ORIGINAL ARTICLE

Surfactant therapy in preterm infants with respiratory distress syndrome and in near-term or term newborns with acute RDS

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Many different surfactant preparations derived from animal sources, as well as synthetic surfactants, are available for the treatment of preterm infants with respiratory distress syndrome (RDS). Natural, modified surfactants containing surfactant-associated proteins appear to be more effective than non-protein-containing synthetic surfactants. Comparative trials with poractant alfa at a higher initial dose of 200 mg/kg appear to be associated with rapid weaning of FiO₂, less need for additional doses, and decreased mortality in infants <32 weeks gestation when compared with beractant. Early rescue (<30 min of age) surfactant therapy is an effective method to minimize over treatment of some preterm infants who may not develop RDS. Surfactant therapy followed by rapid extubation to nasal ventilation appears to be more beneficial than continued mechanical ventilation. In near-term or term newborns with acute RDS, surfactant therapy has been shown to be 70% effective in improving respiratory failure.

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Introduction

Surfactant therapy has become the standard of care in preterm infants with respiratory distress syndrome (RDS), and is used increasingly in near-term and term newborns with acute respiratory distress syndrome (ARDS). Incidence of prematurity is increasing in the United States.¹ Respiratory distress syndrome remains a major cause of morbidity and mortality in preterm infants, especially in the extremely low birth weight infants <1000 g.² The incidence of RDS is inversely proportional to gestational age. With the increasing use of prenatal steroids, the incidence as well as the severity of RDS has decreased by nearly 50% over the last few years.³,⁴ Respiratory distress syndrome occurs in approximately 50% of preterm infants born at <30 weeks gestation, but only in about 25% of those born ≥ 30 weeks. Surfactant therapy has been shown to reduce the combined outcomes of death and bronchopulmonary dysplasia (BPD) in preterm infants with RDS.⁵,⁶

Surfactant therapy for respiratory distress syndrome

Natural, modified surfactants derived from animal sources, and synthetic surfactants that are protein free, have been evaluated extensively. Exogenous synthetic surfactants studied include colfosceril palmitate (Exosurf™, GlaxoSmithKlein, Research Triangle, NC, USA, no longer in market), pumactant, turfsurf, and lucinactant (Surfaxin™, Discovery Laboratories, Warrington, PA, USA). Of these four synthetic surfactants, the first three are no longer available for clinical use and lucinactant is pending approval from the FDA as of 2005. Several different natural, modified surfactant preparations have been studied. They differ in composition, onset of response, and duration of action, dosing volume, and the need for additional doses. Fifteen trials ⁷⁻²⁰ comparing natural vs synthetic surfactants (Table 1), ²¹ and seven studies comparing different natural surfactants have been published (Table 2). ²² Multiple, randomized, controlled trials have consistently shown better clinical outcomes during the acute phase of RDS, and improved survival with natural surfactants than with synthetic surfactants that lack surfactant-associated proteins, especially, surfactant protein-B (SP-B).

Bloom et al.²² compared beractant vs calfactant in the prophylactic treatment of RDS in infants <1250 g. They showed no difference between these two surfactants in mortality or BPD. However, mortality in a subgroup of infants <600 g was significantly lower in the beractant treated group compared to calfactant (26 vs 63%, respectively). The authors also compared these two surfactants in the rescue treatment of RDS in 608 preterm infants. They demonstrated lower FiO₂ and mean airway pressure (MAP) at 72 h of age in the group treated with calfactant as compared with beractant. However, there were no significant differences in death or BPD between these two surfactants in this rescue trial.

In a pilot trial comparing beractant and poractant alfa, Speer et al.²³ showed a significant improvement in oxygenation, and a decrease in peak inspiratory pressure and MAP, which persisted up to 24 h after poractant alfa. They noted no significant differences in mortality or BPD between these two surfactants.
In another study, Baroutis et al.\textsuperscript{24} compared natural bovine surfactant (Alveofact\textsuperscript{19}) vs beractant vs poractant alfa. They demonstrated that treatment with poractant alfa resulted in significantly less days on mechanical ventilation and supplemental oxygen, and shorter length of hospital stay.

