

## Review Articles

# Surfactant Replacement Therapy for Respiratory Distress Syndrome in the Newborn: A Review

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### Abstract

*Respiratory failure secondary to surfactant deficiency is a major cause of morbidity and mortality in low birth weight premature infants. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population. Exogenous surfactant therapy has become well established in newborn infants with respiratory distress. Many aspects of its use have been well evaluated in high-quality trials and systematic reviews. Secondary surfactant deficiency also contributes to acute respiratory morbidity in late-preterm and term neonates with meconium aspiration syndrome, pneumonia/sepsis, and perhaps pulmonary hemorrhage; surfactant replacement may be beneficial for these infants. This article summarizes the evidence and gives recommendations for the use of surfactant therapy for respiratory distress syndrome (RDS) in newborn.*

### Introduction

Exogenous surfactant replacement has been established as an appropriate preventive and treatment therapy for prematurity-related surfactant deficiency. Surfactant therapy also may be indicated for more mature infants with primary pulmonary hypertension or meconium aspiration syndrome. Single and multicenter randomized controlled trials (RCT) using synthetic, modified animal, purified animal, and human surfactants have shown that the use of surfactant replacement in preventive or treatment modes has been safe and efficacious.<sup>1-4</sup> Reduced mortality rates and improved short-term respiratory status for preterm infants with surfactant-deficiency respiratory distress have been confirmed. Current studies continue to address refinements in surfactant use that may optimize its effectiveness. New products, timing, dosage, methods of administration, and modification for particular gestational age groups are among the issues that may improve the effect of surfactants.<sup>2</sup>

Surfactants are organic compounds that lower the surface tension of a liquid lining the alveoli.<sup>2</sup> Surfactants reduce the surface tension of the fluid by adsorbing at the liquid-gas interface.<sup>3</sup> Pulmonary surfactant is a surface-active lipoprotein complex

(phospholipoprotein) formed by type II alveolar cells.<sup>4</sup> By adsorbing to the air-water interface of alveoli with the hydrophilic head groups in the water and the hydrophobic tails facing towards the air, the main lipid component of surfactant, dipalmitoyl phosphatidylcholine (DPPC) reduces surface tension.<sup>4</sup>

### Functions of surfactant

- To increase pulmonary compliance.
- To prevent atelectasis (collapse of the lung) at the end of expiration.
- To facilitate recruitment of collapsed airways.

### What are the benefits of surfactant replacement therapy in RDS?

RDS is usually defined by the presence of acute respiratory distress with disturbed gas exchange in a preterm infant with a typical clinical course or x-ray (ground glass appearance, air bronchograms and reduced lung volume).<sup>5</sup> The lungs of preterm babies with RDS are both anatomically and biochemically immature; they neither synthesize nor secrete surfactant well. Surfactant normally lines the alveolar surfaces in the lung, thereby reducing surface tension and preventing atelectasis.<sup>5</sup> Surfactant replacement therapy, either as a rescue treatment or a prophylactic natural surfactant therapy, reduces mortality and morbidity in babies with RDS.<sup>6,7</sup> These morbidities include deficits in oxygenation, the incidence of pulmonary air leaks (pneumothorax and pulmonary interstitial emphysema) and the duration of ventilatory support. Surfactant replacement increases the

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likelihood of surviving without bronchopulmonary dysplasia (BPD, also known as chronic lung disease of the preterm) largely by improving survival rather than the incidence of BPD. Babies treated with surfactants have shorter hospital stays and lower costs of intensive care treatment compared with randomized control infants receiving no surfactants.<sup>8</sup> The increase in survival is achieved with no increase in adverse neurodevelopmental outcome.<sup>9</sup>

### **What are the risks of exogenous surfactant therapy?**

The short-term risks of surfactant replacement therapy include bradycardia and hypoxemia during instillation as well as blockage of the endotracheal tube.<sup>10</sup> There may also be an increase in pulmonary hemorrhage following surfactant treatment; however, mortality ascribed to pulmonary hemorrhage is not increased and overall mortality is lower after surfactant therapy.<sup>11</sup> The relative risk (RR) for pulmonary hemorrhage following surfactant treatment has been reported at approximately 1.47 (95% CI 1.05 to 2.07) in trials,<sup>12</sup> but unfortunately many of the RCTs on surfactant replacement have not reported this outcome, nor have the data from autopsy studies clearly defined the magnitude of this risk.<sup>13,14</sup> No other adverse clinical outcome has been shown to be increased by surfactant therapy. There is often a very rapid improvement in gas exchange in surfactant-treated infants who are surfactant deficient.<sup>15</sup>

