REVIEW ARTICLE

Surfactant Replacement Therapy Beyond Respiratory Distress Syndrome in Neonates

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Background: Surfactant replacement therapy is an established modality of treatment in preterm neonates with respiratory distress syndrome. In addition, there are various neonatal respiratory disorders which are characterized by surfactant deficiency in which surfactant therapy can be a feasible and safe option.

Objective: To collate the literature on the use of surfactant replacement therapy in neonates beyond respiratory distress syndrome and examine the evidence and newer developments.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE, and EMBASE up to June 2015; and previous reviews, including cross-references, abstracts, and conference proceedings.

Results: Evidence supports surfactant administration via bolus route in neonates with meconium aspiration syndrome, but additional robust evidence is required before its adoption in clinical practice. There is limited evidence to support surfactant therapy in neonates with pneumonia, pulmonary hemorrhage and bronchopulmonary dysplasia. Large multicenter randomized trials are needed to cement or refute the role of surfactant therapy in these disorders.

Keywords: *Management, Newborn, Respiratory disorders.*

Surfactant replacement therapy is an established effective and safe therapy for immaturity-related surfactant deficiency [1]. Meta-analysis of randomized controlled trials (RCTs) has confirmed that natural surfactant administration in preterm infants with RDS reduces mortality, decreases the incidence of pulmonary air leak (pneumothorax and pulmonary interstitial emphysema), and lowers the risk of bronchopulmonary dysplasia (BPD) or death at 28 days of age [2].

Although RDS is characterized by the absence or reduction of surfactant, there are other neonatal lung disorders in which inadequate functional surfactant — either by inactivation or inhibition of synthesis may be a prominent element of the pathophysiology either by inactivation or inhibition of synthesis. These include meconium aspiration syndrome (MAS), pulmonary hemorrhage, pneumonia, congenital diaphragmatic hernia and BPD. The objective of this review is to critically evaluate the role of surfactant replacement therapy in neonatal respiratory conditions other than RDS.

MECONIUM ASPIRATION SYNDROME

The pathophysiology of meconium aspiration syndrome (MAS) is complex and multifactorial. Constituents of meconium, especially bile salts, can inactivate surfactant. Inflammatory mediators, such as cytokines and eicosanoids, can also inhibit surfactant, as can the protein that leaks into the alveolar spaces [3]. Reduced pulmonary blood flow may cause pulmonary ischemia, with damage to the type II cells and reduced surfactant production. Airway obstruction may cause increased resistance and surfactant deficiency. Parenchymal lung changes may require high ventilator support and substantial supplemental oxygen, contributing to lung injury. Thus, surfactant replacement to break this vicious cycle is an attractive option. Two approaches have been attempted: surfactant replacement and surfactant lavage.

Surfactant Replacement

Evidence

In a meta-analysis of four trials (n=326) [4], surfactant replacement by bolus or slow infusion in infants with severe MAS had no statistically significant effect on mortality [typical risk ratio (RR) 0.98, 95% CI 0.41 to 2.39]. The risk of requiring extracorporeal membrane oxygenation (ECMO) was significantly reduced in a meta-analysis of two trials (n=208); [typical RR 0.64, 95% CI 0.46 to 0.9]. Findlay, *et al*. [5], in a trial of 40 term neonates, reported a statistically significant

reduction in the length of hospital stay (mean difference -8 days, 95% CI -14 to -3 days). There was no statistically significant reduction in duration of assisted ventilation, duration of supplemental oxygen, air leaks, chronic lung disease, need for oxygen at discharge or intraventricular hemorrhage. Another meta-analysis incorporated eight RCTs of surfactant for MAS with a total of 512 patients [6]. It reported that surfactant significantly treatment reduced oxygenation index, increased arterial oxygen/alveolar oxygen ratio, shortened hospitalization days and decreased mortality rate. There was no statistical difference in the durations of mechanical ventilation and oxygen therapy, and the incidences of air leaks, pulmonary hemorrhage and intracranial hemorrhage between the two groups.

Surfactant Lavage

An alternative approach to treatment of MAS is the technique of lung lavage. This takes advantage of the detergent-like property of pulmonary surfactant, in which meconium might be solubilized and literally "washed" from the lung. Thus, in addition to replenishing the lung with functional surfactant, lavage might theoretically remove particulate meconium and prevent some of the pathophysiology attributed to obstruction and toxicity [7]. Surfactant lavage has been performed in several animal and human studies, with an optimal total lavage fluid volume of 15 to 30 mL/kg [8-12]. The surfactant was diluted in these studies in physiological saline to obtain a final phospholipid concentration of 5 mg/mL [13].

