surfactant (Curosurf®) has been the object of studies, and results have shown some positive effects in comparison with the usual dosage.[15] Additional 100 mg/kg doses may be administered if necessary.

The response to surfactant therapy may be affected (reduced) because of other associated pathologies (persistent pulmonary hypertension, pulmonary edema, meconium aspiration, etc.), surfactant distribution, surfactant composition, management of mechanical ventilation, or the moment when the therapy is administered. This last variable has been the focus of the most important randomized trials that have been conducted since 1992.

Surfactant therapy is generally indicated for preterm newborns with an established diagnosis of RDS (therapeutic use), or for patients at a very high risk of developing this syndrome (prophylactic use). The therapeutic use of surfactant presupposes a previous RDS diagnosis. The diagnosis is made, in practical terms, by identification of clinical signs, progression of the disease, and radiographic findings compatible with the syndrome. As atelectasis is progressive in this syndrome, it often takes some time for the diagnosis to be clearly defined. Radiographic signs often become evident only when the syndrome has already advanced significantly. Surfactant is, thus, only administered when the clinical diagnosis is made.

The main advantage of the therapeutic approach is that practically only newborns that actually require surfactant are treated. However, when criteria to establish a diagnosis are less stringent, more incorrect diagnoses are made and, therefore, more unnecessary treatments are administered. This is the treatment mode most frequently used for near-term newborns, for whom the risk of lung immaturity and death are lower.

The other surfactant administration mode is prophylactic. This mode was suggested by experimental trials with animals that revealed that immature, surfactant-deficient lungs acquired very early pulmonary lesions secondary to ventilation.[16] Moreover, surfactant has been shown to distribute more evenly when instilled in the airways right after birth, when the lungs are still full of fluid.[17]

Prophylaxis has been used right after birth, before the first ventilation or initial stabilization, and only minutes after birth. If the purpose is to avoid lesions caused by surfactant deficiency in newborns with lung immaturity, medication should ideally be administered even before the first inspiration. However, it has been suggested that immediate prophylaxis is not evidently more beneficial than prophylaxis within 30 minutes of birth.[18] Another problem associated with the immediate use of surfactant, that is, before the first inspiration, is that this procedure may complicate the initial stabilization of the patient.

The high incidence of surfactant deficiency in very immature newborns - less than 30 weeks' gestational age at birth, for example - seems to justify a prophylactic approach to surfactant use. When this preventive mode of

administration is adopted, however, many patients are unnecessarily treated and submitted to an invasive, expensive procedure that has potential risks and undoubtedly causes some discomfort.

Several multi-center randomized clinical trials have compared the prophylactic and therapeutic approaches.[19-25] In these studies, newborns less than 30 weeks' gestational age at birth (6 studies) or less than 32 weeks (1 study) were randomly chosen to receive either a prophylactic dose of surfactant or surfactant therapy after a diagnosis was established.

Most of these studies reported improvement in respiratory function and reduction in the incidence of RDS when the prophylactic approach was adopted. A meta-analysis conducted by Sol and Morley showed a reduction in the incidence of pneumothorax, pulmonary interstitial emphysema, mortality, and the combination of death and bronchopulmonary dysplasia; no complications were reported with the use of prophylactic therapy.[26] Such strong evidence suggests that, of these two therapeutic approaches, prophylaxis with surfactant is indicated for preterm newborns less than 30 weeks' gestational age at birth (some other researchers suggest 28 weeks). Patients that need intubation and mechanical ventilation immediately after birth are probably the ones that benefit the most from this procedure. In cases of surfactant deficiency, there is evidence of lesions secondary to positive pressure ventilation after only a few minutes.[27] Waiting longer and delaying surfactant administration seems to be an inappropriate choice. However, it is unclear whether patients that are born well, with effective natural ventilation, even if at less than 30 weeks' gestational age, should receive the same treatment. The prophylactic medication for preterm newborns without early signs of severe disease, and for whom there is a significant lower incidence of RDS, may not bring significant benefits. No clinical studies have used any criterion other than gestational age to investigate prophylactic treatment.

However, prophylaxis, or very early treatment, with exogenous surfactant should ideally be administered upon confirmation of surfactant deficiency. The chance of obtaining an accurate diagnosis, available either before or right after birth, should benefit patients at risk of developing RDS. However, 100% accurate tests for this purpose are not available. A logical approach for preterms born at 30 or 32 weeks' gestational age would be the use of a test with a close to 100% sensitivity, so that no, or practically no, patient that would eventually develop RDS would fail to receive surfactant as early as possible. If such test had a good specificity, it would significantly reduce the number of patients iatrogenically treated with surfactant.

