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MINIMALLY-INVASIVE SURFACTANT THERAPY: CURRENT PRACTICE AND FUTURE TRENDS

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ABSTRACT

Minimally-invasive surfactant therapy has the potential to ease the burden of respiratory morbidity in preterm infants. It is now recognized that preterm infants ≤28 weeks gestation can be effectively supported from the outset with nasal continuous positive airway pressure. However, this form of respiratory therapy may fail to adequately support those infants with significant surfactant deficiency, with the result that intubation and delayed surfactant therapy are then required. Infants following this path are known to have a higher risk of adverse outcomes, including death, bronchopulmonary dysplasia and other morbidities. In an effort to circumvent this problem, techniques of minimally-invasive surfactant therapy have been developed, in which exogenous surfactant is administered to a spontaneously breathing infant who can then remain on continuous positive airway pressure. This less invasive surfactant administration technique shows some short-term benefits but still cannot be recommended for general use in this vulnerable population. Long-term follow-up studies are needed to allow new recommendations on surfactant therapy in this high-risk population.

KEYWORDS: MIST, Preterm infants, Respiratory distress syndrome.

BACKGROUND

Preterm infants who have respiratory distress syndrome have for many years been managed with a combination of early intubation and exogenous surfactant therapy. It is now recognized that applying continuous positive airway pressure (CPAP) in an extremely preterm infant is a reasonable alternative to early intubation after birth. Meta-analysis of large controlled trials comparing these two approaches suggests a benefit of CPAP, with a small reduction in the risk of the composite outcome of death or bronchopulmonary dysplasia.

In the past decade, there has been an upsurge in the use of CPAP as primary therapy for preterm infants, bringing with it the dilemma of whether and how to give exogenous surfactant. In an effort to circumvent this problem, techniques of minimally invasive surfactant therapy have recently been investigated, aiming to administer surfactant to spontaneously breathing infants, allowing them to remain on CPAP in the critical first days after birth and, hopefully, beyond. These techniques have included administration of exogenous surfactant by brief tracheal catheterization, aerosolization, and laryngeal mask. Of these, the methods involving brief tracheal catheterization have been most extensively studied, with surfactant administered by using both a flexible feeding tube and a semi-rigid vascular catheter.

In recent clinical trials (AMV [Avoidance of Mechanical Ventilation by Surfactant Administration] trial, Take Care study and NINSAPP [Surfactant Application During Spontaneous Breathing With Continuous Positive Airway Pressure in Premature Infants <27 Weeks] trial), surfactant delivery via a feeding tube was found to reduce the need for subsequent intubation and ventilation and to improve short-term respiratory outcomes. Despite the relatively small numbers of infants in these trials, this technique has found its way into clinical practice in some centers. Further randomized controlled trials of surfactant administration via tracheal catheterization are underway or planned, and they will help clarify the place of this therapeutic approach. Additional studies will be needed to identify the best means of infant selection, refine the instillation technique, resolve the uncertainties regarding sedation and determine the optimal surfactant dosage.

Various methods of Minimally-invasive surfactant therapy

In view of the difficulties associated with intubation for surfactant delivery, less invasive means of delivering surfactant have been pursued. Several techniques of "minimally-invasive surfactant therapy" (MIST) have been described in which surfactant is delivered without tracheal intubation, including nasopharyngeal

instillation.[1] laryngeal mask placement.[2] and aerosolisation.[3]

Aerosolized or Nebulized Route

Aerosolized surfactant was evaluated in animal studies in the early 1990s; however, the first human study was published in 1997 by Jorch et al.[4] who conducted an uncontrolled multicenter feasibility study in 20 infants. Since then, this method has been tested in 2 RCTs.18, 32 Arroe et al.[5] conducted an uncontrolled observational study in preterm infants and demonstrated no benefits from nebulized surfactant. Finer et al[6] conducted a feasibility study and suggested that aerosolized surfactant was well tolerated and might reduce the need for endotracheal intubation. No adverse effects were reported apart from transient desaturation.

Berggren et al.[7] compared infants treated with aerosolized surfactant with control infants who did not receive surfactant and reported no difference in the need for mechanical ventilation or incidence of BPD. Minocchieri et al.[8] conducted an RCT of aerosolized porcine surfactant (Curosurf; Chiesi USA, Inc) vs CPAP alone and demonstrated a decrease in the need for intubation in the first 72 hours; however, they found no difference in the incidence of BPD.

LMA-Guided Administration

The first attempt at surfactant instillation using an LMA was described in a case series of 8 infants by Trevisanuto et al.[9] with limited demonstrable benefits. This method was subsequently tested in 1 RCT of 26 newborns by Attridge et al.[10] who reported that surfactant administration via an LMA resulted in a reduction in the mean fraction of inspired oxygen requirement for 12 hours after the intervention; however, no significant difference was reported in the subsequent need for mechanical ventilation or BPD. Adverse events reported included hypoxia and bradycardia during surfactant administration, laryngospasm, and malposition of the LMA.