Ramanathan et al.\textsuperscript{25} compared poractant alfa with beractant in a multicenter, randomized, controlled trial in the United States. Treatment with poractant alfa was associated with faster weaning of oxygen, fewer additional doses, and decreased mortality in preterm infants <32 weeks gestation when compared with...
Cumulatively, 36% of infants randomized to poractant alfa received two or more doses vs 68% in the beractant treated group ($P<0.05$). In a meta-analysis of the two studies comparing beractant vs poractant alfa, neonatal mortality was significantly lower with poractant alfa (odds ratio 0.35, 95% CI 0.13, 0.92). In a recent study comparing these two surfactants, Malloy et al. extended the observations of Ramanathan et al. They showed improvement in oxygenation to persist up to 48 h (Figure 1) after treatment with poractant alfa, and a significantly lower number of additional doses with poractant alfa compared to beractant.

It is also interesting to note that the use of a higher initial dose of poractant alfa at 200 mg/kg vs 100 mg/kg of beractant in three comparison trials have consistently shown a lower mortality favoring poractant alfa (Figure 2). This observation may have been due to a larger dose of a more effective surfactant moderating disease severity during the acute phase of RDS in these ill preterm infants, thus resulting in a better survival. However, none of these trials was powered to evaluate mortality as a primary outcome.

More recently, Bloom and Clark published results from two large but incomplete, prospective, randomized, and masked clinical trials comparing calfactant and beractant. Both these trials were stopped for not meeting enrollment targets after a 32-month recruitment period. Primary outcome of infants alive without BPD were not different between calfactant and beractant in both of these trials. In addition, there were no differences in any of the secondary outcomes between these two surfactants. Investigators from these trials caution about making any definite conclusions due to premature closure of the trials and their inability to accept or reject their null hypothesis.

In a pharmacoeconomic analysis of poractant alfa vs beractant using the data from two randomized studies, Marsh et al. showed a 20–53% reduction in cost with poractant alfa compared with beractant.

**Surfactant therapy and nasal continuous positive airway pressure (NCPAP)**

Clinicians are increasingly attempting to extubate preterm infants following surfactant therapy to decrease the risk of barotrauma and/or volutrauma, and ultimately decrease the incidence of BPD. Since 1999, there have been six trials evaluating the outcome of early surfactant therapy followed by extubation to NCPAP (Table 3). Overall, these reports demonstrated decreased duration of mechanical ventilation and length of stay, and decreased need for additional doses of surfactant. In a recent study by the Texas Neonatal Research Group, rescue surfactant therapy in the more mature preterm population (birth weight $\geq 1250$ g) with mild to moderate RDS not requiring mechanical ventilation showed no benefits following routine elective intubation for surfactant administration when compared to expectant management with intubation and surfactant treatment as clinically indicated. Further studies are needed to evaluate the effects of early surfactant therapy followed by extubation to NCPAP or nasal ventilation on the incidence of BPD. Use of NCPAP with or without surfactant therapy was shown to be consistently associated with a lower incidence of classical as well as the newly defined ‘physiological’ BPD.

**Surfactant therapy for acute respiratory distress syndrome**

Acute respiratory distress syndrome (ARDS) is not an uncommon cause of respiratory failure in near-term and term newborns admitted to neonatal intensive care units. Acute respiratory distress syndrome is often secondary to meconium aspiration syndrome (MAS),
Surfactants in RDS and ARDS

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Table 3 Outcome of early surfactant therapy followed by extubation to nasal CPAP

| Trials (6)                          | Surf+CPAP/Surf+MV | GA (weeks)/age at surf Rx | Key findings                                      |
|------------------------------------|-------------------|---------------------------|---------------------------------------------------|
| Verder et al.29                    | 35/35             | 25–35 weeks               | Curosurf+CPAP: ↓ need for MV                       |
| Verder et al.20                    | 35/27 (early vs late) | <30 weeks/median age at Rx 5.2 vs 9.9 h | Early Curosurf+CPAP: ↓ need for MV; improved oxygenation |
| Haberman et al.31                  | 32/29             | 1250–2000 g/2–24 h        | ↓ Days on MV; early termination of study          |
| D’Angio et al.32                   | 52/53             | 25–56 weeks/24 h          | ↓ Days on MV; early termination of study          |
| Soll et al.33                      | 138/132 (early surf+CPAP vs CPAP with later rescue surf+MV) | 2501–2000 g/2–24 h | ↓ Days on MV                                    |
| Dan et al.14                      | 15/14             | <30 weeks/mean age at Rx 2.7 vs 3.5 h | ↓ Days on MV, O2, NICU LOS and second dose of Curosurf |

Abbreviations: MV, mechanical ventilation; LOS, length of stay; CPAP, continuous positive airway pressure; Surf, surfactant.

cCPAP alone.