The therapeutic approach in a group of patients with high prevalence of the disease does not make any sense if no test is available to identify RDS accurately right after birth. Perhaps the only justifiable reason for a therapeutic approach in patients born at less than 30 weeks' gestational age would be cost reduction. Such cost reduction would be less significant if the decision to adopt this approach were based on test results.

The analysis of these concepts has given rise to renewed interest in older rapid tests to determine surfactant function by means of examination of the amniotic fluid and the newborn's tracheal or gastric aspirates.[28] Of these tests, the stable microbubble test (SMT) seems to be the most promising as its sensitivity and specificity are good.[29,30] Its performance takes less than 10 minutes, and the basic equipment required is a common microscope and a slide graduated in millimeters.

Besides SMT, another test, the lamellar body count, has been evaluated. Lamellar bodies are corpuscles containing endogenous surfactant. The purpose of this test is the same - to take only a few minutes to screen patients for very early use of surfactant. This test can be performed in blood cell analyzers available in clinical laboratories. A meta-analysis study has shown that this test results are similar or even better than results of tests that measure the lecithin/sphyngomyelin ratio.[31]

It is likely that SMT and/or lamellar body counts will soon become widely used in delivery rooms and/or neonatal intensive care units to help decide about the use of exogenous surfactant.

While the efficacy of exogenous surfactant is well established in the treatment of RDS of the newborn, the role of this therapy is still unclear in other diseases or syndromes in which surfactant function is impaired.

The evaluation of therapy results in the NB is complicated because the differential diagnosis of pulmonary disease may be difficult to establish in some situations. Quantitative surfactant deficiency may accompany and even be part of the pathophysiology of some clinical entities that are not routinely associated with surfactant deficiency. An example of such a situation is the case of respiratory problems in term or near-term newborns with a clinical and radiological diagnosis of transient tachypnea of the newborn (TTN) or meconium aspiration syndrome (MAS). Low levels of phosphatidylglycerol have been found in tracheal aspirates[32,33] and in amniotic fluid[34] in TTN, and low surfactant protein levels in MAS.[35] Therefore, it may be difficult to know whether a positive response to surfactant therapy is due to resolution of inhibition, by quantitative replacement for the syndrome under treatment, or to an associated RDS that cannot be easily ruled out.

Surfactant use has been investigated for use in MAS, one of the main clinical syndromes of the newborn. Meconium is a potent surfactant inhibitor. Therefore, it is logical to consider surfactant replacement in severe MAS.

Sun et al.[36] treated term newborn rabbits with exogenous porcine surfactant (200 mm/kg) after induced meconium aspiration, and reported improved oxygenation and lung

compliance. There was a decrease in the mean airway pressure necessary for adequate oxygenation.

Lotze[37] conducted a multicenter study with a population of 328 term newborns (who have MAS more often than preterms) with severe respiratory failure. The pathology described was compatible with MAS in a high percentage of the patients, and no reduction in complications was observed after surfactant treatment, although the percentage of patients that needed extracorporeal membrane oxygenation (ECMO) was lower.

Some non-randomized studies have shown a slight improvement in oxygenation for most newborns with respiratory failure due to meconium aspiration who were treated with surfactant.[38,39] Findlay et al.[40] conducted a randomized study and reported better oxygenation, lower incidence of pneumothorax, faster control of persistent lung hypertension, and less need of ECMO in newborns that received up to four 15-mg/kg doses of surfactant administered in about 20 minutes every 6 hours.

A meta-analysis conducted by Soll and Dargaville revealed that surfactant administration reduces the need of ECMO for newborns with MAS and moderate to severe respiratory failure.[41]

Lung lavage with diluted surfactants is another form, still experimental, of use of this medication. This technique seems to be more efficient in increasing the removal of substances such as meconium than pure saline solution, and to reduce the effect of surfactant removal from the lungs caused by saline solution. This therapeutic mode has been studied in animal models of meconium aspiration syndrome[42] and acute respiratory distress syndrome,[43] and its effects seem to be positive. Lam and Yeung published results of a preliminary study that revealed a significant improvement in the lung function of six newborns with severe MAS treated with tracheobronchial lavage with 15 ml/kg diluted surfactant (5mg/100 ml saline solution) administered in 2 ml aliquots.[44] Wiswell et al.[45] have more recently published results of a multicenter randomized study with 15 newborns with severe MAS treated with artificial surfactant bronchoalveolar lavage, and 7 control patients treated according to standard care. They reported positive trends, though not statistically significant, for treated newborns to be weaned from mechanical ventilation earlier and to have better oxygenation indices.

