Effects of surfactants on preterm infant lungs

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Lack of surfactant is the commonest cause of death in preterm infants. Their lungs may contain as little as 10 mg/kg of surfactant at birth, a tenth of the amount normally found at term. Surfactants (animal origin or synthetic) can reduce mortality by 40% in infants with less than 30 weeks of gestation. Poractant is the surfactant derived from minced porcine lungs, Beractant from minced bovine lungs. Bronchoalveolar lavage with diluted poractant is effective in mechanically ventilated term infants with severe acute respiratory distress syndrome due to meconium aspiration syndrome. Nebulized surfactant and mask airway surfactant do not require intubation. Alternatively, surfactant may be administered via a thin catheter during spontaneous breathing. In conclusion, surfactants reduce the mortality in preterm infants.

KEYWORDS: beractant; poractante; calfactant; neonate; surfactant.

■ INTRODUCTION

Bronchopulmonary dysplasia is the most common respiratory complication in preterm infants who survive prolonged mechanical ventilation. Surfactant administration reduces distress syndrome and consequently ventilation and prolonged oxygen therapy.[1] Surfactant preparations have been shown to improve the clinical outcome of infants at risk for respiratory distress syndrome. In clinical trials, animal-derived surfactant preparations reduce the risk of pneumothorax and mortality. Four native surfactant proteins have been identified, known as SP-A, B, C, and D. They are essential in maintaining the surface-tension-lowering properties of pulmonary surfactant. SP-A and SP-D are hydrophilic and are not retained in commercial animal-derived products; they probably have a role in recycling surfactant and improving host defense.[2] SP-B and SP-C are hydrophobic. Animal-derived products may have some batch-to-batch variation regarding the levels of native pulmonary surfactant proteins. In addition, there is concern regarding infection from animal sources. New surfactant preparations, composed of synthetic phospholipids and essential hydrophobic surfactant protein analogs, have been developed. They have been produced by peptide synthesis and recombinant technology to provide a new class of synthetic surfactants that may be a suitable alternative to animal-derived surfactants.

Animal-derived and synthetic surfactants have been extensively evaluated in the treatment of respiratory distress syndrome in preterm infants.[3] Three commonly available animal-derived surfactants include Beractant, Calfactand (bovine) and Poractant alfa (porcine). Prospective and retrospective studies comparing Beractant and Calfactant have shown no significant differences in clinical and economical outcomes. Randomized, controlled clinical trials have shown that treatment with Poractant is associated with rapid weaning of oxygen and ventilatory pressure, fewer additional doses, cost benefit and survival advantage when compared with Beractant or Calfactant. Differences in outcomes between these animal derived surfactants may be related to a higher amount of phospholipids and plasmalogens in Poractant alfa. To date, animal-derived surfactants seem to be better than synthetic surfactants during the acute phase of respiratory distress syndrome and in decreasing neonatal mortality.

■ BIBLIOGRAPHIC SEARCH

The bibliographic search was performed electronically using PubMed database as search engine; November 2014 was the cutoff point. The following key words "effect surfactant", "effect natural surfactant", "effect synthetic surfactant" and "comparison effect natural synthetic surfactant neonate" were used. In addition, the books Neonatal Formulary[4] and NEOFAX by Young and Mangum[5] were consulted.

■ RESULTS

Monitoring of infants treated with surfactants

Oxygen saturation, electrocardiogram, and blood pressure should be monitored continuously during dosing. Impairment of gas exchange caused by blockage of the airway must be checked. After dosing, frequent assessments of oxygenation and ventilation should be performed to prevent post-dose hyperoxia, hypocarbia, and over-ventilation.[5]

The treatment with surfactant is superior for infants with gestational ages less than 30 weeks. Natural surfactants

(containing proteins) are more effective than synthetic products (protein free), now infrequently used. Natural surfactants batches vary and may not be equivalent in their effects. The porcine surfactant Poractant acts more rapidly than the bovine preparation (Beractant) in infants with moderate to severe respiratory distress syndrome. A meta-analysis of 5 comparative studies suggests that a dose of 200 mg/kg of Poractant alfa is associated with lower mortality compared with 100 mg/kg of Beractant. Chronic lung disease remains a problem but it is hoped that early treatment with surfactant combined with extubation to continuous positive airway pressure (CPAP) will reduce this complication of prematurity. The newer synthetic surfactants, containing analogues of surfactant protein B or C, have undergone trials for treatment of respiratory distress syndrome.[6]

Dose and administration of surfactants

Poractant alfa: the initial dose is 2.5 ml/kg per dose intratracheally, divided into 2 aliquots followed by up to two subsequent doses of 1.25 ml/kg per dose administered at 12-hour intervals if needed.[5] Calfactant: the initial dose is 3 ml/kg per dose intratracheally, divided into 2 aliquots followed by up to three subsequent doses of 3 ml/kg per dose administered at 12 hour intervals if needed.[5] Beractant: the initial dose is 4 ml/kg per dose intratracheally, divided into 4 aliquots. For prophylaxis a first dose is given as soon as possible after birth, with up to three additional doses in the first 48 hours of life. For rescue treatment of respiratory distress syndrome the dose is up to four doses in the first 48 hours of life. A new mode of surfactant administration without intubation (less invasive surfactant administration) has recently been described.[7] The spectrum of reported less invasive methods includes (i) aerosol administration, (ii) pharyngeal deposition, (iii) laryngeal masks, (iv) short term intubation followed by surfactant administration and rapid extubation; it also includes an approach that keeps infants on spontaneous breathing with support and administering surfactant by laryngoscopy via a small diameter tube. Less invasive surfactant administration was tolerated by 94% of all infants, and 68% of infants remained in CPAP by day 3. Comparison with controls, found significantly higher survival rates, less intraventricular hemorrhage and cystic periventricular leukomalacia; only persistent patent ductus arteriosus and retinopathy of prematurity occurred significantly more often. Thus, surfactant can be effectively and safely delivered via less invasive administration.

