Newborn Guideline 6

SURFACTANT REPLACEMENT THERAPY IN NEONATES

1. INTRODUCTION

Pulmonary surfactant is necessary for normal lung function throughout post-natal life. Surfactant is a lipid/protein compound formed in alveolar type II cells. Surfactant phospholipids form a monolayer at the alveolar air-liquid interface that reduces surface tension forces to a minimum, facilitating alveolar expansion. Surfactant proteins (apoproteins A, B, C and D) are necessary for formation of the phospholipid monolayer and also play a role in host defense mechanisms.

A primary deficiency of surfactant in pre-term infants prevents the normal transition at birth from a fluid filled to an aerated lung, manifesting as neonatal respiratory distress syndrome (RDS). A secondary deficiency of surfactant may occur when pulmonary surfactant is inactivated by protein leak, infection or meconium aspiration.

Surfactant therapy may be used to reduce the risk of RDS in pre-term infants (prophylactic therapy) or to treat already established RDS (rescue therapy). Clinical trials in pre-term infants have demonstrated that surfactant therapy, given as prophylaxis or rescue, results in physiological improvements in lung function, reduction in complications of RDS and reduced mortality. Surfactant therapy may also benefit mature infants with meconium aspiration syndrome or pneumonia.

Meconium aspiration syndrome (MAS) generally occurs in term or post-term infants and may be associated with severe respiratory failure and persistent pulmonary hypertension. The presence of meconium in the lung inactivates pulmonary surfactant, causing secondary surfactant deficiency. There is evidence that surfactant therapy can partially reverse the surfactant inactivation and improve lung function. The limited data from controlled clinical trials indicate that surfactant therapy reduces the need for extracorporeal life support (ECLS) in infants with MAS.

The benefits of surfactant therapy are such that it should be considered a part of standard therapy in neonatal units providing at least short-term neonatal stabilization

2. BENEFITS OF SURFACTANT THERAPY

Clinical trials in infants with established RDS and in preterm infants at risk of developing RDS, have demonstrated consistent improvements in:

- Oxygenation and ventilation
- Reductions in rates of pneumothorax and pulmonary interstitial emphysema
- Reduced early mortality
Effects on bronchopulmonary dysplasia (BPD) have been less obvious although a reduction in the combined outcome of BPD and death has been found in some trials.

3. COMPLICATIONS OF SURFACTANT THERAPY

There are few adverse effects of surfactant therapy. Some infants may experience the following:

- Serious transient hypoxemia/bradycardia during surfactant administration (especially in very ill term infants) may limit the quantity of surfactant that can safely be given.
- Pulmonary hemorrhage, a complication of extremely low birth weight, is somewhat more frequent in surfactant treated infants.

4. INDICATIONS FOR USE

4.1 INFANTS WITH ESTABLISHED RDS (Hyaline membrane disease, HMD)

- Most common indication for surfactant therapy, sometimes termed “surfactant rescue therapy”.
- Usually occurs <34 weeks gestation, but more mature infants occasionally develop RDS.
- Eligible infants should fulfill the usual clinical and radiographic criteria for a diagnosis of RDS and must be tracheally intubated and mechanically ventilated for surfactant administration.
- Therapy is indicated for infants with at least moderately severe RDS, usually defined by oxygenation criteria such as:
  
  i. \( \text{FiO}_2 > 0.35 \) and patient \( \text{PaO}_2 \) 60-80 mm Hg or (pulse oximeter) \( \text{SpO}_2 \) 88-93%
  
  or

  ii. Arterial/alveolar oxygen tension ratio, \( \text{PaO}_2/\text{PAO}_2 \) (or a/A ratio) < 0.22

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\text{Alveolar oxygen tension calculation:} \\
\text{P}_A\text{O}_2 = [\text{FiO}_2 \times 713] – \text{PaCO}_2
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\( \text{PaO}_2 \) and \( \text{PaCO}_2 \) are determined directly by arterial blood gas analysis.

4.2 PREMATURE INFANTS AT RISK OF DEVELOPING RDS

Surfactant may be administered prophylactically to infants at high risk of developing RDS because of short gestation or low birth weight. However, routine treatment of infants at risk, defined by gestational age or birth weight, unnecessarily exposes some infants to the risks of intubation, mechanical ventilation and surfactant administration. At BC’s Children’s Hospital, infants born at or less than 26 weeks gestation are treated routinely, based on the literature and the local observation that 2/3 of these infants qualified for rescue surfactant therapy by the oxygenation criteria (\( \text{PaO}_2/\text{PAO}_2 < 0.22 \)). Clinical trials have shown that this approach may be more effective than treating only infants with established respiratory distress, particularly for the
most preterm infants. Infants delivered \( \leq 26 \) weeks should be delivered and treated in a Level III perinatal unit where feasible.

4.2 MECONIUM ASPIRATION SYNDROME

Term infants with severe respiratory failure secondary to meconium aspiration syndrome may benefit from surfactant instillation (multiple doses may be required) or lavage. Because data are limited, specific treatment criteria cannot be provided. Surfactant should be administered with caution to such patients as they may decompensate acutely.