These results demonstrate a clear need for further studies to accurately define indications and adequate administration modes of surfactant in newborns with severe meconium aspiration. New surfactants with protein preservation or the addition of molecules that may block or minimize surfactant-inhibiting activity may determine a significant improvement in the prognosis of severe MAS.

Pneumonia and sepsis affect surfactant function in different ways - the damage to the alveolocapillary barrier permits the flooding of the alveoli with plasma proteins and other blood products that are well-known inhibitors of

surfactant activity.[46] Lesions to type II cells impair the production and secretion of surfactant, and phospholipases secreted by bacteria are also capable of inhibiting the reduction in surface tension.[47]

Clinical experience in using exogenous surfactants in pneumonia of the newborn is still limited. Many times the patients are premature, and RDS may also be present. The radiographic patterns for *Streptococcus agalactie* pneumonia may be very similar to those for RDS. Some studies with a small number of patients have shown an improvement in oxygenation,[48] and a reduction in airway mean pressure and in the need for oxygenation in treated newborns.[49] More recently, the role of surfactant proteins A and D, which are not found in surfactants commercially available, has become evident in the defense against infection. The addition of these proteins to exogenous surfactants, as well as their use to carry specific antibodies into the lungs, may well become an important advancement in the treatment of neonatal pneumonia in the near future.

Surfactant therapy has also been studied for other neonatal clinical entities, such as pulmonary hypoplasia and diaphragmatic hernia. Some positive, though transient, effects have been reported. Further studies should be conducted for an objective evaluation of this therapy in these cases.

Summing up, surfactant therapy of the newborn for conditions other than RDS is still controversial, and questions about its use even in RDS remain to be answered. It is important, moreover, to point out that RDS also occurs in patients born at 37 or 38 weeks' gestational age. Therefore, the fact that the patient was a term newborn does not rule out this diagnosis.

Surfactant therapy should, thus, be considered for newborns with severe respiratory failure on the first days of life even if the diagnosis is not RDS. Clinical results are many times surprising. One of the main problems for the indication of surfactant therapy in these cases is the cost of the medication, but it should be kept in mind that other expensive therapies, such as nitric oxide, might be avoided if surfactant is used. Moreover, surfactant therapy is generally very safe.

Use of surfactant after the neonatal period

Changes in the surfactant system can be observed in pediatric as well as adult patients in several situations. Inhibition is the most common cause of these changes, but a decrease in production may also occur in certain situations. One of the greatest difficulties in the study of potential indications of surfactant therapy is the high cost of this medication. Such costs are directly proportional to the patient's weight.

Positive clinical responses have been reported for patients with respiratory failure due to different etiologies at times other than the neonatal period. However, the experience in

using surfactant in such situations is still limited. The expectation remains that new products, more resistant to inhibition, may be developed in the coming years, and bring about better results.

Severe viral bronchiolitis

Severe viral bronchiolitis is the most frequent lung infection in infants, and is caused by the respiratory syncytial virus in 70-80% of the cases.

Clinical progression is usually benign, but this disease may lead to hospitalization in some special situations. A number of patients will develop severe acute respiratory failure, have to be hospitalized in pediatric intensive care units, and require invasive ventilation. Patients more susceptible to severe clinical conditions are those that have bronchopulmonary dysplasia.

Lesions of the type II pneumocyte lead to a qualitative surfactant dysfunction, which contributes to alveolar collapse and an increase in capillary permeability, thus further impairing, by inactivation, surfactant functional activity.[50,51]

Surfactant therapy in this disease has been proposed because of its potential to stabilize terminal bronchioles and alveoli and to improve gas exchanges.

Lucchetti et al.[52] conducted a randomized study with infants with acute viral bronchiolitis, and showed an improvement in oxygenation, decrease in $PaCO_2$ and in ventilator parameters, and a reduction in length of time of invasive ventilation support and hospitalization.

