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Review

Ancillary therapies to enhance success of non-invasive modes of respiratory support – Approaches to delivery room use of surfactant and caffeine?

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SUMMARY

During recent decades, non-invasive respiratory support has become popular for treating neonates with respiratory failure. Several prospective randomized controlled trials have been performed to compare use of continuous positive airway pressure (CPAP) as primary respiratory support in preterm infants with respiratory distress syndrome (RDS) to endotracheal intubation, mechanical ventilation and surfactant therapy. Systematic reviews of these studies suggest that routine CPAP at delivery is efficacious in decreasing bronchopulmonary dysplasia (BPD), death, or both. This led to the recommendation to consider CPAP to avoid endotracheal intubation. As surfactant therapy is known to reduce BPD and death, several ways to combine CPAP with surfactant have been described. With the increasing use of CPAP immediately after birth, the early use of caffeine to stimulate respiration has become a point of discussion. This review focuses on different modes of surfactant application during CPAP and on the early use of caffeine as ancillary therapies to enhance CPAP success.

1. Introduction

During recent decades, non-invasive respiratory support has become widely used to treat full-term and preterm neonates with respiratory failure. All non-invasive modes share some basic principles: the delivered airway pressure stabilizes the upper airways, preserves surfactant function, avoids end-expiratory alveolar collapse, and raises the intra-alveolar pressure that counteracts the hydrostatic pressure in small pulmonary vessels. Clinicians consider several potential indications for the use of non-invasive respiratory support. It applies positive pressure, which stabilizes the alveoli at the end of expiration, and it preserves surfactant, which is useful in preterm infants with respiratory distress syndrome (RDS). The same principles suggest that it may also benefit neonates with secondary surfactant deficiency, such as in the case of aspiration syndromes or bacterial pneumonia. In neonates with wet lungs, it supports the resorption of amniotic fluid; in infants with apnea of prematurity it may stabilize the upper airways and thereby ameliorate apnea caused by upper airway obstruction. Furthermore, it may benefit infants with congestive heart failure and/or increased pulmonary re-circulation (i.e. in preterm infants with hemodynamically significant persistent ductus arteriosus (PDA), where it may decrease pulmonary edema. However, non-invasive respiratory support may only be a symptomatic treatment or 'bridge' – until the underlying disease is treated appropriately.

Despite all these numerous possible indications, there are two main uses in neonates: first, RDS in preterm infants, as a primary support immediately after birth; second, to prevent extubation failure after initial stabilization using invasive mechanical ventilation. Here it may prevent respiratory failure and/or treat apnea of prematurity.

This article focuses on ancillary therapies to enhance the success of non-invasive modes of respiratory support during the early course of RDS after birth to avoid endotracheal intubation and mechanical ventilation. Several prospective randomized controlled trials (RCTs) studied the use of continuous positive airway pressure (CPAP) as primary respiratory support as compared to endotracheal intubation, mechanical ventilation, and surfactant replacement therapy [1–3]. Recently published systematic reviews of these

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studies suggest that routine CPAP at delivery is efficacious in decreasing BPD, death, or both [4–6]. This led to the recommendation to consider non-invasive modes of respiratory support to avoid endotracheal intubation by the European Association of Perinatal Medicine and the American Academy of Pediatrics [7,8].

However, CPAP failure remains an issue of major concern, as it seems to be associated with an increased rate of severe complications such as pneumothorax, severe intraventricular hemorrhage (IVH), or death [9]. Therefore, strategies to prevent CPAP failure are urgently needed.

For the therapy of RDS early after birth, non-invasive modes aim to stabilize aeration of the lungs, to preserve surfactant function, and to avoid alveolar collapse at the end of expiration. Surfactant deficiency may be at least in part responsible for the end-expiratory collapse of alveoli. In this situation, CPAP or other modes of non-invasive support may serve as a "bridge" until endogenous production of surfactant is sufficient or until surfactant replacement therapy can be provided.

In fact, the combination of non-invasive modes of respiratory support with surfactant replacement therapy may be an ideal combination of two highly effective interventions. Strategies to combine surfactant with non-invasive modes avoid the dilemma of withholding surfactant, a particular concern when non-invasive modes of respiratory support are being used. The use of surfactant as an "add-on" to non-invasive modes of respiratory support may therefore further improve therapy of RDS in order to avoid endotracheal intubation, mechanical ventilation, and eventually ventilator-induced lung injury, or death. Until now, several ways to combine surfactant with non-invasive modes have been described.