Evidence

In a recent meta-analysis of surfactant lavage, lung lavage with diluted surfactant was shown to be beneficial to infants with MAS in terms of reduction in composite outcome of death or use of ECMO (RR 0.33, 95% CI 0.11 to 0.96; *n*=88) [14]. Additional controlled clinical trials of lavage therapy should be conducted to confirm this effect, to refine the method of lavage, and to compare lavage with other approaches including surfactant bolus therapy [14]. In a study of newborn lambs with respiratory failure and pulmonary hypertension induced by MAS, gas exchange and lung compliance were improved by lung lavage with dilute surfactant but not by bolus treatment [15]. Till further robust evidence is available, lung lavage with surfactant in MAS should be considered as an experimental therapy. In infants with MAS, if ECMO is not available, surfactant administration may reduce the severity of respiratory illness, mortality and decrease the number of infants with progressive respiratory failure requiring support with ECMO.

Recent Developments

Henn, *et al*. [16] assessed the effect of surfactant administration in 21 newborn pigs, preceded or not by bronchoalveolar lavage (BAL) with dilute surfactant, on pulmonary function in experimental severe MAS. BAL with dilute surfactant, followed by an additional dose of surfactant, produced significant improvements in arterial blood gases and pulmonary mechanics as compared with a single dose of surfactant.

A synthetic surfactant (CHF5633), containing SP-B and SP-C analogs, was tested in 26 newborn pigs for resistance to meconium inactivation in comparison to poractant alfa.

Surfactant was inactivated in both groups 6 hours after meconium instillation, but CHF5633 was more resistant than poractant alfa in terms of lipid peroxidation. This study indicates that CHF5633 may be as efficient as poractant alfa in experimental MAS [17].

In a recent study by Mikolka, *et al*. [18], budesonide was added into surfactant preparation curosurf to enhance efficacy of the surfactant therapy in experimental model of MAS. Combined therapy improved gas exchange, and showed a longer-lasting effect than surfactant-only therapy. In conclusion, budesonide additionally improved the effects of exogenous surfactant in experimental MAS.

PNEUMONIA

Surfactant inactivation may be associated with pneumonia [19,20]. Facco, *et al*. [21] studied kinetics of surfactant's major component, disaturated-phosphatidylcholine (DSPC), in neonatal pneumonia and concluded that DSPC half-life and pool size were markedly impaired in neonatal pneumonia, and that they inversely correlated with the degree of respiratory failure. In a small randomized trial of surfactant rescue therapy, the subgroup of infants with sepsis showed improved oxygenation and a reduced need for ECMO compared with a similar group of control infants [19]. Newborn infants with pneumonia or sepsis receiving rescue surfactant also demonstrated improved gas exchange compared with infants without surfactant treatment [20].

PULMONARY HEMORRHAGE

Experimental data suggest that the molecular components involved in pulmonary haemorrhage can biophysically inactivate endogenous lung surfactant, and exogenous surfactant replacement may be capable of reversing this process even in the continued presence of inhibitor molecules [22,23].

Evidence

In two clinical studies, the mean oxygenation index

improved in preterm and term infants who received surfactant following clinically significant pulmonary hemorrhage, with no clinical deterioration in any patient [24,25]. Case reports have also described the successful use of surfactant treatment after idiopathic [26] or iatrogenic [27] pulmonary hemorrhage. However, a recent systematic review [28] found no randomized or quasi-randomized trials evaluating the effects of surfactant in pulmonary hemorrhage in neonates, suggesting the need for such trials.

Recent Developments

A recent study evaluated the impact of surfactant upon *in-vitro* clot formation in order to assess the role of surfactant in the pathogenesis of pulmonary haemorrhage. The presence of surfactant impairs coagulation *in vitro* hence conferring greater risk of pulmonary haemorrhage in extremely preterm infants [29]. Bozdað, *et al*. [30], in an RCT compared efficacy of two natural surfactants (poractant alfa and beractant) for pulmonary haemorrhage in 42 very low-birth-weight (VLBW) infants. They concluded that both natural surfactants improved oxygenation, and the type of surfactant did not seem to have any effect on BPD and mortality rates in these patients.

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Pulmonary hypoplasia and pulmonary hypertension are the hallmarks of CDH, but morphologic and biochemical immaturity of the lung have also been noted, and exogenous surfactant as adjuvant treatment for the severe respiratory distress associated with this disease is an attractive concept. Data from human studies in CDH are conflicting. In human fetuses with CDH, amniotic fluid lecithin to sphingomyelin (L/S) ratios and phosphatidylglycerol (PG) levels have been inconsistent; some investigators have found normal values and others document values suggestive of lung immaturity [31-35]. Moreover, surfactant phosphatidylcholine synthesis and pool size do not appear to be altered by CDH, although turnover of phosphatidylcholine is faster in CDH, possibly due to increased catabolism and/or recycling [36]. Of the few studies that have examined surfactant proteins (SP) expression in CDH, data are available only for SP-A. The concentration of SP-A in tracheal aspirates of infants with CDH has been shown to be either unchanged [37] or reduced [38] by CDH.

Evidence

There have been no multicenter randomized trials of surfactant for respiratory failure due to CDH. In two retrospective analyses of patients in the CDH Study Group, surfactant treatment did not improve outcomes [39], and was associated with increased ECMO use, a higher incidence of chronic lung disease, and lower survival [40]. In preterm infants with CDH, the usage of surfactant was associated with a lower survival rate [41].

