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Exogenous surfactant replacement: how to deliver it?

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Abstract. Exogenous surfactant is a therapeutic option for newborns, children and adults with acute respiratory distress disorders. Although tracheal instillation is still reputed as the classical method of surfactant delivery, alternative techniques have been investigated. Surfactant administration by using thin intra-tracheal catheters, bronchoscopy, laryngeal mask airway, or nebulisation, although variably effective, appear to be less invasive when compared to tracheal intubation. However, further research is still needed to better clarify this matter. (www.actabiomedica.it)

Key words: exogenous surfactant, delivery method, ARDS, ALI

Introduction

Exogenous surfactant therapy is considered an effective strategy for the prevention and treatment of the acute respiratory distress syndrome of the newborn (RDS).(1-3) Conversely, due to some contradictory results observed in paediatric and adult patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), there is still controversy as to the feasibility and the efficacy of surfactant therapy in adults and in children beyond the neonatal age (4-11).

Regardless the age group, several other issues remain controversial or unsolved, such as the indications for surfactant treatment in different pulmonary diseases, the optimum timing for the first dose (or for additional doses), the best sedation and analgesia during the administration procedure, the best type of surfactant to be used (synthetic or of animal origin).

In addition, the safest and most effective delivery method for exogenous surfactant therapy is still a matter of debate. In general, surfactant replacement therapy requires an endotracheal tube in place, through which surfactant is instilled into the patient's lungs, either with a syringe, a thin catheter or a bronchoscope.

However, tracheal intubation is an invasive procedure which is associated with an increased risk of airways and lung injury, particularly in small preterm infants (12-14).

This implies that surfactant replacement should be administered by well-trained providers, capable to perform the intubation procedure safely and to deal with potential complications, such as transient oxygen desaturation, apnea, endotracheal tube obstruction, pneumothorax, bradycardia or cardiac arrest.

For these reasons, efforts to identify less invasive ways for administering surfactant, i.e. without the need of tracheal intubation and mechanical ventilation, have been performed by several authors.

In this brief review, we will summarize the main methods for delivering surfactant in adults, children and newborns with respiratory failure. Some potential advantages and main limitations of each single technique are indicated in the table 1.

Table 1. Different methods for surfactant delivery: main advantages and disadvantages

Methods of surfactant delivery	Advantages	Disadvantages
Instillation via intra-tracheal tube (4, 8, 9-11)	• Direct instillation within the lungs • Possibility to ventilate after the procedure • Airway secured	• Requires intubation or tracheal tube already in place • Invasive manoeuvre • Special skill required
Instillation via flexible bronchoscopy (5, 6, 15, 16)	• Instillation under direct vision • Possibility to selective treatment to segment of the lungs • Allows bronchoalveolar lavage • Easily repeatable	• Requires a relative large endotracheal tube to fit the bronchoscope • Special technology and expertise required
Instillation via laryngeal mask (22-24)	• Minimally invasive, not passing the vocal cords • Easier procedure compared to tracheal intubation • Possibility to ventilate after the procedure	• Dispersion of unknown amounts of surfactant in the digestive tract • Airways not secured • Special expertise required • Smallest size not suitable for extremely low birth weight infants
Nebulisation/aerosolisation (7, 25-28)	• Non invasive • Easily repeatable	• Special devices required • Unknown dose delivered to peripheral airways • Possible alteration of surfactant compounds • Less effective than instillation
Instillation via intra-tracheal insertion of a thin catheter (29-32)	• Minimally invasive (thin catheter instead of a regular ET tube) • Avoid mechanical ventilation	• Requires spontaneously breathing patients • Need for laryngoscopy • Potential dislodgement of the catheter during the instillation • No possibility to ventilate if needed
Intrapartum pharyngeal administration (33)	• Minimally invasive • Easy to perform	• Dispersion of unknown amounts of surfactant in the digestive tract • Cumbersome procedure • Tested for prophylaxis only
Intra-amniotic administration (34)	• Non invasive for the fetus	• Invasive technique for the mother • Not known how much surfactant is assumed by the fetus before delivery • Requires active respiratory efforts of the fetus

Exogenous surfactant administration in children and adults

Several studies addressing the safety and efficacy of exogenous surfactant administration in children and adults with ARDS/ALI, by means of different delivery methods, have been published in the last two decades.

In a controlled randomized study, the efficacy of a calf-lung surfactant (Infasurf®), instilled through the tracheal tube, was investigated in 42 children with severe acute respiratory failure. Children in the surfactant treated group showed a rapid improvement in oxygenation, a reduced duration of mechanical ventilation, and an earlier discharge from the paediatric intensive care unit (10).

These data were confirmed by a larger phase III paediatric trial, in which the group treated with exogenous surfactant therapy (Calfactant®) showed better oxygenation and survival. Surfactant was administered in four aliquots instilled intratracheally via a small catheter. Patient positions were changed between aliquots, while sedation and neuromuscular blockade were given for the procedure (11).

Few studies have reported the administration of surfactant by bronchoscopic instillation in children. Nakamura et al. tried to rescue a 9-year-old patient, who developed severe respiratory insufficiency 40 days after bone marrow transplantation. The patient progressively deteriorated, with bilateral, diffuse alveolar and interstitial infiltrates. Surfactant was administered via a bronchoscope, with some transient improvement of the oxygenation, even though the patient eventually died.(15) More recently, a 3-year-old boy, with sand aspiration ad respiratory failure from near-drowning, was successfully treated with sequential lung washing in both lungs, performed by a flexible bronchoscope inserted through the endotracheal tube, followed by exogenous bovine surfactant replacement (3 ml/kg) (16).

