EXOGENOUS SURFACTANT SUPPLEMENTATION

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Introduction

The utility of surfactant treatment was demonstrated in premature animal models by Enhorning and Robertson and confirmed in the premature infant by Fujiwara and his colleagues in 1980. These reports resulted in an explosion in interest in surfactant for the treatment of RDS and possibly for other lung diseases in which surfactant deficiency can be suspected.

Natural and artificial surfactant

Pulmonary surfactant is a complex mixture of lipids and specific apoproteins, 80% phospholipid, 8% neutral lipids and 10-12% proteins. The phospholipid component consists of 60% saturated phosphatidylcholine (PC), 20% unsaturated PC and anionic phospholipids, phosphatidylglycerol (PG) and phosphatidylinosotol. The main active component is dipalmityl phosphotidylcholine (DPPC) which is responsible for reducing surface tension and maintaining alveolar stability,

Both animal and artificial surfactants are available on the market. The former, derived from bovine and porcine lungs, contains surfactant proteins B and C. It is more effective than artificial surfactant which lacks these surfactant proteins.

Administration of surfactant

There are two different modes of administration of surfactant, either direct instillation into the distal end of the tracheal tube via a premeasured bronchial suction catheter, or via nebuliser in the ventilator gases. Direct instillation of surfactant is less efficient and leads to surfactant losses in the endotracheal tube. The most uniform distribution of surfactant is by nebuliser during a brief period of manual ventilation (2-3 minutes), with respiratory physiotherapy and postural drainage. Administration of surfactant in 2-4 divided doses avoids early deterioration in gas exchange and unwanted vagal reflexes. The airways should not be suctioned for the first hour after surfactant administration. Several studies have demonstrated the beneficial effects of applied PEEP in improving and sustaining the therapeutic effect of surfactant.

Selective bronchial instillation of surfactant has been suggested using a conventional tube introduced in one main bronchus or using a bilumen tube or via a bronchoscope. The advantages deriving from this method are the deliver of large doses to distal regions of lung and the reduction of dose instilled (costs). The disadvantages are connected with the complexity of procedures and long time treatment.

Adverse effects of surfactant
Transient airway obstruction (correlated with transient hypoxemia and hypotension) has been demonstrated in premature babies and in newborns and the risk of pulmonary trauma and hemorrhage from dramatically increased tidal volumes from improved compliance has been suggested immediately after surfactant supplementation. Changes in cerebral perfusion from rapid redistribution of pulmonary blood flow into cerebral circulation can be present in very premature babies.

After impressive results in the treatment of neonatal respiratory distress syndrome (RDS), the use of surfactant has been proposed in several forms of lung pathology.

Clinical trials of exogenous surfactant supplementation have been conducted:
1. Neonatal Respiratory Distress Syndrome
2. Neonates with lung injury not related to prematurity
    - Congenital diaphragmatic hernia, before and after surgical repair
    - Meconium aspiration syndrome
3. Neonates, infants and children with lung injury
    - Inhalation syndrome
    - Treatment of bacterial pneumonia
    - Bronchiolitis
4. ARDS
    - Sepsis-induced
    - Trauma
    - Hypoxemic respiratory failure
    - Oncohematologic childern and adolescents

The use of surfactant in Respiratory Distress Syndrome (RDS) of premature babies
Controlled clinical trials for neonatal respiratory distress syndrome (RDS) have demonstrated significant improvement of gas exchange, reduced mortality, and a lowered incidence of air-leak complications. These beneficial effects have been obtained with human surfactant isolated from amniotic fluid, modified natural surfactant of bovine or porcine origin, as well as with protein-free synthetic surfactant.

A significant improvement in oxygenation is a consistent finding after administration of surfactant. The improvement in oxygenation is due to the ability of surfactant to stabilize the alveoli on expiration and allow an increase in FRC and possibly via an effect on pulmonary blood flow. The improvement in oxygenation is not matched temporally by an improvement in compliance. This appears more slowly but can be seen within the first 24 h.

Surfactant treatment results in a striking decrease in pneumothorax and other air leaks, with a tendency for greater decrease with animal surfactant preparation. Beneficial effects on neonatal mortality have been reported irrespective of the type of surfactant used or whether the surfactant was given prophylactically or by rescue treatment.

The expectation that surfactant, by lowering mechanical ventilatory requirements, the duration of oxygen exposure and other factors associated with bronchopulmonary dysplasia (BPD), e.g. pneumothoraces, would decrease the overall incidence of BPD has not been realized. No trial has shown a significant reduction in patent ductus arteriosus (PDA); in prophylactic trials an increase in PDA has been documented. The incidence or not of intraventricular hemorrage (IVH) remains controversial.

The debate between prophylactic and rescue therapy is not fully resolved. Arguments for the former are: administration immediately after birth facilitates earlier lung aeration and reabsorption of lung fluid, possibly ameliorating the barotrauma induced by ventilation, decreasing the leakage of inhibitor proteins, and improving the distribution of exogenous surfactant. Arguments against prophylaxis are: the expense of treating large numbers of infants based solely on birthweight or gestational age.

The initial response to surfactant depends not only by the severity of the underlying RDS, the degree of asphyxia and high pulmonary vascular resistance, and the presence of infection or pulmonary hypoplasia, but also depends by the number of dosed, the time of administration, the method of administration and appropriate ventilatory treatment following instillation.

The use of surfactant in lung pathologies of infants and children
After impressive results in the treatment of neonatal RDS, the use of surfactant has been proposed in several forms of lung pathology in infants and children. Several lung pathologies have been more widely investigated as meconium aspiration syndrome, inhalation syndrome, pneumonia, ARDS from different origins and bronchiolitis.

1. **The use of surfactant in meconium aspiration syndrome and inhalation syndrome**
The complex pathological changes in meconium aspiration syndrome of newborns and inhalation syndrome of infants include a chemical pneumonitis, airway plugging and a secondary deficiency of surfactant. Exogenous surfactant may be beneficial and bronchoalveolar lavage using diluted doses of surfactant has been very promising. The place of surfactant in relation to other interventions such as high frequency oscillatory ventilation, extra corporeal membrane oxygenation (ECMO) or inhaled nitric oxide remains unclear.

2. The use of surfactant in Acute Respiratory Distress Syndrome (ARDS)
Despite the introduction of novel treatments, the mortality from ARDS in the pediatric age group remains high. ARDS is characterised by damage to the arteriolar-capillary endothelium and alveolar epithelium, including type I and type II pneumocytes. Damage to the latter results in secondary surfactant deficiency and atelectasis. Response to surfactant treatment is unpredictable and ranges from no response to variable response or good response. Poor response may be due to inhibition of administered surfactant by plasma components filling the alveolar space. Better results have been obtained using higher or multiple doses of surfactant.

3. The use of surfactant in bronchiolitis
Surfactant has been used with success in the treatment of severe bronchiolitis. It is more effective during artificial ventilation in the presence of PEEP as the latter helps to keep the terminal bronchioles open.

Unanswered questions remains:
- how much surfactant to should be used? The efficacy of surfactant is related to the dose used as well as the severity of the lung pathology;
- when should supplementary doses of surfactant be used, and how much;
- what is the role of the immunological response after surfactant supplementation?

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