Natural surfactants contain proteins (surfactant protein-A, surfactant protein-B) from bovine or porcine sources and questions have been raised about the immunological effects.<sup>16</sup> To date, there is no evidence that there are immunological changes of clinical concern.<sup>17</sup> Babies with RDS have detectable circulating immune complexes directed toward surfactant proteins, but these do not appear to be more frequent in babies that are treated with surfactants.<sup>18</sup> One study showed a lower incidence of antisurfactant protein-A and antisurfactant protein-B in babies treated with surfactant compared with controls.<sup>19</sup>

### **Which is better: Natural or synthetic surfactants?**

A total of 11 randomized studies comparing natural to synthetic surfactants for babies with RDS have been subject to systematic review.<sup>10</sup> The review showed that overall mortality is decreased by the use of natural surfactants compared with synthetic surfactants (RR

of death = 0.86, 95% CI 0.75 to 0.99; absolute risk difference (ARD) = 0.025, 95% CI -0.047 to -0.003; number needed to treat (NNT) with natural surfactants rather than synthetic surfactants to prevent one death = 40, 95% CI 21 to 333).<sup>20</sup> Most of the studies showed that babies treated with natural surfactants have lower needs for oxygen and ventilatory support for at least three days following dosing compared with babies treated with synthetic surfactants. Pulmonary air leak syndrome is less common in babies treated with natural surfactants (RR of pneumothorax = 0.63, 95% CI 0.52 to 0.76; ARD=0.044, 95% CI -0.061 to -0.027; NNT=23, 95% CI 16 to 37; evidence level 1a).<sup>21</sup> The incidence of BPD is not different in babies given natural or synthetic surfactants, but because mortality is reduced in babies given natural surfactants, the combined outcome of death or BPD is reduced (RR=0.95, 95% CI 0.90 to 1.01).<sup>21</sup> Therefore, natural surfactants improve survival without BPD and with a lower incidence of air leak, and they are to be preferred over synthetic surfactants.<sup>22</sup>

### **Which is better: Surfactants given as prophylaxis or rescue therapy for preterm babies with RDS?**

A number of studies have evaluated whether surfactant should be given to all babies at significant risk for developing RDS or only after the development of RDS. Soll and Morley reviewed seven RCTs of prophylactic versus rescue therapy.<sup>23</sup> These were all trials that used natural surfactants. Six of the RCTs enrolled babies less than 30 weeks of gestation and one enrolled babies of 29 to 32 weeks of gestation. Mortality both before 28 days and before hospital discharge, was reduced by prophylactic surfactant treatment (RR of neonatal mortality = 0.61, 95% CI 0.48 to 0.77; ARD=-0.046, 95% CI -0.067 to -0.024; NNT=22, 95% CI 15 to 42).<sup>23</sup> The incidence of RDS, pneumothorax (RR=0.62, 95% CI 0.42 to 0.89; ARD=-0.021, 95% CI -0.037 to -0.005; NNT=50, 95% CI 27 to 200) and pulmonary interstitial emphysema (RR=0.54, 95% CI 0.36 to 0.82; ARD=-0.026, 95% CI -0.043 to -0.009; NNT=38, 95% CI 23 to 111) were all decreased in babies treated prophylactically.<sup>23</sup> There was no difference in the incidence of BPD.<sup>23</sup> With the current mortality rates at tertiary centres, a reasonable option would be to give surfactant prophylactically to all infants less than 26 weeks gestation, and to those of 26 to 27 weeks gestation who have not received the benefit of antenatal steroids.<sup>21</sup> Infants who are at a significant risk of RDS

should receive prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation.<sup>23</sup>

### **How should the surfactant replacement therapy be given?**

For all of the surfactant replacement therapy trials, surfactant was instilled in liquid form via the endotracheal tube.<sup>21</sup> Some trials instilled all of the surfactant at once, while others instilled it in smaller aliquots.<sup>22</sup> Only one very small trial compared a slow infusion with bolus administration of surfactant. It concluded that slow infusion was at least as effective as bolus therapy.<sup>24</sup> There is no evidence to support the practice of placing the infant in multiple different positions during the administration of surfactant.<sup>24</sup>

### **What dosage should be used?**

Dosages have varied from 25 mg to 200 mg phospholipids/kg body weight as single doses in the different clinical trials. Surfactant-TA (a natural bovine surfactant) was more effective at a dose of 120 mg/kg than 60 mg/kg.<sup>24</sup> Curosurf (Chiesi Pharmaceuticals, Italy) (a natural porcine surfactant) was more effective acutely at 200 mg/kg than 100 mg/kg.<sup>25</sup> It may well be that lower doses would be appropriate for prophylaxis while higher doses might be required for treatment of established RDS when antisurfactant proteins are present in the airspaces.<sup>25</sup> Thus, it appears that improvements in outcomes are seen up to a dose of about 120 mg phospholipids/kg body weight for the first dose, larger initial doses do not lead to further improvements in outcomes.<sup>25</sup>