Kanmaz et al.[8] described in 2013 the feasibility of early administration of surfactant via a thin catheter during spontaneous breathing ("Take Care" procedure) and compared it with the "Intubate-Surfactant-Extubate" procedure. Preterm infants, who were < 32 weeks and stabilized with nasal CPAP in the delivery room, were randomized to receive early surfactant treatment either by the "Take Care" or "Intubate-Surfactant-Extubate" procedures. Poractant alfa was trachea-instilled via a 5-F catheter during spontaneous breathing under nasal CPAP. The mechanical ventilation requirement in the first 72 hours of life and bronchopulmonary dysplasia were significantly lower in the "Take Care" group vs. the intubated procedure group; Thus the "Take Care" procedure is feasible for the treatment of respiratory distress syndrome in infants with very low birth weight and significantly reduces both the need and duration of

mechanical ventilation, and thus bronchopulmonary dysplasia rate in these patients.

Thus, preterm neonates with respiratory distress syndrome benefit from early application of nasal CPAP. However, it is not clear whether surfactant should be administered early as a routine to all such infants or later in a selective manner. Kandraju et al.[9] compared the efficacy of early routine (within 2 hours of life) versus late selective surfactant treatment in reducing the need for mechanical ventilation in infants born between the 26th and 33rd weeks of gestation with respiratory distress syndrome on nasal CPAP. They claim that the need for mechanical ventilation was significantly lower in the early routine surfactant group. The incidence of pneumothorax and the need for supplemental O_2 at 28 days were similar in the two groups.

Nebulized surfactant has the potential to deliver surfactant to the infant lung with the goal of avoiding endotracheal intubation and ventilation, ventilator-induced lung injury and bronchopulmonary dysplasia. Abdel-Latif and Osborn[10,11] determined the effect of nebulized surfactant administration either as prophylaxis or treatment, compared to placebo and report no significant difference between the groups; they found no studies on prophylactic or early laryngeal mask airway administration and they conclude that there are insufficient data to support or refute the use of nebulized surfactant in clinical practice.

Lung lavage with diluted surfactant has also emerged as an innovative treatment for meconium aspiration syndrome. However, the treatment effect has not yet been fully established. Choi et al.[12] investigated the effects of surfactant lavage therapy for meconium aspiration syndrome. From the results of the meta-analysis of randomized controlled trials, surfactant lavage significantly decreased death or the need for extracorporeal membrane oxygenation.

Effects of natural surfactants on preterm infant lungs

The benefits of synthetic or animal-derived surfactants for prevention or treatment of respiratory distress syndrome are well established.[13] Ghaemi et al.[14] determined the effect of surfactant therapy reduction of the mortality rate in premature neonates with respiratory distress syndrome and assessed the relationship between the efficacy of surfactant therapy and some risk factors associated to respiratory distress syndrome. Overall, 34 (38.2%) out of 89 neonates who received surfactant survived. The higher efficacy of surfactant replacement therapy was observed in neonates with gestational age of more than 32 weeks (47.5%), and in those who received the first dose of surfactant within the first 24 hours of life (43.3%). Surfactant replacement therapy in neonatal respiratory distress syndrome should be started as soon as possible after birth. The efficacy of surfactant therapy for neonatal distress syndrome may be associated with gestational age, Apgar score, birth weight, starting time of surfactant therapy and maternal steroid therapy.

Lista et al.[15] evaluated the meconium aspiration syndrome treated by bronchoalveolar lavage with 15 ml/kg of diluted (5.3 mg phospholipid/ml) porcine surfactant saline suspension in 2.5 ml: they report: (i) radiological improvements in all eight patients compared with pre-bronchoalveolar values; (ii) significant improvement in mean values for partial pressure of oxygen in arterial blood, arteriolar/alveolar O_2 ratio at 3 and 6 hours after bronchoalveolar lavage; (iii) in all

patients, tracheal fluids that had been meconium-stained prior to bronchoalveolar lavage were clear of meconium after the lavage.

Szymankiewicz et al.[16] examined the effect of surfactant lung lavage on pulmonary functions in neonates with severe meconium aspiration syndrome using beractant. The infants had a gestational age of 37.7 ± 1.8 weeks and a body weight of 3178 ± 238 g. Measurements of dynamic compliance, airway resistance, mean airway pressure and time constant were compared in the study vs. control groups and between the groups before surfactant lung lavage and 24 and 48 hours after surfactant lung lavage. A significant increase in dynamic compliance and a drop in both airway resistance and mean airway pressure were observed 48 hours after surfactant lung lavage. These data suggest that surfactant lung lavage is associated with a rapid and significant improvement in pulmonary mechanics, together with an improvement in oxygenation in newborns with severe meconium aspiration syndrome. The beneficial effects of surfactant lung lavage on pulmonary mechanics persisted for at least 48 hours after the introduction of the procedure.

