Surfactant for Neonatal RDS: Impact on Ventilation

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Disclosure

• Nothing to disclose.

Objectives

1. Summarize surfactant replacement therapy in neonates

2. Understand the role of surfactant in neonatal respiratory physiology

3. Be made aware of the current impact of surfactant therapy on ventilation for neonatal RDS
Abbreviations

- SA = surfactant
- PT = preterm
- RDS = respiratory distress syndrome
- BPD = bronchopulmonary dysplasia
- PIE = pulmonary interstitial emphysema
- MAS = meconium aspiration syndrome
- CPAP = continuous positive airway pressure

Introduction

- Surfactant (SA) replacement – established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s.
- Systematic reviews of RCTs:
  - prophylactic SA administration in PT infants or as rescue therapy for PT with established RDS reduces mortality, decreases the incidence of air leak (pneumothoraces and PIE), and lowers the risk of chronic lung disease or death at 28 d of age, and improved survival without BPD.
  - Recent RCTs indicate that the benefits of prophylactic SA are no longer evident in groups of infants when continuous positive airway pressure (CPAP) is used routinely.

Introduction

- SA trials have included:
  - 23 and 34 weeks’ gestation
  - birth weight between 500 and 2000 g

- SA therapy decreased mortality rates most effectively in:
  - < 30 weeks’ gestation
  - birth weight <1250 g
Introduction

• **Prophylactic, or preventive, surfactant strategy**
  – intubation and SA administration to infants at high risk of developing RDS for the primary purpose of preventing worsening RDS rather than treatment of established RDS
  – SA administration in the delivery room before initial resuscitation efforts or the onset of respiratory distress
  – mostly, after initial resuscitation but within 10 - 30 min after birth.

• **Rescue or treatment surfactant strategy**
  – SA is given only to PT infants with established RDS.
  – most often administered within the first 12 hours after birth, when specified threshold criteria of severity of RDS are met.
    • Early rescue - within 1 to 2 hours of birth,
    • Late rescue - 2 or more hours after birth.

Introduction

• Delivery of SA can result in rapid improvement in:
  – lung volume,
  – functional residual capacity
  – compliance.

• Expeditious changes in mechanical ventilator settings may be necessary to minimize the risks of lung injury and air leak.

Introduction

• SA administration strategies have been based on manufacturer guidelines for individual SA.

• The dose of SA, frequency of administration, and treatment procedures have been modeled after research protocols.

• Given the long half-life for SA in PT infants with RDS, redosing should not be needed more often than every 12 h, unless SA is being inactivated by an infectious process, meconium, or blood.

• Dosing intervals shorter than 12 h recommended by some manufacturers are not based on human pharmacokinetic data.
Surfactant Deficiency States

1. **Primary Surfactant Deficiency**
   **RDS:**
   - Surfactant replacement: ↓ RDS incidence, mortality, lung air leaks; no ↓ in BPD or IVH

2. **Secondary Surfactant Deficiency / Dysfunction**
   - Surfactant Inhibition
     - meconium
     - blood & inflammatory proteins
     - cell membrane phospholipids
   - Surfactant degradation by bacterial phospholipases

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Let’s review!

Surface Tension, Lung Surfactant and Lung Function

- At end expiration, surface tension is ~0 mN/m, so there is no collapsing force and alveoli remain open.
- As each alveoli expands its surface tension keeps rising, generating a force that brakes further expansion, and providing the mechanism for equal aeration of all 300,000,000 alveoli
Natural Lung SA composition

- Phospholipids 85%
- Neutral lipids 5%
- Apoproteins 10%

~50% of phospholipids are Di-saturated

Function of Surfactant Components

- Surfactant phospholipids form a surface film

- Hydrophobic proteins
  - SP-B & SP-C inserts lipids onto the surface to move them in and out of the film during breathing