Vitola et al.[53] have described the use of surfactant in a patient with severe acute viral bronchiolitis who needed high ventilation parameters to keep a PaO_2 of 60-80 mmHg. The use of surfactant (Exosurf Glaxo – 50 mmHg) was followed by an improvement in ventilation and a reduction in the parameters used for that patient.

Data in the literature are scarce but promising in terms of the use of surfactants for severe bronchiolitis as an adjuvant therapy, particularly in chronic pneumopathy, such as in patients with bronchopulmonary dysplasia.

Bronchopneumonia

The pathogenic activity of viruses, bacteria and fungi may cause abnormalities in the different fractions - proteins and phospholipids - that compose surfactant. Also, a reduction in surfactant production may be observed in the presence of inflammation and intense edema of the lower airways.

Improvement in hypoxemia in adults has been reported,[54] as well as in newborns with severe pulmonary conditions caused by group B Streptococci.[55] Data are still not enough to justify any indication of surfactant therapy in this disease.

Acute Respiratory Distress Syndrome (ARDS)

Ranieri and Slutsky have provided classical descriptions of lesions caused by mechanical ventilation, such as the increase in epithelial and endothelial pulmonary permeability and the consequent change in surfactant production.

Several studies with bronchoalveolar lavage have demonstrated quantitative changes in alveolar surfactant in ARDS. Plasma proteins that migrate into the alveoli also inactivate surfactant. Surfactant will thus undergo inhibition or change its optimal structural composition - changes in phospholipids or proteins - due to the action of inflammatory mediators that are knowingly present in ARDS. Surfactant will be incorporated into the hyaline membrane, and there will be changes in the synthesis and release of surfactant due to lesions in type II pneumocytes.

In 1996, Anzueto et al.[56] published a randomized controlled study with 725 patients with ARDS who were administered aerosolized surfactant. They reported no improvement in gas exchanges (oxygenation) or in survival. The aerosolized form of surfactant administration adopted in their study was criticized because only 5% of the administered dose reaches the alveoli in this administration form.

Lopez-Herce, in 1999,[57] published results of a study with 20 children (13 with ARDS and 7 with cardiopathy) and reported a significant improvement in the PaO_2/FiO_2 ratio in the oxygenation index after surfactant use in 10 of the 13 patients with ARDS. The same effect was not observed for patients with cardiopathies. Those authors discussed the possible beneficial effects of early use and of tracheal instillation of the medication.

Willson and Zaritsky, in 1999,[58] studied 42 children with ARDS, 21 treated with surfactant and 21 controls. They used one dose of exogenous surfactant and obtained an improvement in the oxygenation and ventilation indices in the group of children treated with surfactant. This group needed ventilation support for 4.2 days less than controls, and were weaned earlier. Mortality rate was 11.9%.

Data in the literature about adult patients favors the use of surfactant as there were fewer patients with negative results.

Commercial Surfactants Available

Several surfactants are offered for clinical use worldwide. Surfactants commercialized in more recent years in Brazil are made from porcine lung extract (Curosurf®), bovine lung extract (Survanta®), bovine lung lavage (Alveofact®), or are synthetic surfactants (Exosurf®). The first three contain surfactant proteins B and C, but proteins A and D are eliminated during the preparation process. The synthetic surfactant contains associated proteins. All are efficient in the treatment of RDS, but natural surfactants have been shown to be more advantageous than synthetic ones. Soll and Blanco conducted an updated review of the efficiency of these two types of surfactants. They concluded that patients treated with natural surfactants have a faster improvement of ventilation parameters, less air escape, and lower

mortality rates.[59] The studies reviewed reported a higher incidence of ventricular hemorrhage, but not when only the most severe hemorrhages were taken into consideration. Those authors suggested that natural surfactants are better than synthetic ones in the treatment of RDS.

Several attempts to improve synthetic surfactants have been made by the addition of surfactant proteins, and a change in results may be seen in a few years. Table 1 shows the characteristics of the most common surfactants found in Brazil.

Administration Technique

Surfactants are administered through an endotracheal tube, which must be adequately positioned. The medication is instilled in one or more aliquots, with the patient in supine position or in different positions, according to recommendations provided by each laboratory. The increase in the number of aliquots may not make much difference,[60] but the recommendations follow protocols that were used for testing each product. However, some commercial surfactants are too diluted, and the administration in one single aliquot may temporarily impair ventilation. Surfactants may be

should be adjusted according to the changes observed immediately after administration.