2. Combination of surfactant replacement therapy and non-invasive modes of respiratory support

2.1. INSURE procedure

A well-established way of combining non-invasive support with surfactant is the so-called "INSURE" approach (INtubation, SURfactant, Extubation): infants are intubated only for surfactant replacement therapy and rapidly extubated to non-invasive respiratory support as soon as they are considered stable. It was described first by Verder et al. in 1992 [10]. Since then, numerous observational studies and some prospective randomized trials of high quality have been published. Recently Isyaama et al. performed a meta-analysis of studies comparing early INSURE with nasal (n)CPAP alone in preterm infants with RDS who had never been intubated before [11]. Nine trials with 1551 infants were included in this meta-analysis. There were no statistically significant differences comparing INSURE with CPAP alone for the outcome variables chronic lung disease and/or death and/or for air leaks, although the pooled number of randomized infants was suboptimal. None the less, the point estimates of the relative risk estimates of these outcomes appear to favour INSURE over nCPAP alone. Adequately powered clinical trials are required to clarify this issue.

The main problem with the INSURE strategy remains that it still requires endotracheal intubation and a short period of positive pressure ventilation – a potentially traumatic procedure that is clearly associated with complications.

2.2. Strategies for surfactant application without endotracheal intubation and mechanical ventilation

As even short periods of positive pressure ventilation may induce lung injury, clinicians and clinical researchers are urgently looking for strategies to provide surfactant replacement therapy without use of endotracheal intubation, and for any mechanical ventilation that could be described as "non-invasive," "less invasive," or "minimally invasive."

More et al. recently reviewed the different approaches that have been reported and discusssed in the literature [12]. These include surfactant application into the pharynx, surfactant nebulization, and surfactant application via a laryngeal mask and via a thin endotracheal catheter.

2.3. Surfactant application into the pharynx

Surfactant administration via the nasopharynx was the approach first tested in a randomized trial by the Ten Centre Study group [13]. The idea is that infants "inspire" surfactant when they initiate spontaneous breathing, leading to surfactant spreading at the fluid–air interface. Inherently, a weakness of this method of surfactant delivery is that the dose delivered into the airways may be highly variable and cannot be measured easily. In this small trial [13], infants with a gestational age of 27–29 weeks were randomized to surfactant or 1 mL saline, administered into the oropharynx immediately after birth, and without non-invasive positive pressure support. The authors observed a decreased severity of RDS, less mechanical ventilation during the first 10 days, and a lower mortality (19% vs 30%, $P < 0.01$) in the intervention group. However, the interpretation of some of the study findings is hampered by the fact that, per protocol, a substantial number of study infants who were intubated for resuscitation received a second dose of surfactant via the endotracheal tube, and those who were still intubated at 1 h and 24 h after birth received a third and a fourth dose via the tube.

The method was only evaluated in one further study, where surfactant was delivered into the nasopharynx immediately after presentation of the shoulders at birth [14]. The intrapartum surfactant administration was combined with CPAP support postnatally. In this study, 13 out of 15 babies delivered vaginally were weaned quickly to room air, whereas five out of eight infants who received nasopharyngeal surfactant as well, but who were delivered by cesarean section, had to be intubated soon after birth. Thus, fluid clearance during vaginal birth may have an additive beneficial effect to this mode of surfactant delivery.

Surfactant administration into the nasopharynx certainly seems to be an attractive approach as it is really "minimally invasive." However, too few infants have been studied, and further research is necessary to determine the optimal preparation, dose, and the optimal timing of surfactant replacement therapy, as well as the ideal strategy to combine it with non-invasive respiratory support.

2.4. Surfactant nebulization

Using surfactant as "aerosol" is another well-known idea. Again it would be a genuinely "non-invasive" approach that would allow surfactant delivery without the potential trauma of laryngoscopy or mechanical ventilation. However, there are many technical difficulties: although data suggest that the ideal particle size is 0.5–2.0 μm, the substance must be stable during nebulization. Furthermore, the loss of substance is extremely high, causing significant costs. Only two prospective RCTs have been performed. Berggren et al. [15], examining the need for ventilation and rate of BPD, found no differences between infants who were treated with surfactant nebulization and control infants. In a more recent trial, Minocchieri et al. showed a decreased need for endotracheal intubation within the first 72 h but there was no difference in BPD incidence between groups [16]. Currently there are several studies ongoing.