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Clinical Pearl: Surfactant: Potential for an Even Less Invasive Future?

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Surfactant has remained the mainstay of treatment for neonates with respiratory distress syndrome for over twenty years. The new 2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommends surfactant administration to all infants born at or prior to 30 weeks of gestation intubated for stabilization and all infants, regardless of gestational age managed with non-invasive respiratory support who require a FiO_2 >0.3 on CPAP (continuous positive airway pressure) >6 cm H_20 (1). In hopes of reducing the incidence of bronchopulmonary dysplasia (BPD) with gentle ventilation, an increasing number of centers have started relying on non-invasive modes of respiratory support even in very premature infants (2), leading to an increased interest in non-invasive surfactant administration.

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Traditionally, surfactant has been primarily administered via an endotracheal (ET) tube and then distributed with invasive positive pressure ventilation, followed by a gradual wean of respiratory support (3). However, alternative methods of surfactant administration have been around for quite some time. INSURE (intubate— surfactant— extubate) as well as LISA (less invasive surfactant administration) or MIST (minimally invasive surfactant treatment) were both described by Verder et al. in 1992 (3,4). The INSURE technique allows for intubation, ET surfactant administration, followed by only brief ventilation and planned, rapid extubation to CPAP. It has been associated with reduced lung injury (1).

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In contrast, LISA (less invasive surfactant administration) allows surfactant administration via a thin catheter and its distribution via spontaneous breaths and non-invasive CPAP ventilation. Several studies have demonstrated that LISA minimizes the need for mechanical ventilation and is associated with improved outcomes in preterm infants, including decreased BPD incidence at 36 weeks and decreased risk of intraventricular hemorrhage compared to infants receiving surfactant via INSURE. As a result, the 2022 European RDS guidelines recommend using the LISA/MIST technique when possible (1,3).

The largest trial looking at LISA/MIST, the OPTIMIST-A trial, was a multicenter, randomized clinical trial by Dargaville and colleagues that examined the effect of MIST specifically in preterm infants with a gestational age of 25 to 28 weeks who were supported with CPAP and required a fraction of inspired oxygen of 0.30 or greater within six hours of delivery (5). The infants were randomized to the MIST group, or the control group where they received sham treatment. The authors note no significant difference concerning the primary outcome of death or BPD. Regarding secondary outcomes, the MIST group significantly decreased the need for intubation within 72 hours of delivery, mechanical ventilation, CPAP duration, and the rate of pneumothoraces. However, the authors noted that their data suggested an increased mortality risk associated with MIST in the gestational age range of 25-26

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weeks. Given this, the authors cautioned using MIST within this patient population (5).

However, the findings from this clinical trial require careful interpretation. Firstly, there was a difference in baseline variables between the two groups within the gestational age groups of 25-26 weeks. Infants within the MIST group for this gestational age range had a higher frequency of male sex, multiple births, and no or incomplete exposure to antenatal corticosteroids compared to the control group. This implies that subgroup analyses by gestational age may have been affected by an imbalance in baseline variables which may have contributed to findings favoring the control group at 25-26 weeks gestational age (6). Additionally, the authors note that the deaths were due to various causes in both groups and had occurred at various points throughout the first months of life.

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Although recommendations still seem to lean towards less invasive surfactant administration, specific characteristics of the ideal technique have yet to be determined. The use of LISA/MIST may help to reduce airway inflammation; however, it still requires instrumentation of the airway, which can be painful for the infant and has the potential to cause a vasovagal reaction. Additionally, there have been concerns that the instillation of surfactant directly into the trachea has led to brief periods of cyanosis and bradycardia associated with decreased cerebral blood flow, with a theoretical risk for intraventricular hemorrhage. However, as previously mentioned, that risk seems to be minimized with LISA (1,3).

These observations have led to a search for an even less invasive mechanism for surfactant delivery. A recent meta-analysis completed by Gaertner and colleagues demonstrated that surfactant nebulization reduced the intubation rate in preterm infants with no difference in mortality outcomes as well as morbidities, including sepsis, air leak, grade 3 and 4 IVH, moderate or severe BPD and NEC (7). In this study, surfactant nebulization was most effective in infants over 28 weeks gestation, using a pneumatically driven nebulizer, and in infants receiving ≥ 200mg/kg of animal-derived surfactant. Given the limitations of standardization amongst the studies included in this meta-analysis, the quality of evidence from this study is limited. However, the initial evidence is promising and calls for further, well-designed trials designed to measure mortality and other relevant secondary outcomes as more and more institutions move towards less invasive surfactant administration.

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