Administration by means of nebulization has been attempted in some occasions, and has shown to have some beneficial effects in studies with animals. However, no aerosolized administration mode has been shown to be a good alternative for the administration through instillation, although its main benefit would be to avoid tracheal intubation.[61]

Other aspects, such as ventilation techniques and alveolar recruiting, in conjunction with surfactant therapy, may also have an impact in the results of this therapy.

Conclusion

Exogenous surfactant therapy should be further investigated, even for its use in RDS. In current clinical practice, meconium aspiration and respiratory failure are indications for the possible use of exogenous surfactant, especially in the first two days of life. After the first days of life, indications are not as clear.

Surfactants may still be improved, particularly to resist inhibition, and other forms of uses in diseases other than RDS should be developed. This topic seems extremely promising as a research field.

Table 1 -   Characteristics of surfactants currently available in the Brazilian market

Surfactant	Laboratory	Container	Concentration	Recommended dose
Curosurf ®	Farmalab-Chiesi	1.5 and 3 ml	80 mg/ml	100 to 200 mg/kg
Survanta ®	Abbott	8 ml	25 mg/ml	100 mg/kg
Alveofact ®	Boeringer	1.2 ml	40 mg/ml	100 mg/kg
Exosurf ®	Wellcome		13.5 mg/ml(DPPC)	5 ml/kg

administered through a line passed through the endotracheal tube or directly into the endotracheal tube, and there does not seem to be any difference between these two techniques.

Surfactant should be warmed before administration by holding its container between the hands. The endotracheal tube should be disconnected from the respirator, and the instillation should be fast, accomplished in less than 30 seconds; the patient should be immediately reconnected to the respirator. It may also be administered through systems for which there is no possibility of disconnection. Heart beat and transcutaneous saturation should be monitored during the procedure. Aspiration of the endotracheal tube should be avoided in the first six hours after administration. Ventilation parameters and oxygen inspiratory fraction

References

1. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 1959;97:517-23.
2. Enhörning G, Robertson B. Lung expansion in the premature newborn rabbit fetus after tracheal deposition of surfactant. Pediatrics 1972;50:55-66.
3. Robertson B, Enhörning G. The alveolar lining of the premature newborn rabbit after pharyngeal deposition of surfactant. Lab Invest 1974;34:54-9.
4. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980;1:55-9.
5. Greenough A, Morley CJ, Wood S. Effect of artificial surfactant on lung function in preterm neonates. Prog Respir Res 1984;18:263-6.
6. Halliday H, McClure G, Reid MMcD. Controlled trial of artificial surfactant to prevent respiratory distress syndrome. Lancet 1984;1:476-8.

7. Ten Center Study Group. Ten centre trial of artificial surfactant in very premature babies. BMJ 1987;294:991-6.

8. Enhörning G, Shennan A, Possmeyer F. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant. A randomized clinical trial. Pediatrics 1985;76:145-53.

9. Halman M, Merritt TA, Jarvenpaa A, Gluck L. Exogenous human surfactant for treatment of severe respiratory distress syndrome. A randomized prospective clinical trial. J Pediatr 1985;106:963-9.

10. Kwong M, Egan R, Notter R, Shapiro DL. Double-blind clinical trial of calf lung surfactant extract for the prevention of hyaline membrane disease in extremely premature infants. Pediatrics 1985;76:585-92.

11. Shapiro DL, Notter R, Morin FC, Cox C. Double-blind, randomized trial of a calf lung surfactant extract administered at birth to very premature infants for prevention of respiratory distress syndrome. Pediatrics 1985;76:593-9.

12. Wilkinson A, Jenkins P, Jeffrey JA. Two controlled trials of dry artificial surfactant: early effects and later outcome in babies with surfactant deficiency. Lancet 1985;2:287-91.

13. Soll RF. Natural surfactant extract treatment of RDS. In: Sinclair JL. Neonatal module of Cochrane Database of Systematic Reviews. The Cochrane Collaboration: Issue 1. Oxford: Update Software; 1997.

14. Soll RF. Synthetic surfactant treatment of RDS. In Sinclair JL. Neonatal module of Cochrane Database of Systematic Reviews. The Cochrane Collaboration: Issue 1. Oxford: Update software, 1997.

15. Fiori RM, Diniz EMA, Lopez JMA. Surfactant replacement therapy: a multicentric trial comparing two dosage approaches. Acta Biomed Ateneo Parmense 1997;68:55-63.