Finally, in a recent case report, two doses of natural surfactant (Poractant Alfa) were given by aerosol, using a pneumatic nebulizer and a space chamber, to a 18-month female who accidentally inhaled talc powder during a nappy change. The child fully recovered in few days (17).

In adults with acute respiratory failure, Gregory et al. reported a significant improvement in gas exchange, as well as a reduced mortality, by using repeated intratracheal administration of Survanta®, a natural bovine surfactant preparation, with cumulative doses between 400 and 800 mg/kg body weight (4).

In another study, the safety and efficacy of a bronchoscopic instillation of 300 mg/kg of Alveofact®, a bovine surfactant product, were studied in 10 adults with severe, sepsis-induced ARDS. The surfactant was delivered through a flexible bronchoscope to each segment of the lung, resulting in improved oxygenation, recruitment of formerly collapsed alveoli and intrapulmonary shunt reduction (5).

In contrast, a randomized, placebo controlled study, enrolling more than 700 patients with sepsis-induced ARDS, showed no benefits by using a synthetic surfactant preparation (Exosurf®) given via aerosol (7). Yet, the interpretation of the study is somehow complicated by the aerosolization technique used by the investigators, by which only a little amount of the surfactant (about 4.5%) reached the lungs, possibly resulting in a scarcely effective dose of the drug (7).

Exogenous surfactant administration in term and preterm newborns

Nowadays, most often the administration of surfactant is performed in the NICU after stabilization of the newborn in the first hours or days of life, following specific clinical indications, mainly based on oxygenation and ventilation criteria (1-3, 18).

Usually, the administration of exogenous surfactant entails the need for intubation of the patient, with instillation of the drug through the tube into the trachea, followed by a variable period of mechanical ventilation. Given the inherent risk of lung injury and infection due to invasive mechanical ventilation, many centres are now administering surfactant in infants with RDS using the "INSURE" technique (intubation, surfactant, extubation), i.e. via transient intubation with rapid extubation to nasal CPAP. This approach seems to reduce both the need for mechanical ventilation and the incidence of pneumothorax (19, 20).

However, also the INSURE technique implies a tracheal intubation, which remains an invasive and sometimes difficult procedure, especially in extremely premature infants, and requires experienced personnel (12, 13, 21).

Thus, alternative and possibly less invasive methods of surfactant administration, able to avoid the need for endotracheal intubation and mechanical ventilation, have been investigated by several authors.

Surfactant administration via the laryngeal mask (LMA)

The LMA is a supraglottic device widely used in adults as an alternative to the endotracheal tube. In recent years, smaller sizes to be used in newborn weighing over 1000-1500 grams have become available. The use of the laryngeal mask in neonates requires little or no reactivity of the patient and a skilled healthcare provider. Although the experience on the use of the laryngeal mask in neonates with RDS requiring surfactant is still limited, preliminary data have shown a good oxygenation response and no complications (22-24).

Nebulised surfactant administration

Few studies have demonstrated the feasibility of nebulised surfactant administration, mainly in experimental models or small series of patients (25-28). The major advantage of this approach would be that intubation and mechanical ventilation could be spared in spontaneously breathing patients. However, several technical problems are still pending, mainly related to the lack of dedicated equipment for administration, the physical characteristics of different types of surfactant, which might deteriorate during nebulisation, and finally the difficulty of measuring the effective dose of drug reaching the peripheral airways.

Surfactant administration by a thin catheter inserted in the trachea

Another technique for spontaneously breathing preterm newborns has been recently proposed by Kribs et al., in which surfactant is administered through a thin catheter, inserted in the trachea under classical laryngoscopic visualization. According to the authors, the main advantage of this method is that neither endotracheal intubation nor mechanical ventilation are required (29-31).

Notably, Gopel et al., have recently observed similar results in a multicentre randomised controlled trial, testing the value of this minimally invasive method of early surfactant administration in spontaneously breathing preterm infants, during CPAP support (32). In this study, 220 VLBW infants, (GA 26-28 weeks), were randomly assigned to receive either early surfactant administration during spontaneous breathing (108 infants) or a standard approach of intubation when judged appropriate, then surfactant administration during mechanical ventilation (112 infants). On day 2 or 3 after birth, 28% of infants in the intervention group were mechanically ventilated versus 46% in the standard treatment group ($p=0.008$). During their hospital stay, 33% of infants in the intervention group were mechanically ventilated compared with 73% in the standard treatment group ($p<0.0001$). The intervention group had also significantly fewer median days on mechanical ventilation and a lower need for O_2 at 28 days. However, in terms of mortality and incidence of serious adverse events there were no differences between groups (32).

Other methods for surfactant administration

Surfactant via intrapartum hypopharyngeal instillation or by intra-amniotic administration may have some promise as techniques for delivering prophylactic surfactant without intubation, but further studies are needed (32, 33).

Conclusions

The standard treatment with surfactant in neonates, children and adults with ARDS/ALI implies the direct instillation of the drug through a tube placed into the trachea. Interestingly, alternative techniques of administration, which include the use of thin intra-tracheal catheters, bronchoscopy, laryngeal mask airway, or nebulisation, appear to be less invasive and apparently just or nearly as effective. However, further research is still needed in order to prove their safety and applicability in different clinical conditions and populations.

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