Less invasive surfactant administration: Will it change the outcome of preterm infants with respiratory distress syndrome?

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Respiratory distress syndrome (RDS) is a common acute respiratory dysfunction in preterm infants. Its major pathogenesis is due to insufficiency of pulmonary surfactant and fail to effectively open their lungs after birth. Non-invasive ventilation is usually the first choices for preterm infants who can breathe spontaneously after birth. Early nasal continuous positive airway pressure (NCPAP) with or without non-invasive positive pressure ventilation (NIPPV) has become standard initial respiratory supports for those infants with mild to moderate RDS in many neonatal intensive care units. However, NCPAP/NIPPV failure may occur in some cases who require intubation some hours later. Invasive mechanical ventilations supports gas exchange for patients with respiratory failure or significant apnea, but the ventilation-related complications are well known. Searching better respiratory management protocol continues a major goal to reduce complications and improve outcome of preterm infants with moderate to severe RDS.

Surfactant replacement has been investigated since 1960s and become one of the standard treatment for very-low-birth-weight preterm infants since early 1990s.[1,2] In the past, clinical trials have demonstrated that exogenous surfactant supplementation effectively improve clinical outcome by either prophylactic or rescue administration for preterm infants less than 30 weeks' gestation.[3]

The administration ways for instilling exogenous surfactant into preterm infants' lungs are not only one. Traditionally, exogenous surfactant is instilled via the endotracheal tube (ETT) in the mechanically ventilated infant and that procedure allows rapid deposition and perhaps get homogenous surfactant distribution into distal alveolar spaces.[2] However, both ETT intubation and mechanical ventilation are invasive and well known to have many potential risks of complications.

The Intubate-SURfactant-Extubate (INSURE) procedure is a modified way for surfactant instillation followed by rapid extubation. This procedures usually require short-acting sedatives for intubation on awake with spontaneously breathing infants, but some of them might require longer periods of ventilation or even reintubation due to prolonged respiratory suppression of sedatives.[2] Nevertheless, no evidence suggests that either early INSURE or NCPAP alone is superior to the other in the published meta-analysis report by Isayama et al.[4] Further studies to elucidate the efficacy of using INSURE procedure on moderate RDS are required for future clinical application.

Other reported alternative ways for surfactant instillation include pharyngeal, aerosolized, laryngeal mask airway-guided, and thin catheter administration.[5] Among them, thin catheter administration way seems to be the most permissive way, which is called as minimally invasive surfactant administration (MISA) or less invasive surfactant administration (LISA). The way of MISA/LISA slowly administers exogenous surfactant (usually 1–3 minutes) via a thin catheters (feeding tubes, suction catheters, umbilical arterial catheters, etc.) which is usually introduced into the larynx by using a Magill forceps.[2,5–10] The most common indication of applying MISA/LISA on RDS infants is that the requirement of fractional inspired oxygen gets 0.3 or higher.[10] The best benefit of MISA/LISA is no need of inserting an ETT. During surfactant instilling period, the infants breathe spontaneously and be supported with NCPAP or NIPPV. Usually, little or no sedation is applied for the procedure. However, slow application of surfactant and closely monitoring is necessary because coughing and surfactant reflux may occur.[2] Coughing may also influence the deposition of supplemented surfactant in lungs.[2] In a study to evaluate the changes in lung volume while performing MISA/LISA, the investigators also demonstrated a rapid and homogeneous increase in patients' end-expiratory lung volume associated with an improvement in oxygenation.[11] Effective reduction of NCPAP failure rate and risk of pneumothorax in infants of 29–32 weeks' gestation by using MISA/LISA were reported.[12] Therefore, MISA/LISA in combination with NCPAP in preterm infants with RDS have been suggested,[13] but caution is still required because there is still not enough evidence to support its potential clinical benefits.[14]

We are happy to introduce the meta-analysis report of Cho ZL et al, published in the February issue of the *Journal of the Chinese Medical Association*, on the clinical value of LISA in preterm infants with RDS.[15] The authors concluded 10 clinical trials which were reported from 2013 to 2018, enrolling 3341 preterm infants (n = 1666 in LISA group and n = 1675 in control group). The average gestational ages of preterm infants in

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those enrolled trials were around 25–31 weeks. The exogenous surfactants applied in the enrolled trials are all porcine-derived surfactant (Curosurf, Poractant alfa).[15] Their meta-analysis revealed that LISA procedure significantly reduced the incidence of mechanical ventilation requirement, bronchopulmonary dysplasia, intraventricular hemorrhage/periventricular leucomalacia and retinopathy of prematurity. They also demonstrated that LISA did not increase the risks of death, pulmonary hemorrhage, or pneumothorax in enrolled infants.[15] Their conclusion is that LISA is an effective and safe treatment for preterm infants with RDS.[15]

MISA/LISA was getting more widely used in treating very-low-birth-weight and extremely-low-birth-weight preterm infants during past years. Its safety and effectiveness are the major concerns in clinical practice. We congratulated the successful meta-analysis of Yang Y and Cho ZL et al. Although we get more information regarding to the beneficial contribution of MISA/LISA in caring preterm infants with mild to moderate RDS, there are still some concerns to be clarified in the future. Therefore, future researches and more clinical trials in MISA/LISA, including facility and technique refinements, other or new synthetic surfactant preparations, and combination therapy with other medications or therapeutic method, are required to further improve outcome of very-low-birth-weight preterm infants with various severities of RDS.

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