### **Should multiple or single doses of surfactant be used?**

Two trials of multiple versus single doses of surfactant replacement therapy (which included 394 babies in total) have been reviewed.<sup>24</sup> These studies compared infants treated with a single dose with either retreatment with up to three doses within the first 72 h for infants who had a deterioration (shown by a 0.1 increase in the fraction of inspired oxygen [FiO<sub>2</sub>] after an initial response) or retreatment with up to three doses at 12 h and 24 h after the initial dose for infants who remained intubated and required oxygen.<sup>25</sup> It should be noted that the babies studied were a heterogeneous group with gestational ages that ranged from 30 to 36 weeks in one study and a birthweight range of 700 g to 2000 g in the other.<sup>24</sup> Meta-analysis of the trials showed a reduction in the risk of pneumothorax (RR=0.51, 95% CI 0.30 to 0.88; ARD=

0.09, 95% CI -0.15 to -0.02) and a trend toward a reduction in mortality (RR=0.63, 95% CI 0.39 to 1.02; ARD=-0.07, 95% CI -0.14 to 0.0).<sup>24</sup> No complications associated with multiple dose treatment were identified.<sup>24</sup>

Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72 hr of life should have repeated doses of surfactant.<sup>24</sup> Administering more than three doses has not been shown to have a benefit.<sup>24</sup> One RCT showed that for synthetic surfactants, babies who received three prophylactic doses rather than one had decreased oxygen and ventilatory needs in the first week of life and lower mortality at 28 days and one year of life.<sup>24</sup>

### **What are the criteria for and timing of retreatment?**

Retreatment should be considered when there is a persistent or recurrent oxygen requirement of 30% or more and it may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose.<sup>26</sup>

### **How should ventilatory management be approached after surfactant therapy?**

Because of the rapid changes in lung mechanics and the ventilation/perfusion matching that occurs after rescue surfactant therapy, and the prevention of serious lung disease by the prophylactic use of natural surfactants, many infants can be very rapidly weaned and extubated to nasal continuous positive airway pressure (CPAP) within 1 hr of intubation and surfactant administration.<sup>21</sup> To do this, the premedication used for intubation should only cause a brief duration of respiratory depression and staff must be trained and skilled in rapid ventilator weaning. Such weaning is often performed with few or no blood gases, relying instead on the infant's clinical condition and spontaneous respiratory effort and with consideration of the oxygen requirements as determined from pulse oximetry and sometimes with the use of transcutaneous carbon dioxide measurements.<sup>21</sup>

There is currently no proof that a rapid wean and extubation approach improves long-term outcomes compared with the more traditional weaning approach. In two small randomized trials, such an approach led to a decrease in the need for more than 1 h of mechanical ventilation.<sup>25</sup>

### **If we can give surfactant therapy, do we still need to use antenatal steroids?**

According to current guidelines, expectant mothers with threatened preterm labour should be given a single

course of steroids. Large cohort studies indicate that the combination of surfactant and steroids is more effective than exogenous surfactant alone.<sup>27</sup> A secondary analysis of data from surfactant trials also indicates a reduction in disease severity in babies who received antenatal steroids. Two other RCTs have confirmed that antenatal steroids continue to reduce the risk of poor outcome, even in centres where surfactant is available;<sup>27</sup> one showed a reduction in RDS as well as an increase in survival without ventilatory support and both showed significant reductions in severe intraventricular hemorrhage.<sup>27</sup>

### Conclusion

Exogenous surfactant therapy is safe and has major benefits in the treatment of several respiratory diseases in the newborn. It has been well studied in RCTs of excellent quality, which have clearly documented that its administration should be standard in the treatment of RDS and as prophylaxis in identified groups of preterm babies. Evidence continues to be accumulated for its use in other newborn respiratory diseases. The Canadian Paediatric Society makes the following recommendations.

### Recommendations

1. Mothers at risk of delivering babies with less than 34 weeks gestation should be given antenatal steroids according to established guidelines regardless of the availability of postnatal surfactant therapy.
2. Intubated infants with RDS should receive exogenous surfactant therapy.
3. Infants who are at a significant risk for RDS should receive prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation.
4. Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72 h of life should have repeated doses of surfactant. Administering more than three doses has not been shown to have a benefit.
5. Retreatment should be considered when there is a persistent or recurrent oxygen requirement of 30% or more, and it may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose.
6. Options for ventilatory management that are to be considered after prophylactic surfactant

therapy include very rapid weaning and extubation to CPAP within 1 h.

7. Mothers with threatened delivery before 32 weeks gestation should be transferred to a tertiary centre if at all possible.
8. Infants who delivered at less than 29 weeks gestation outside of a tertiary centre should be considered for immediate intubation followed by surfactant administration after stabilization, if competent personnel are available.
9. Further research into retreatment criteria and the optimal timing of prophylactic therapy is required.

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