Congenital pneumonia, sepsis-induced ARDS, viral pneumonia, pulmonary hemorrhage and partial or complete deficiency of SP-B. In these conditions, surfactant inactivation or dysfunction has been shown to be a major factor. Major mechanisms of surfactant inactivation in ARDS include decreased synthesis and secretion of surfactant by the type II pneumocytes, decrease in surface active small aggregates of surfactant in the alveoli, and direct inhibition of surfactant function by substances like meconium, blood, serum proteins or proteinaceous edema fluid.37

Exogenous surfactant therapy has been shown to be beneficial 70% of the time in patients with ARDS.38 In a randomized, controlled trial using beractant in forty newborns with MAS, Findley et al.39 demonstrated a significant reduction in the need for extracorporeal membrane oxygenation (ECMO) therapy. Lotze et al.40 performed a large, multicenter study in 328 term newborns with ARDS secondary to MAS, sepsis-induced ARDS or persistent pulmonary hypertension. They showed a significant reduction in the need for ECMO in patients with MAS and sepsis-related ARDS. They also showed that surfactant therapy was more beneficial when used early and in patients with an oxygenation index of <23. In a meta-analysis of data from these two studies, relative risk for ECMO therapy was significantly reduced to 0.64 (95% confidence intervals 0.46, 0.91).31

Eight, non-randomized studies using different surfactants have also been reported. Most of these studies used bolus surfactant therapy in an attempt to overcome the inactivation of endogenous surfactant. Three of the studies used either saline lavage followed by surfactant therapy or lavage using a dilute surfactant solution. In all these studies, there was improvement in oxygenation following surfactant therapy. No adverse effects were reported. In a multicenter study, Wiswell et al.42 examined the use of surfactant lavage for MAS using lucinactant, a synthetic surfactant. Although it was potentially safe and effective, lucinactant failed to show a significant advantage with surfactant lavage. The researchers were able to recruit only 15 patients in the surfactant group and seven patients served as controls.

In preterm infants with group B streptococcal pneumonia, different surfactant preparations have been shown to be effective.36 Newborns with congenital diaphragmatic hernia (CDH) have been shown to have surfactant abnormalities. In a multicenter, randomized study, Anderson et al.55 demonstrated significant adverse outcomes among infants treated with surfactant. They concluded that surfactant therapy offers no benefits in newborns with CDH. In preterm infants with evolving BPD, surfactant dysfunction has been reported. In an observational study, surfactant therapy resulted in improvement in lung function. Recently, poractant alfa treatment in infants with respiratory syncytial virus pneumonia has been shown to improve gas exchange and lung compliance.44

Conclusion

In summary, when published data from different surfactant comparison studies in preterm infants with RDS are evaluated, treatment with poractant alfa at a higher initial dose of 200 mg/kg has been shown to be associated with faster response, fewer additional doses, and a decrease in mortality, in addition to be cost effective. Furthermore, early rescue (<30 min of age) surfactant therapy, followed by rapid extubation to NCPAP or nasal ventilation should be considered to minimize lung injury and BPD. In near-term or term newborns with ARDS secondary to MAS, sepsis induced ARDS, aspiration pneumonia, bacterial or viral pneumonia, and in patients with pulmonary hemorrhage, surfactant therapy appears to be beneficial. A dose of 50 to 100 mg/kg administered at 6 to 12 h intervals may be appropriate. Surfactant containing higher amounts of saturated phosphatidyl choline and SP-B, such as poractant alfa, may be preferable over other surfactants. However, no randomized trials comparing different surfactants in ARDS have been reported. Bolus instillation of surfactant or mini-saline lavage using 3 to 5 ml/kg, followed by bolus surfactant therapy appears to be well tolerated and effective in near-term and term newborns with ARDS.
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