Understanding SA Apoproteins

<table>
<thead>
<tr>
<th>Group Name</th>
<th>Functions</th>
<th>Gene defect effect</th>
<th>Knock-out mice status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, &gt;25 kD hydrophilic</td>
<td>surfactant microstructures, anti-bacterial</td>
<td>None</td>
<td>No disease</td>
</tr>
<tr>
<td>SP-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP-D</td>
<td>surfactant re-uptake, anti-bacterial</td>
<td>None</td>
<td>Mild adult disease</td>
</tr>
<tr>
<td>Small, &lt; 8 kD hydrophobic</td>
<td>Essential for full dynamic properties</td>
<td>Lethal RDS</td>
<td>Lethal RDS at birth</td>
</tr>
<tr>
<td>SP-B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, &lt; 8 kD hydrophobic</td>
<td>Aids adsorption and re-spreading</td>
<td>Late ILD</td>
<td>No disease</td>
</tr>
</tbody>
</table>
### Comparison of US Surfactant Drugs

<table>
<thead>
<tr>
<th></th>
<th>Infasurf (calfactant)</th>
<th>Curosurf (poractant alfa)</th>
<th>Survanta (beractant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>calf lung surfactant</td>
<td>minced pig lung tissue</td>
<td>minced cow lung tissue</td>
</tr>
<tr>
<td>Lipids</td>
<td>surfactant only</td>
<td>surfactant + lung tissue</td>
<td>surfactant+ lung tissue+ synthetic</td>
</tr>
<tr>
<td>Proteins</td>
<td>SP-B 0.7%</td>
<td>0.38%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td></td>
<td>SP-C 1.0%</td>
<td>0.88%</td>
<td>1.0%</td>
</tr>
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</table>

### Surfactant Therapy

**SUMMARY**

Surfactant replacement therapy for preterm and term neonates with respiratory distress. (Ref: Pediatrics 2014;133;156)

- Respiratory failure secondary to SA deficiency is a major cause of morbidity and mortality in PT infants. SA therapy substantially reduces mortality and respiratory morbidity for this population.

- Secondary SA deficiency also contributes to acute respiratory morbidity in late-PT and term neonates with meconium aspiration syndrome, pneumonia/sepsis, and perhaps pulmonary hemorrhage; SA replacement may be beneficial for these infants.
Surfactant Therapy: Summary of the Science
Pediatrics 2014;133;156

1. Surfactant replacement, given as prophylaxis or rescue treatment, reduces the incidence of RDS, air leaks, and mortality in preterm infants with RDS (level of evidence (LOE 1).

2. Both animal-derived and newer synthetic surfactants with SP-B-like activity decrease acute respiratory morbidity and mortality in preterm infants with RDS (LOE 1).

3. Early rescue surfactant treatment (<2 hours of age) in infants with RDS decreases the risk of mortality, air leak, and chronic lung disease in preterm infants (LOE 1).

4. Early initiation of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic surfactant therapy (LOE 1).

5. Surfactant replacement has not been shown to affect the incidence of neurologic, developmental, behavioral, medical, or educational outcomes in preterm infants (LOE 2).

6. Surfactant treatment improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with meconium aspiration syndrome (LOE 2).

7. Surfactant treatment of infants with congenital diaphragmatic hernia does not improve clinical outcomes (LOE 2).

8. Antenatal steroids and postnatal surfactant replacement independently and additively reduce mortality, the severity of RDS, and air leaks in preterm infants (LOE 2).

SA Replacement Rx: Clinical Implications

• Preterm infants born at <30 weeks’ gestation who need mechanical ventilation because of severe RDS should be given surfactant after initial stabilization. (Strong Recommendation).

• Using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants. (Strong Recommendation).
SA Replacement Rx: Clinical Implications

- Rescue SA may be considered for infants with hypoxic respiratory failure attributable to secondary SA deficiency (e.g., pulmonary hemorrhage, meconium aspiration syndrome, or sepsis/pneumonia) (Recommendation).

- Preterm and term neonates who are receiving SA should be managed by nursery and transport personnel with the technical and clinical expertise to administer SA safely and deal with multisystem illness. Therefore, pediatric providers who are without expertise, or who are inexperienced or uncomfortable with SA administration or managing an infant who has received SA should wait for the transport team to arrive.