Recent Developments

Janssen, *et al*. [42] studied endogenous surfactant metabolism in the most severe CDH patients who required ECMO. These patients have a decreased surfactant phosphatidylcholine synthesis that may be part of the pathogenesis of severe pulmonary insufficiency and has a negative impact on weaning from ECMO. Cogo, *et al*. [43] measured DSPC and SP-B concentration in tracheal aspirates and their synthesis rate in infants with CDH compared to infants without lung disease. Infants with CDH had a lower rate of synthesis of SP-B and less SP-B in tracheal aspirates. In these infants, partial SP-B deficiency could contribute to the severity of respiratory failure and its correction might represent a therapeutic goal [43].

BRONCHOPULMONARY DYSPLASIA (BPD)

BPD describes the end product of a multitude of injuries and exposures to the preterm lung occurring prenatally, perinatally, and postnatally. The etiology of BPD is multifactorial, and involves derangements in multiple aspects of lung function (for example, surfactant production), repair from injury (for example, elastin deposition), and growth and development (for example, alveologenesis). These derangements of normal development are likely mediated, in part, by chronic inflammation that develops in the immature lung exposed to repetitive ventilator stretch with oxygen-enriched gas, often complicated by infection [44]. Surfactant dysfunction (defined as elevation in the values of minimum surface tension *in vitro*) occurs in a high proportion (43-76%) of preterm infants who remain intubated and ventilated at 1-2 weeks of age [45-47]. Infants are twice as likely to develop surfactant dysfunction during episodes of respiratory deterioration or infection, and higher minimum surface tension is directly correlated with an index of lung disease severity [45,46]. In these ventilated preterm infants, elevated minimum surface tension as measured in tracheal aspirates was associated with altered lipid composition, lower total protein in the surfactant fraction, and markedly lower content of surfactant proteins B and C. SP-B content had the strongest correlation with surface tension and was inversely related [45]. Similar findings relating SP-B content to surfactant dysfunction have been described in acute lung injury, thereby supporting the validity of using SP-B content as an indicator of surfactant function [48]. Heavy isotope labeling studies

of intubated infants with BPD have demonstrated altered surfactant phospholipid pools and reduced recycling of alveolar surfactant phospholipids [49,50].

Evidence

There is limited data evaluating late surfactant therapy for premature infants who require continuing ventilatory support beyond one week of life. Pandit, *et al*. [51] found that FiO_2 decreased significantly at 24 to 72 h after a single dose of surfactant to ten premature infants. Bissinger, *et al*. [52] also demonstrated a transient improvement in oxygenation of premature infants >7 days after treatment with two doses of surfactant. Katz and Klein [53], in a retrospective cohort study of 25 premature infants, found that late surfactant treatment was well tolerated, and that 70% of those treated had a short-term improvement in respiratory status. Laughon, *et al*. [54] in a multicenter pilot study administered surfactant to 136 intubated infants on days 3 to 10 of life, and reported a trend toward improved survival without BPD. Merill, *et al*. [47] in an open label pilot study of 87 very low birthweight infants reported a nonsignificant increase in the proportion of survivors without BPD when the number of late doses was increased.

Recent Developments

Keller, *et al*. [55] conducted a study to assess the safety and efficacy of late administration of SP-B containing surfactant (calfactant) in combination with prolonged inhaled nitric oxide (iNO) in infants ≤1,000g birth weight. They randomized 85 preterm infants ventilated at 7-14 d after birth to receive late administration of surfactant (up to 5 doses) plus prolonged iNO or iNO alone. Late administration of surfactant had minimal acute adverse effects. Clinical status as well as surfactant recovery and SP-B content in tracheal aspirate were transiently improved as compared to the controls; these effects waned after 1 day. They concluded that late therapy with surfactant in combination with iNO is safe and transiently increases surfactant SP-B content, possibly leading to improved short- and long-term respiratory outcomes [55].

An ongoing trial multi-center, blinded, randomized controlled clinical trial (NCT01022580) aims to evaluate the effects of booster doses of exogenous surfactant in addition to iNO on the outcome of survival without BPD at post-menstrual age of 36 weeks in extremely low gestational age infants.

CONCLUSION

Evidence demonstrating the utility of surfactant replacement therapry across the varied spectrum of neonatal respiratory disorders other than RDS exists, but there still remains a paucity of high-quality RCTs to recommend routine incorporation into clinical practice. Considering the evidence in support of surfactant replacement therapry as an effective management strategy in infants with MAS, large multicentric trials comparing bolus route and lung lavage route should be conducted. The outcomes should include short- and long-term clinical outcomes and any adverse effects. In addition, future studies should focus on carefully designed RCTs of surfactant replacement therapy in term or late preterm infants with proven bacterial pneumonia. In addition, experimental studies exploring the pharmacokinetics, optimal dose and dosing interval, concentration, method of delivery and duration of treatment regimen in each of these conditions are needed to further optimize neonatal outcomes.

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