Hermon et al.[17] determined whether surfactant application during extracorporeal membrane oxygenation improves lung volume, pulmonary mechanics, and chest radiographic findings in children with respiratory failure or after cardiac surgery. Seven patients received surfactant before weaning from extracorporeal membrane oxygenation was started. They were compared to six patients treated with extracorporeal membrane oxygenation who did not receive surfactant. The groups did not differ with regard to demographic data, duration of extracorporeal membrane oxygenation, ventilator settings, and hospital days. Application of surfactant doubled mean tidal volume and significantly increased lung compliance compared to untreated controls. However, authors note that an extensive prospective trial is required to confirm this report.

Attar et al.[18] compared the immediate changes in lung compliance following the administration of two commercially available natural surfactants. Forty preterm infants required surfactant and received either calfactant or beractant. Infants given beractant required more doses per patient (4 vs. 2) and were more likely to require more than 2 doses.

Soll and Morley[19] and reviewed the effect of surfactant used (i) as prophylactic administration vs. (ii) as treatment of established respiratory distress syndrome in premature infants. Eight studies were identified that met the inclusion criteria. The majority of included studies noted an initial improvement in the respiratory status and a decrease in the incidence of respiratory distress syndrome in infants who received prophylactic surfactant. The meta-analysis supports a decrease in the incidence in pneumothorax. They conclude that prophylactic surfactant administration to infants judged to be at risk of developing respiratory distress syndrome (infants less than 30 to 32 weeks gestation) compared to selective use of surfactant in infants with established respiratory distress syndrome has been demonstrated to improve clinical outcome.

Connatal pneumonia caused by B streptococcal infection may be associated with surfactant dysfunction. Herting et al.[20] investigated the effects of surfactant treatment in term and preterm neonates with group B streptococcal infection and respiratory failure, in comparison with corresponding data from a control population of non-infected infants treated with surfactant for respiratory distress syndrome. The study comprised 118 infants with respiratory failure, clinical and/or laboratory signs of acute inflammatory disease, and group B streptococcal infection proved by culture results. A non-randomized control group of 236 non-infected infants was selected for comparison. The primary parameters evaluated were oxygen requirement, ventilator settings, and incidence of complications. Median birth weight in the study group was 1,468 g. The incidence of complications in the study group (mortality: 30%; pneumothorax: 16%; intracranial hemorrhage: 42%) was substantial (considering the relatively high mean birth weight of the treated infants), compared with the infants with respiratory distress syndrome, and repeated surfactant doses are often needed.

Pandit et al.[21] determined whether pulmonary hemorrhage after surfactant treatment increases short and long term morbidity and mortality in neonates weighing 917 ± 238 g at birth, with a gestational age of 27 ± 1.9 weeks. Pulmonary hemorrhage was severe in 46%, moderate in 26%, mild in 27% of cases. Moderate and severe pulmonary hemorrhage were associated with chronic lung disease or death. Pulmonary hemorrhage was associated with major intraventricular hemorrhage. In the survivors who could be assessed at ≥ 2 years, the neurodevelopmental outcome appeared to be within the normal range.

Bevilacqua et al.[22] evaluated the efficacy of modified porcine surfactant administered at birth to prevent the development of respiratory distress syndrome in 287 premature infants with a gestational age of 24 to 30 weeks; they were randomized to prophylactic treatment or to a control group receiving no surfactant treatment in the delivery-room. Infants in both groups were eligible for rescue treatment with surfactant (200 mg/kg) if they developed clinical symptoms of respiratory distress syndrome and required mechanical ventilation. The main endpoint was to obtain, in the prophylaxis group, a 30% reduction in the incidence of grade 3 to 4 of respiratory distress syndrome. Median gestational age was 28 weeks in both groups and median birth weight was 1010 and 1002 g, respectively for prophylaxis and control infants. There was a 32% reduction in the incidence of grade 3 to 4 of respiratory distress syndrome in the prophylaxis group. This was associated with a significant reduction in mean maximum fraction of inspired oxygen (0.57 versus 0.66%). Multiple and logistic regression analysis confirmed that high gestational age and surfactant prophylaxis were independently associated with a lower degree of respiratory distress syndrome and a lower mortality.

Eighteen preterm infants severely ill with respiratory distress syndrome who required assisted ventilation were given bovine modified natural surfactant by an endotracheal tube.[23] The gestational age was 31.2 ± 0.4 weeks (range 28 to 34 weeks) and the birth weight of 1,562 ± 71 g (range 1160 to 2010 g). The average time of initial surfactant administration was 15 ± 1.7 hours (range 5 to 24 hr.). No significant side effects were found during surfactant instillation. Post surfactant, the air intake improved, oxygenation and arterial/alveolar gradients increased, and the levels of inspired oxygen could be reduced. Some of the radiological abnormalities were resolved. There were 4 cases of pulmonary air leak, 5 cases of pulmonary hemorrhage and 8 cases of bronchopulmonary dysplasia. Four infants expired, two because of severe asphyxia/shock and two of

unrelated causes. Among the 14 survivors, two cases of retinopathy of prematurity occurred, which gradually regressed; one patient had cerebral palsy and delayed development. Surfactant rescue therapy is a supplemental beneficial treatment for severe respiratory distress syndrome while newborn intensive care is necessary for efficient diagnosis and treatment of respiratory distress syndrome.