16. Robertson B. Pathology and pathophysiology of neonatal surfactant deficiency. In: Robertson B. Amsterdam, Elsevier Science Publisher; 1984. p. 384-418.

17. Jobe A, Ikegami M, Glatz T. Duration and characteristics of treatment of premature lambs with natural surfactant. J Clin Invest 1981;67:370-5.

18. Fujiwara T, Robertson B. Pharmacology of exogenous surfactant. In: Robertson B, Van Golde LMG, Batenburg JJ. Pulmonary surfactant from molecular biology to clinical practice. Amsterdam: Elsevier Science Publisher; 1992. p. 561-592.

19. Bevilacqua G, Parmigiani S, Robertson B and the Italian Collaborative Multicentre Study Group. Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomized trial. J Perinat Med 1996;24:1-12.

20. Dunn MS, Shennan AT, Zyack D, Possmayer F. Bovine surfactant replacement therapy in neonates of less than 30 weeks' gestation: a randomized controlled trial of prophylaxis vs treatment. Pediatrics 1991;87:377-86.

21. Egberts J, DeWinter JP, Sedin G, deKleine MJK, Broberger U, VanBel F, et al. Comparison of prophylaxis and rescue treatment with Curosurf in neonates less than 30 weeks gestation: a randomized trial. Pediatrics 1993;92:768-74.

22. Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, et al. Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 weeks' gestation. Pediatrics 1993;92:90-8.

23. Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991;324:865-71.

24. Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK, Jaaskelainen J, et al. Randomized, placebo-controlled trial of human surfactant given at birth vs rescue administration in very low birthweight infants with lung immaturity. J Pediatr 1991;118:581-94.

25. Walti H, Paris-Llado J, Breart G, Couchard M, and the French Collaborative Multicentre Study Group. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: a randomized multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-21.

26. Soll RF, Morley, CJ. Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4. Oxford: Update Software; 1999.

27. Jonson B. Ventilation patterns, surfactant and lung injury. Biol Neonate 1997;71 Suppl 1):13-17.

28. Pattle RE, Robards GJ, Sutherland PD. Method for demonstrating difference between surface properties of sheep and human amniotic fluids, and attempting to predict human respiratory distress syndrome [proceedings]. J Physiol 1976;263:110-1.

29. Chida S, Fujiwara T, Konishi M, Sasaki M. Stable microbubble test for predicting the risk of respiratory distress syndrome: II. Prospective evaluation of the test on amniotic fluid and gastric aspirate. Eur J Pediatr 1993;152:152-6.

30. Fiori HH, Varela I, Fiori RM. Stable microbubble test and click test on gastric aspirates of preterm infants not ventilated at birth to predict respiratory distress syndrome. Biol Neonate 2000; 77(1):21.

31. Wijnberger LDE, Huisjes AJM, Voorbij HAM, Franx A, Bruinse HW, Mol BWJ. The accuracy of lamellar body count and lecithin/sphingomyelin ratio in the prediction of neonatal respiratory distress syndrome: a meta-analysis. Brit J of Obstet Gynaecol 2001;108:583-88.

32. Hallman M, Feldman BH, Kirkpatrick E, Gluck L. Absence of phosphatidylglycerol (PG) in respiratory distress syndrome in the newborn. Study of the minor surfactant phospholipids in newborns. Pediatr Res 1977;11(6):714-20.

33. Bourbon JR, Francoual J, Magny JF, Lindenbaum A, Leluc R, Dehan M. Changes in phospholipid composition of tracheal aspirates from newborns with hyaline membrane disease or transient tachypnoea. Clin Chim Acta. 1990;189:87-94.

34. Gross TL, Sokol RJ, Kwong MS, Wilson M, Kuhnert PM. Transient tachypnea of the newborn: the relationship to preterm delivery and significant neonatal morbidity. Am J Obstet Gynecol 1983;146(3):236-41.

35. Boo NY, Cheong KB, Lye MS, Zulfiqar MA. Usefulness of stable microbubble test of tracheal aspirate for diagnosis of neonatal respiratory distress syndrome. J Paediatr Child Health 1997;33:329-34.

36. Sun B, Cursted T, Song GW, Robertson B. Surfactant improves lung function and morphology in newborn rabbits with meconium aspiration. Biol Neonate 1993;63:96-104.

37. Lotze A, Mitchell BR, Bulas DI, Zola EM. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. J Pediatr 1998;132:40-7.