Clinical Comparisons of Surfactant Efficacies

- Survanta-Exosurf; Infasurf-Exosurf; Infasurf-Survanta

<table>
<thead>
<tr>
<th>Treatment of RDS</th>
<th>Surv</th>
<th>Exo</th>
<th>Infa</th>
<th>Surv</th>
<th>Infa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>306</td>
<td>308</td>
<td>213</td>
<td>190</td>
<td>305</td>
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<table>
<thead>
<tr>
<th>1st Outcomes</th>
<th>Surv</th>
<th>Exo</th>
<th>Infa</th>
<th>Surv</th>
<th>Infa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>23%</td>
<td>26%</td>
<td>20%</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>BPD</td>
<td>33%</td>
<td>29%</td>
<td>38%</td>
<td>41%</td>
<td>48%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>9%</td>
<td>13%</td>
<td>15%</td>
<td>6%</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>χ2(0-72hrs)/72</th>
<th>Surv</th>
<th>Exo</th>
<th>Infa</th>
<th>Surv</th>
<th>Infa</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2</td>
<td>42%</td>
<td>50%</td>
<td>45%</td>
<td>38%</td>
<td>44%</td>
</tr>
<tr>
<td>MAP</td>
<td>6.9</td>
<td>7.6</td>
<td>8.6</td>
<td>7.6</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Gold values are significantly better than comparator, P<0.05

One can only separate surfactants based on differential effects on RDS; Differential effects on mortality of BPD cannot be demonstrated.

INSURE (INTubation-SURfactant-Extubation)

In preterm infants with respiratory distress syndrome (RDS), INSURE has been found to reduce the:

- need for MV
- duration of respiratory support
- need for SA

This method may fail in some patients with:

- birth weight <750 g
- pO2/FiO2 <218
- a/ApO2 < 0.44

at the first ABG were independent risk factor for INSURE failure in <30 wks AOG infants.
INSURE (INtubation-SURfactant-Extubation)

INSURE treatment can be repeated (respiratory outcome similar in infants treated with single or multiple INSURE procedures).

It is possible that the multiple INSURE strategy might decrease the failure rate of INSURE and increase its effectiveness in preventing the need for mechanical ventilation (MV).

CPAP for RDS

Extremely PT infant during nCPAP care. Note loose fitting of nasal prongs, comfortable nesting and positioning of infant.

Key points for CPAP care

1. Infants on CPAP are completely dependent on open nasal passages.
2. Find the optimal body position for the infant (NIDCAP).
3. Use PT pacifier to minimize loss of pressure from open mouth.
4. Try to avoid suctioning the nose and use saline drops instead, then suction the oropharynx.
5. Use adequate humidification of gases.
6. Avoid using excessive force when fixating the nasal prongs.
7. The nosepiece should not be pulled tightly against the nose, rather positioned from under the nose.
8. Use the largest size prong that will sit without support in the nose.
9. Inspect the fixation when you see that the nosepiece is pressing too tightly against the nose or the CPAP pressure is difficult to hold.
10. Change to a larger prong as the baby grows.
AAP Committee on Fetus and Newborn: Resp Support in PT Infants at Birth  

- Current practice guidelines recommend administration of SA at or soon after birth in PT infants with RDS.

- However, recent multicenter randomized controlled trials indicate that early use of CPAP with subsequent selective SA administration in extremely PT infants results in lower rates of BPD/death when compared with treatment with prophylactic or early SA therapy.

- CPAP started at or soon after birth with subsequent selective SA administration may be considered as an alternative to routine intubation with prophylactic or early SA administration in PT infants.

AAP: Conclusions

1. Based on a meta-analysis of prophylactic SA versus CPAP as well as on other trials of more selective early use of SA versus CPAP not included in the meta-analysis, the early use of CPAP with subsequent selective SA administration in extremely PT infants results in lower rates of BPD/death when compared with treatment with prophylactic or early SA therapy (Level of Evidence: 1).

2. PT infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with SA is delayed or not given (Level of Evidence: 1).

3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy. (Level of Evidence: 1).

4. Infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care.

Care for these infants is provided in a variety of care settings, and thus the capabilities of the health care team need to be considered.
AAP: Recommendation

1. Using CPAP immediately after birth with subsequent selective SA administration may be considered as an alternative to routine intubation with prophylactic or early SA administration in PT infants. (Level of Evidence: 1, Strong Recommendation).

2. If it is likely that respiratory support with a ventilator will be needed, early administration of SA followed by rapid extubation is preferable to prolonged ventilation. (Level of Evidence: 1, Strong Recommendation)

Thank you!

Questions?