There is now convincing evidence that the severity of neonatal respiratory distress syndrome can be reduced by surfactant replacement therapy; however, the optimal therapeutic regimen has not been defined.[24] This randomized European multicenter trial was designed to determine the beneficial effects of a single large dose vs. multiple doses of porcine derived surfactant (200 mg/kg) in infants with severe respiratory distress syndrome. In both groups (single dose: n = 175, multiple doses: n = 167) there was a rapid improvement in oxygenation as reflected by a threefold increase in arterial to alveolar oxygen tension ratio within 5 min after surfactant instillation. In addition, ventilatory requirements (peak inspiratory pressure, ventilatory efficiency index) were reduced in the multiple-dose group 2 to 4 days after randomization.

Effects of synthetic surfactants on preterm infant lungs

Synthetic surfactant has been a cornerstone of therapy either given prophylactically in the delivery room or later as selective therapy to infants with established respiratory distress syndrome.[25] With the evolution and refinement of intensive care for preterm infants the role of synthetic surfactant therapy is changing. However, about 50% of these newborns will require intubation for surfactant delivery because of evolving respiratory distress syndrome during the course of hospitalization. In view of the difficulties and side effects that may be associated with intubation for delivery, less invasive means of surfactant administration have been pursued.

Cogo et al.[26] studied the kinetics of exogenous disaturated phosphatidylcholine surfactant in preterm infants with respiratory distress syndrome who were treated with 100 or 200 mg/kg porcine surfactant. The half-life and pool size and the endogenous disaturated phosphatidylcholine synthesis rates were calculated. They concluded that porcine surfactant given to preterm infants with respiratory distress syndrome at a dose of 200 mg/kg resulted in a longer disaturated phosphatidylcholine half-life, fewer retreatments, and better oxygenation index values.

Miedema et al.[27] assessed regional changes in lung volume, mechanics, and ventilation during a day after synthetic administration. Surfactant increased lung volume by 61 ± 39% within a median time of 6 minutes. The ventral to dorsal ratio in lung volume changed significantly from 1.16 before to 0.81 after surfactant administration. Surfactant increased maximal compliance of the respiratory system, and this effect was reached at lower airway pressures. Surfactant caused a transitional decrease in oscillatory volume but did not alter its regional distribution. Surfactant treatment in high-frequency oscillatory ventilated preterm infants with respiratory distress syndrome caused a rapid increase and subsequent stabilization of lung volume, which is prominent in dependent lung regions. It increased maximal compliance, but this effect is only reached at lower airway pressures.

Synthetic surfactants differ by their protein content and physiologic effects. Beresford and Shaw[28] measured bronchoalveolar lavage, surfactant protein content and physiologic effects. These authors aimed to measure bronchoalveolar lavage and surfactant protein concentrations from preterm infants ventilated for respiratory distress syndrome and to assess their association with clinical outcome. Bronchoalveolar lavage surfactant proteins A, B and D concentrations for the whole cohort rose significantly during the first week. Surfactant protein-A concentration did not differ between outcome groups (survivors vs. non-survivors). Surfactant protein-B concentration rose significantly in lungs that were not supplemented with surfactant protein-B. Non-survivors had significantly lower surfactant protein-B concentrations on day 2 and 6 compared with survivors. Surfactant protein-D concentrations were significantly lower on day 2 and 3 among infants in supplemental oxygen on day 28 compared with those in air. Surfactant protein-A and D concentrations did not differ significantly between infants randomized to receive a natural or synthetic surfactant. Lower surfactant protein-B and D but not surfactant protein-A concentrations were associated with worse clinical prognosis.

Taeusch and Keough[29] hypothesized that the surfactants most resistant to inactivation in vitro will be the ones that are most effective in treatment of animal models of acute lung injury. Synthetic surfactant therapy has been a significant advance in the management of preterm infants with respiratory distress syndrome. It has become established as a standard part of the management of such infants.[30] Natural surfactants have additional advantages over currently available synthetic surfactants. The use of prophylactic surfactant administered after initial stabilization at birth to infants at risk for respiratory distress syndrome has benefits compared with rescue surfactant given to treat infants with established respiratory distress syndrome. In infants who do not receive prophylaxis, earlier treatment (before 2 hours) has benefits over later treatment. The use of multiple doses of surfactant is a superior strategy to the use of a single dose, whereas the use of a higher threshold for retreatment seems to be as effective as a low threshold. Adverse effects of surfactant therapy are infrequent and usually not serious. Long-term follow-up of infants treatment with surfactant in the neonatal period is reassuring.

A single dose of a synthetic surfactant administered prophylactically to premature neonates with birth weight between 700 and 1,100 g was compared to air placebo in a double blind procedure.[31] The effects of this treatment on neurodevelopmental, neurologic, and ophthalmologic outcomes, impairments, and general health status were examined during a follow-up evaluation at 1 year. Administration of a single prophylactic dose of synthetic surfactant increases survival in preterm infants; however, neurodevelopmental outcome and growth in survivors were equivalent treated vs. placebo infants.