38. Diniz EMA, Fiori RM. Curosurf therapy in severe meconium aspiration syndrome. Biol Neonate 1995;67 Suppl 1:86.

39. Halliday HL, Speer, Robertson B. Treatment of severe meconium aspiration syndrome with porcine surfactant. Eur. J Pediatr 1996;155:1047.

40. Findlay RD, Taeusch HW, Walter FJ. Surfactant replacement therapy for meconium aspiration syndrome. Pediatrics 1996;97: 48-52.

41. Soll RF, Dargaville P. Surfactant for meconium aspiration syndrome in full term infants Dates (Cochrane Review). Cochrane Database Syst Rev 2000; (2): CD002054 Review first published: Issue 2, 2000.

42. Paranka MS, Walsh WF, Stancombe BB. Surfactant lavage in the piglet model of meconium aspiration syndrome. Pediatr Res 1992;31(6):625-8.

43. Balaraman V, Meister J, Ku TL. Lavage administration of dilute surfactants after acute lung injury in neonatal piglets. Am J Respir Crit Care Med 1998;158:12-7.

44. Lam BC, Yeung CY. Surfactant lavage for meconium aspiration syndrome: a pilot study. Pediatrics 1999;103:1014-18.

45. Wiswell TE, Knight GR, Finner NN, Donn SM, Desai H, Walsh WF, Sekar KC, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. Pediatrics 2002;109(6):1081-7.

46. Holm BA, Enhörning G, Notter RH. A biophysical mechanism by which plasma proteins inhibit lung surfactant activity. Chem Phys Lipids 1988;49:49-55.

47. Holm BA, Keicher L, Liu M. Inhibition of pulmonary surfactant function by phospholipases. J Appl Physiol 1991;71:317-21.

48. Auten RL, Notter RH, Kendig JW. Surfactant treatment of full-term newborns with respiratory failure. Pediatrics 1991;87:101-7.

49. Fetter WPF, Baerts W, Bos AP. Surfactant replacement therapy in neonates with respiratory failure due to bacterial sepsis. Acta Paediatr 1995;84:14-16.

50. Keer MH. Surfactant protein levels in severe respiratory syncytial virus infection. Am J Respir Crit Care Med 1999;159:1115-8.

51. Dargaville PA, South M, McDougall PN. Surfactant abnormalities in infants with severe viral bronchiolitis. Arch Dis Child 1996;75:133-6.

52. Lucchetti M, Casiraghi G, Valsecchi R, Galassini E, Marraro G. Porcine-derived surfactant treatment of severe bronchiolitis. Acta Anaest Scand 1998;42:805-10.

53. Vitola LS, Piva JP, Garcia PCR, Bruno F, Miranda AP, Martha VF. Surfactante exógeno no tratamento da bronquiolite viral grave. J Pediatr (Rio J) 2001;77:143-7.

54. Mikawa K, Maekawa N. Selective intrabronchial instillation of surfactant in a patient with pneumonia: a preliminary report. Eur Respir J 1993;6:1563-6.

55. Herting E, Gefeller O, Robertson B, Land M, van Sorenden L, Harms K. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Pediatrics 2000; 106(3):957-64.

56. Anzueto A, Bauglman RP, Guntupallli KK. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. N Engl J Med 1996;334:1417-21.

57. Lopez-Herce J, de Lucas N, Carrillo A, Bustinza A, Moral R. Surfactant treatment for acute respiratory distress syndrome. Arch Dis Child 1999;80(3):248-52.

58. Willson DF, Zaritsky A, Bauman LA, Dockery K, James RL, Conrad D, et al. Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. Members of the Mid-Atlantic Pediatric Critical Care Network. Crit Care Med 1999;27(1):188-95.

59. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants [review]. Cochrane Database Syst Rev 2001;(2):CD000511.

60. Zola EM, Gunkel JH, Chan RK, Lim MO, Knox I, Feldman BH, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. J Pediatr 1993;122(3):453-9.

61. Jobe AH. Techniques for administering surfactant. In: Robertson B, Taeusch HW. Surfactant Therapy for Lung Disease. New York: Marcel Dekker Inc.; 1995. p. 309-24.

Corresponding author:
Norberto A. Freddi
Alameda Jaú, 759
CEP 01420-001 – São Paulo, SP, Brazil
Tel.: +55 (11) 288.4266 – Fax: +55 (11) 288.5836
E-mail: nafreddi@uol.com.br