4.4 OTHER INDICATIONS

Other conditions associated with surfactant deficiency (primary or secondary) include pneumonia, pulmonary hemorrhage and congenital diaphragmatic hernia. There are no clinical trials of surfactant therapy in these conditions; however, many infants with pneumonia and primary or secondary surfactant deficiency have received surfactant therapy with probable benefit.

5. TREATMENT

5.1 GENERAL

Prior to the administration of surfactant, be sure that all equipment needed to both monitor and treat the infant is readily available. Infants should be continuously monitored throughout treatment. This includes:

- Heart rate monitor
- Pulse oximeter
- Transcutaneous PCO\(_2\) monitor (optional)
- Airway pressure monitor
- Tidal volume monitor (optional)
- Indwelling arterial line (optional)
- Blood gas analyzer

5.2 THERAPEUTIC SURFACTANT PREPARATIONS

Most therapeutic surfactants are natural products, derived from animal lungs. Synthetic surfactants, containing phospholipids and recombinant surfactant proteins, are being developed. A synthetic surfactant containing phospholipids and chemical spreading agents (Exosurf) was recently withdrawn from the market.

Two surfactant preparations are currently available in Canada:

1. BLEST™ (Bovine Lipid Surfactant), BLES Biochemicals Inc., London, ON.
2. Survanta® (Beractant), Abbott Laboratories Limited, Saint-Laurent, QC.
Both these natural surfactants are of bovine lung origin, containing surfactant proteins B and C.

5.3 MANUFACTURERS’ RECOMMENDED DOSE

1. BLES  135 mg phospholipids/kg/dose (5 mL/kg)  
   Repeat up to 3 times within the first 5 postnatal days if oxygenation difficulties persist (see manufacturer’s recommendation).

2. Survanta  100 mg of phospholipids/kg/dose (4 mL/kg)  
   Repeat no sooner than 6 hours after the preceding dose if the infant remains intubated and requires at least 30% oxygen to maintain a \( \text{PaO}_2 \leq 80 \text{ mm Hg} \).

Local treatment criteria using BLES (Children’s and Women’s Health Centre of BC)

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<th>GESTATIONAL AGE</th>
<th>INITIAL TREATMENT</th>
<th>REPEAT TREATMENT</th>
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| 26 weeks or less | **Surfactant prophylaxis:**  
  • Routine intubation  
  • Give BLES to all babies by 30 minutes of age | • Ventilated  
  • >25% oxygen  
  • 8 hours or more since last dose |
| 27 weeks or more | **Surfactant treatment:**  
  • Ventilated  
  • \( \text{FiO}_2 >0.35 \) (\( \text{SpO}_2 88-93\% \)) or \( a/A <0.35 \) | • Ventilated  
  • >35% oxygen  
  • 8 hours or more since last dose |

5.4 TREATMENT NOTES

- Surfactant treatment should be administered with minimal delay after diagnostic and oxygenation criteria are met.
- Surfactant prophylaxis is effective when administered after the initial newborn resuscitation.
- It is unusual for an infant to require more than 3 doses of surfactant.
- Dosing recommendations are not precise and rounding up or down by 10% is reasonable.
- Smaller and more frequent doses may be indicated in unstable infants especially those with pulmonary hypertension.

5.5 METHOD OF ADMINISTRATION

- Ensure endotracheal tube is appropriately positioned.
- Suction, if necessary to clear airway.
• Defrost/warm surfactant to room temperature.
• Instill surfactant intratracheally through a 5Fr catheter placed in the infant’s endotracheal tube*.
• Administer in aliquots per manufacturers instructions.
• Assess adequacy of ventilation by:
  • Observing chest expansion/abdominal excursion
  • Monitoring tidal volume/transcutaneous PCO₂
• Adjust ventilation pressure/tidal volume as required during and after administration.
• Maintain satisfactory SpO₂/PaO₂ by adjusting FiO₂ as required. Oxygenation may improve rapidly after administration and FiO₂ must be reduced according to oximeter/blood gas results.
• Position baby during and after administration as per manufacturer’s instructions.

*Note: At BC Children’s Hospital, BLES has been administered via an endotracheal tube side-port connector, while continuing mechanical ventilation, with good results. This method of administration is slower and less likely to provoke bradycardia and desaturation than bolus administration through a catheter inserted in the endotracheal tube.

5.6 ADMINISTRATION COMPLICATIONS

• Oxygen desaturation – usually transient and may require a temporary increase in FiO₂, an increase in ventilator pressure/tidal volume or interruption of surfactant administration.
• Bradycardia – may be associated with oxygen desaturation or vagal stimulation; may require temporary interruption of administration.
• Increased PCO₂/reduced tidal volume – due to transient airway obstruction by surfactant.
• Leak of surfactant around ETT into the pharynx – ETT may be too small.
• Administration to one lung only – when ETT is in right main stem bronchus or if infant is not appropriately positioned for each aliquot of surfactant.

5.7 FAILURE TO RESPOND TO SURFACTANT MAY SUGGEST AN ALTERNATIVE DIAGNOSIS

• Pneumonia
• Pulmonary hypoplasia
• Congenital heart disease
• Myocardial dysfunction
• Congenital deficiency of surfactant protein

REFERENCES


Soll RF. 2003. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews. 1,


ACKNOWLEDGEMENTS

The BCRCP would like to acknowledge the contributions for the following practitioners in the update of this guideline:

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