Skelton and Jeffery[32] defined the individual neonatal response to the artificial surfactant, Exosurf. Eighty-two consecutive preterm neonates with respiratory distress syndrome who received Exosurf less than 12 hours after birth were studied. Within the first 12 hours, 11% of the neonates showed no response, 5% a mild response and 84% a good response, but 34% relapsed. By 24 hours, 6% still showed no response and died, 11% showed a mild response and 83% a good response; however, half of these relapsed.

Kaapa et al.[33] evaluated the effects of the synthetic surfactant Exosurf as replacement therapy on the pulmonary artery pressure in 10 infants with respiratory distress syndrome; they received two or four doses of the synthetic surfactant. Surfactant instillation decreased pulmonary artery pressure significantly on 17 of 18 occasions, but did not change systemic blood pressure, but pulmonary artery pressure measured on 9 occasions returned to the preterm level. No change in the velocity or magnitude of the ductal left-to-right shunting due to exogenous surfactant was found. Synthetic surfactant replacement therapy in infants with respiratory distress syndrome induces a significant, but transient decrease in systolic pulmonary artery pressure with no effect on ductal shunt.

In a prospective, randomized, controlled clinical trial, the immediate and longitudinal effects of synthetic surfactant therapy on pulmonary mechanics were evaluated in extremely premature infants during mechanical respiration.[34] Ninety-four infants weighing between 600 and 1250 g received either synthetic surfactant or sham (air) therapy in the delivery room and up to three additional doses in the first 48 hours of life if they were (i) ventilator-dependent, (ii) had fractional inspiratory oxygen requirements greater than or equal to 0.30, and (iii) radiographic findings consistent with hyaline membrane disease. Oxygenation, assessment by the ratio of alveolar to arterial oxygen pressure, was significantly greater in the surfactant group during the first 52 hours of life; the greatest difference was noted at 24 hours.

In a multicenter, double-blind, placebo-controlled rescue trial conducted at 12 Canadian hospitals, two 5 ml/kg doses of a synthetic surfactant or air placebo were administered to 224 infants with birth weights of 500 to 749 g who had established respiratory distress syndrome and an arterial/alveolar oxygen tension ratio of less than 0.22.[35] The first dose was given between 2 and 24 hours of age; the second dose was given 12 hours later to the infants still receiving mechanical ventilation. Infants were stratified at study entry by birth weight and gender. Infants receiving synthetic surfactant exhibited significant improvements: (i) in oxygen requirements; (ii) in the alveolar-arterial oxygen tension gradient and in mean airway pressure at 6 hr. post-treatment; significant improvements in alveolar-arterial oxygen tension gradient, arterial/alveolar oxygen tension ratio, and oxygen and ventilator requirements were still present at day 7. Overall mortality at 28 days was not significantly different between the two groups (50% versus 46%, for air placebo and synthetic surfactant groups, respecively). Similarly, neither the incidence of bronchopulmonary dysplasia (37% versus 30%) nor the incidence of survival without bronchopulmonary dysplasia at 28 days (17% versus 26%) were different between groups. These findings indicate that rescue therapy with synthetic surfactant results in physiologic improvements in very tiny premature infants, but improvements in overall mortality or other complications of respiratory distress syndrome were not documented.

A different result was obtained in a multicenter, double-blind, placebo-controlled rescue trial conducted at 21 USA hospitals, where two 5 ml/kg doses of a synthetic surfactant (Exosurf neonatal) or air placebo were administered to 419 infants weighing 700 to 1,300 g with respiratory distress syndrome and an arterial/alveolar oxygen pressure ratio less than 0.22.[36] The first dose was given between 2 and 24 hours of age and the second 12 hours later, but only to

those infants remaining on ventilatory support. Infants were stratified at entry by birth weight and gender. Among infants receiving synthetic surfactant, significant improvements were recorded: (i) in alveolar-arterial oxygen pressure ratio, and oxygen and ventilator needs through 7 days of age, (ii) in death from respiratory distress syndrome, which was reduced by two thirds (21 versus 7), and (iii) in the overall neonatal mortality rate, which was reduced by half (50 versus 23).

An artificial surfactant composed of dipalmitoylphosphatidylcholine and unsaturated phosphatidylglycerol in a ratio of 7:3 (w/w) and a dose of 50 to 100 mg was used at birth as a prophylaxis against the respiratory distress syndrome and its complications in a randomized prospective trial involving 341 infants (23 to 34 weeks gestation) regardless of their antenatal problems.[37] The surfactant had little effect in infants above 29 weeks gestation and was most beneficial in infants under 30 weeks gestation (67 controls and 69 surfactant treated infants). This artificial surfactant significantly reduced the inspired oxygen and peak ventilator pressure requirements during the first 96 hours, the incidence of intraventricular hemorrhage from 40% to 19%, the overall mortality from 36% to 17%, the need for more than 28 days oxygen from 37% to 21% and the use of pancuronium in ventilated infants from 52% to 27%. There were no apparent side effects. This protein free, artificial surfactant should be a useful addition to the therapy of infants under 30 weeks gestation to reduce the severity of their respiratory distress syndrome and the incidence of serious complications.

Comparison of clinical responses to natural and synthetic surfactants

Pfister et al.[38,39] reviewed and compared the effect of synthetic surfactant containing surfactant protein mimics vs. animal derived surfactant extract on the risk of mortality, chronic lung disease, and other morbidities associated with prematurity in preterm infants at risk for having respiratory distress syndrome. Randomized and quasi-randomized trials were considered. Studies that enrolled preterm infants or low birth weight infants at risk for having respiratory distress syndrome who were treated with either a synthetic surfactant containing surfactant protein mimics or an animal-derived surfactant preparations were included. They conclude that no statistically clinical differences between synthetic vs. natural surfactants in death and chronic lung disease were noted.

Da Costa et al.[41] conducted a randomized clinical trial to compare the effects of a synthetic and natural surfactant in infants with neonatal respiratory distress syndrome in 89 infants randomly allocated to receive one of the two surfactants. Primary outcome variables were the acute and long-term effects of the surfactant preparation, i.e., ventilatory requirements at 24 hours of age as judged by oxygenation index, and the combined incidence of chronic lung disease or death at 28 days. They conclude that both preparations are reasonable choices for the treatment of respiratory distress syndrome of prematurity.

Murdoch and Kempley[41] evaluated the effect of different surfactants on fluid balance in respiratory distress syndrome. They studied 24 premature infants who were randomized to receive either natural or synthetic surfactant. Ventilatory requirements decreased more rapidly in infants

receiving natural surfactant, with significantly greater reductions in mean airway pressure from 1 to 48 h and oxygenation index from 1 to 18 hours. There were no differences in fluid intake and serum electrolytes. Mean daily urine output was higher in the group receiving natural surfactant. This group also had a greater weight loss from birth weight. Natural surfactant produces an earlier reduction in ventilatory requirements with an earlier diuresis. This should influence fluid managements in respiratory distress syndrome.

Forty-five infants were enrolled consecutively in the OSIRIS trial using synthetic surfactant, while 21 infants were subsequently enrolled in a natural porcine surfactant group.[42] There were no significant differences between the groups for mean birth weight, gestational age, inspired oxygen (FiO$_2$), or arterial:alveolar ratio prior to surfactant administration. Oxygen requirements fell significantly at a more rapid rate within the first 24 hours for patients treated with the natural vs. the synthetic surfactant. The Mean duration of a >40% oxygen requirement was significantly shorter in the natural (2.6 days) vs. the synthetic (8.0 days) groups. Mean duration of oxygen therapy was also significantly shorter in the natural group (10.2 days) compared to 17.1 days in the synthetic group. Ten infants (24%) in the synthetic group developed intraventricular hemorrhage compared to none in the natural group. As oxygen requirements appear to decrease more rapidly following administration of the natural surfactant, a large prospective randomized multicenter trial needs to be performed to compare the effects of these surfactants on both short and long-term outcome.

In a study by Choukroun et al.[43] 13 infants were given artificial surfactant and 11 infants received porcine surfactant. As in most other studies, the natural surfactant appeared to be more active than its synthetic counterpart with regard to immediate pulmonary changes in ventilator treated premature infants with respiratory distress syndrome.

■ DISCUSSION

Preterm infants are unable to produce surfactant and surfactant replacement in infants with respiratory distress syndrome reduces mortality. The lungs of preterm infants contain 10% of of the amount of surfactant found in term infants. Whilst labor and/or birth trigger a surge of surfactant production, this takes 48 hours to become effective. Endogenous surfactants have a half-life of about 12 hours, after which some is recycled and some degraded. Infants who are deficient at birth, therefore, need to be given 100 mg/kg of surfactant as soon as possible to prevent atelectasis; if destruction initially exceeds production one (and occasionally two) further doses 12 and 24 hours later should be administered. Inactivation seems to occur more rapidly when there is infection or meconium aspiration, rendering a larger dose appropriate.[4]

It is now widely accepted that non-invasive respiratory support should be provided for infants who are surfactant deficient at birth and that this procedure will reduce the number of infants with chronic oxygen dependency. The first critical step is to aerate the lungs as gently as possible at birth using pressure sustained for several seconds to achieve initial lungs expansion before even thinking of ventilating the infants. The second critical step is to prevent atelectasis.

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension and thereby stabilizing the alveoli. In infants with respiratory distress syndrome, synthetic surfactants therapy reverses atelectasis and improves fractional residual capacity, with rapid improvements in oxygenation. All preparations reduce mortality from respiratory distress syndrome. Natural surfactants are more effective than synthetic surfactants in reducing pulmonary air leak. There are no significant differences between preparations in chronic lung disease or other long term outcomes. All commercially available preparations contain surfactant apoprotein C (SP-C), whereas none contain SP-A. The lung-minced extract Survanta and Curosurf contain less than 10% of the SP-B contained in the lung-wash extract Infasurf.[5]

Infasurf is a sterile, non-pyrogenic natural surfactant extracted from calf lungs containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Survanta is a modified natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C, to which Colfosceril palmitate, palmitic acid, and tripalmitin are added. Survanta is suspended in normal saline solution and heat sterilized. Curosurf is a modified porcine-derived minced lung extract containing phospholipids, neutral lipids, fatty acids and surfactant-associated proteins B and C.[5]

Administration of exogenous surfactants should be restricted to highly supervised clinical settings, with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Reflux of exogenous surfactant up the endotracheal tube and falls in oxygenation occur frequently. If the infant becomes cianotic, pale or agitated, heart rate slows, oxygen saturation falls more than 15%, or surfactant backs up the endotracheal tube, dosing should be slowed or halted. If necessary, the ventilator setting and/or FIO$_2$ should be turned up. Pulmonary hemorrhage occurs in 2% to 4% of treated infants, primarily the smallest patients with untreated patent ductus arteriosus. This may be due to hemorrhagic pulmonary edema caused by the rapid fall in pulmonary vascular resistance and resulting increased pulmonary blood flow.[5]

In infants with respiratory distress syndrome, exogenous surfactant therapy reverses atelectasis and increases functional respiratory capacity, with rapid improvements in oxygenation. All preparations reduce mortality from respiratory distress syndrome. Natural surfactants are more effective than synthetic surfactants in reducing pulmonary air leak. There are no significant differences between preparations in chronic lung disease or other long term outcomes.

■ CONCLUSION

Synthetic and natural surfactants are a considerable advantage in the treatment of respiratory distress syndrome and reduce significantly the mortality of preterm infants.

■ CONFLICT OF INTERESTS

■ ACKNOWLEDGEMENTS

■ EFEITOS DE SURFACTANTES NOS PULMÕES DE RECÉM-NASCIDOS PREMATUROS

■ RESUMO

A falta de surfactante é a causa mais comum de morte em recém-nascidos prematuros. Os pulmões podem conter apenas 10% da quantidade encontrada a termo. Surfactantes (de origem animal ou sintética) podem reduzir a mortalidade em até 40% em crianças com menos de 30 semanas de gestação. O poractante é o surfactante derivado de pulmões suínos, o beractante e o calfactante derivam de pulmões bovinos. A lavagem bronco-alveolar com poractante diluído é eficaz em crianças nascidas a termo e sob ventilação mecânica com síndrome da angústia respiratória aguda grave secundária a aspiração de mecônio. Surfactante por nebulização e máscara de vias aéreas não necessitam de intubação. Como alternativa, o surfactante pode ser administrado através de um cateter fino durante a respiração espontânea. Em conclusão, os surfactantes reduzem a mortalidade em recém-nascidos prematuros.

UNITERMOS: beractante; poractante; calfactante; recém-nascido; surfactante

■ REFERENCES

1. Bancalari E, del Moral T. Bronchopulmonary dysplasia and surfactant. Biol Neonate. 2001;80(Suppl 1):7-13.
2. Pfister RH, Soll RF. New synthetic surfactants: the next generation? Biol Neonate. 2005;87(4):338-44.
3. Ramanathan R. Animal-derived surfactants: where are we? The evidence from randomized, controlled clinical trials. J Perinatol. 2009;29(Suppl 2): S38-S43.
4. Neonatal Formulary. Sixth edition. John Wiley & Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis, West Sussex, PO22 9NQ, UK; 2011, 248-249.
5. Young TE, Mangum B. Neofax, A Manual of Drugs used in neonatal care. Respiratory drugs. Edition 23rd. Thomson Reuters, Montvale 07645, New Jersey, USA; 2010, 282-286.
6. Halliday HL. History of surfactant from 1980. Biol Neonate. 2005;87(4):317-22.
7. Klebermass-Schrehof K, Wald M, Schwindt J, Grill A, Prusa AR, Haiden N, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. Neonatology. 2013;103(4): 252-8.
8. Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics. 2013;131(2):e502-9.
9. Kandraju H, Murki S, Subramanian S, Gaddam P, Deorari A, Kumar P. Early routine versus late selective surfactant in preterm neonates with respiratory distress syndrome on nasal continuous positive airway pressure: a randomized controlled trial. Neonatology. 2013;103(2):148-54.
10. Abdel-Latif ME, Osborn DA. Nebulized surfactant in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2012;10:CD008310.
11. Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2011;(7):CD008309.
12. Choi HJ, Hahn S, Lee J, Park BJ, Lee SM, Kim HS, et al. Surfactant lavage therapy for meconium aspiration syndrome: a systematic review and meta-analysis. Neonatology. 2012;101(3):183-91.
13. Moya F. Synthetic surfactants: where are we? Evidence from randomized, controlled clinical trials. J Perinatol. 2009;29(Suppl 2):S23-8.
14. Ghaemi S, Mohamadymasodi M, Kelishadi R. Evaluation of the effects of surfactant replacement therapy in neonatal respiratory distress syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2009;11(3):188-90.
15. Lista G, Bianchi S, Castoldi F, Fontana P, Cavigioli F. Bronchoalveolar lavage with diluted porcine surfactant in mechanically ventilated term infants with meconium aspiration syndrome. Clin Drug Investig. 2006;26(1):13-9.
16. Szymankiewicz M, Gadzinowski J, Kowalska K. Pulmonary function after surfactant lung lavage followed by surfactant administration in infants with severe meconium aspiration syndrome. J Matern Fetal Neonatal Med. 2004;16(2):125-30.
17. Hermon M, Burda G, Male C, Boigner H, Ponhold W, Khoss A, et al. Surfactant application during extracorporeal membrane oxygenation improves lung volume and pulmonary mechanics in children with respiratory failure. Crit Care. 2005;9(6):R718-24.
18. Attar MA, Becker MA, Dechert RE, Donn SM. Immediate changes in lung compliance following natural surfactant administration in premature infants with respiratory distress syndrome: a controlled trial. J Perinatol. 2004;24(10):626-30.
19. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001;(2):CD000510.
20. Herting E, Gefeller O, Land M, van Sonderen L, Harms K, Robertson B. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Members of the Collaborative European Multicenter Study Group. Pediatrics. 2000;106(5):957-64.
21. Pandit PB, O'Brien K, Asztalos E, Colucci E, Dunn MS. Outcome following pulmonary haemorrhage in very low birthweight neonates treated with surfactant. Arch Dis Child Fetal Neonatal Ed. 1999;81(1): F40-4.
22. Bevilacqua G, Parmigiani S, Robertson B. Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomized trial. J Perinat Med. 1996;24(6): 609-20.
23. Horpaopan S, Sangtaveesin V, Ratrisawasdi V. Surfactant treatment in the neonate with severe respiratory distress syndrome. J Med Assoc Thai. 1996;79(4):222-8.
24. Speer CP, Robertson B, Curstedt T, Halliday HL, Compagnone D, Gefeller O, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Corusurf. Pediatrics. 1992;89(1):13-20.
25. Martinelli S, Gatelli I, Proto A. Surfactant administration during spontaneous breathing via a thin endotracheal catheter. Acta Biomed. 2013;84(Suppl 1):22-4.
26. Cogo PE, Facco M, Simonato M, Verlato G, Rondina C, Baritussio A, et al. Dosing of porcine surfactant: effect on kinetics and gas exchange in respiratory distress syndrome. Pediatrics. 2009;124(5):e950-7.
27. Miedema M, de Jongh FH, Frerichs I, van Veenendaal MB, van Kaam AH. Changes in lung volume and ventilation during surfactant treatment in ventilated preterm infants. Am J Respir Crit Care Med. 2011;184(1):100-5.
28. Beresford MW, Shaw NJ. Bronchoalveolar lavage surfactant protein a, B, and d concentrations in preterm infants ventilated for respiratory distress syndrome receiving natural and synthetic surfactants. Pediatr Res. 2003;53(4):663-70.
29. Taeusch HW, Keough KM. Inactivation of pulmonary surfactant and the treatment of acute lung injuries. Pediatr Pathol Mol Med. 2001;20(6): 519-36.
30. Suresh GK, Soll RF. Current surfactant use in premature infants. Clin Perinatol. 2001;28(3):671-94.
31. Sell M, Cotton R, Hirata T, Guthrie R, LeBlanc M, Mammel M, et al. One-year follow-up of 273 infants with birth weights of 700 to 1100 grams after prophylactic treatment of respiratory distress syndrome with synthetic surfactant or air placebo. American Exosurf Neonatal Study Group I. J Pediatr. 1995;126(5 Pt 2):S20-5.
32. Skelton R, Jeffery HE. Factors affecting the neonatal response to artificial surfactant. J Paediatr Child Health. 1996;32(3):236-41.
33. Kääpä P, Kero P, Saraste M. Synthetic surfactant replacement therapy decreases estimated pulmonary artery pressure in respiratory distress syndrome. Am J Dis Child. 1992;146(8):961-4.
34. Couser RJ, Ferrara TB, Ebert J, Hoekstra RE, Fangman JJ. Effects of exogenous surfactant therapy on dynamic compliance during mechanical breathing in preterm infants with hyaline membrane disease. J Pediatr. 1990;116(1):119-24.
35. Smyth J, Allen A, MacMurray B, Peliowski A, Sankaran K, Volberg F, et al. Double-blind, randomized, placebo-controlled Canadian multicenter trial of two doses of synthetic surfactant or air placebo in 224 infants weighing

500 to 749 grams with respiratory distress syndrome. Canadian Exosurf Neonatal Study Group. J Pediatr. 1995;126(5 Pt 2):S81-9.

36. Long W, Thompson T, Sundell H, Schumacher R, Volberg F, Guthrie R. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. The American Exosurf Neonatal Study Group I. J Pediatr. 1991;118(4 Pt 1):595-605.

37. Morley CJ, Greenough A, Miller NG, Bangham AD, Pool J, Wood S, et al. Randomized trial of artificial surfactant (ALEC) given at birth to babies from 23 to 34 weeks gestation. Early Hum Dev. 1988;17(1):41-54.

38. Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2007; (3): CD006069.

39. Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment

of respiratory distress syndrome. Cochrane Database Syst Rev. 2007; (4): CD006069.

40. da Costa DE, Pai MG, Al Khusaiby SM. Comparative trial of artificial and natural surfactants in the treatment of respiratory distress syndrome of prematurity: experiences in a developing country. Pediatr Pulmonol. 1999;27(5):312-7.

41. Murdoch E, Kempley ST. The effects of synthetic and natural surfactant on fluid balance in acute respiratory distress syndrome. Eur J Pediatr. 2000;159(10):767-9.

42. Rollins M, Jenkins J, Tubman R, Corkey C, Wilson D. Comparison of clinical responses to natural and synthetic surfactants. J Perinat Med. 1993;21(5):341-7.

43. Choukroun ML, Llanas B, Apere H, Fayon M, Galperine RI, Guenard H, et al. Pulmonary mechanics in ventilated preterm infants with respiratory distress syndrome after exogenous surfactant administration: a comparison between two surfactant preparations. Pediatr Pulmonol. 1994;18(5):273-8.