Pharyngeal Route

The first trial of nasopharyngeal surfactant administration was conducted by the Ten Centre Study Group in 1987 in 328 infants.[11] A decrease in the severity of RDS, the use of mechanical ventilation in the first 10 days, and incidence of mortality were observed .

However, with the theoretical uncertainty about the amount of surfactant that actually gets delivered into the trachea, this approach has only been investigated further in a small case series by Kattwinkel et al.[12] None of these methods appears ready for clinical application on a wider scale at present.

MIST using a feeding tube

Another method of MIST in which the trachea is catheterised with a feeding tube has been reported.[13,14,15,16] The technique involves insertion of a 5 French gauge feeding tube into the trachea with Magill's forceps. Surfactant is then administered over 1–5 minutes and the catheter thereafter removed. A randomised controlled trial of MIST using this technique (the AMV trial) has recently been conducted in infants 26–28 weeks gestation having $FiO2 > 0.30$ in the first 12 hours.[17] Compared to controls, surfactant-treated infants had a lower rate of subsequent mechanical ventilation (28% vs 45%); no difference in the rate of pneumothorax or other adverse events was noted. A further trial comparing this method of MIST with standard intubation in very preterm infants (23–26 weeks gestation) has now been completed and the results are awaited.

An alternative approach in which a flexible feeding tube is passed through the vocal cords without using Magill's forceps has recently been reported.[18] Surfactant delivery with this method was compared with INSURE in infants <34 weeks gestation, with the finding of a reduction in early mechanical ventilation and a decreased incidence of BPD. This method would amount to a procedural challenge for most practitioners and is thus unlikely to be widely adopted.

The "Hobart method" of MIST

Surfactant instillation by flexible feeding tube has several technical difficulties that may limit its widespread application. Clinicians who solely practice oral intubation will be unfamiliar with Magill's forceps, and may find them cumbersome and hard to use. Additionally, the highly flexible feeding tube may on occasions be difficult to insert through the vocal cords, and also difficult to maintain in position once inserted. For these reasons and with the recognition of the potential benefits of MIST, one of research group has developed an alternative and novel MIST technique using a narrow bore vascular catheter (16 gauge Angiocath, Product No. 382259, Becton Dickinson, Sandy, UT, USA). This catheter has an external diameter of 1.7 mm and a length of 135 mm and is made from fluorinated ethylene propylene polymer. It has the dual properties of sufficient stiffness to allow guidance towards and beyond the vocal cords and sufficient elasticity and softness to avoid damage to the vocal cords and other vital structures. This catheter can be advanced through the vocal cords under direct vision using a laryngoscope, without the need for Magill's forceps. A curvature in the catheter can be fashioned if desired to facilitate placement. Surfactant can then be administered in one or several boluses and respiratory support continued with nasal CPAP. A video of the technique can be accessed at the OPTIMIST-A trial website (http://www.menzies.utas.edu.au/optimist-trials).

Clinical experience with the Hobart method

A preliminary evaluation of the Hobart method of MIST was conducted at RHH and a two-site feasibility study was undertaken at RHH and RWH.[36] In the initial study at RHH, MIST was performed in 25 infants, of gestational age range 25–34 weeks and birth weight

range 500–3000 g. The MIST procedure was performed in the delivery room in 2 cases, and after arrival in the Neonatal Intensive Care Unit. No pre-medication was used. Surfactant (Curosurf, Chiesi Farmaceutici, Parma, Italy) was delivered at a dosage of approximately 100 mg/kg, given in 1 or 2 boluses. The surfactant was successfully administered in every infant, with two attempts at catheterisation needed in 9 (35%). Brief bradycardia (heart rate <100 beats per minute) was noted in 11 infants (44%), usually contemporaneous with insertion of the laryngoscope blade, and in all cases self-resolving within 10 seconds. Positive pressure inflations were required after surfactant administration in 11 infants (44%).

The further feasibility study of the Hobart method of MIST enrolled 61 infants of 25–32 weeks gestation. Eligibility for MIST was based on the need for CPAP pressure ≥7 cm H2O and FiO2 ≥ 0.30 (25–28 weeks) or ≥0.35 (29–32 weeks). At RHH, 3 infants in the 25–28 week gestation group were treated with FiO2 < 0.30; each had a CPAP pressure of 8 cm H2O and signs of respiratory distress. Overall, the 25–28 week group received MIST at a mean age of 3.5 ± 3.5 hrs (mean ± SD) and the 29–32 week infants at 10.8 ± 7.5 hrs. Surfactant was successfully administered in all cases, with two catheterisation attempts required in 20%. Positive pressure inflations by mask were used in 39% of infants prior to reinstitution of CPAP.

Respiratory course and outcomes in infants treated with MIST have been compared with like-gestation historical controls achieving the same CPAP and FiO2 thresholds (data from the RHH-RWH preterm CPAP cohort). Within each gestation range, the control infants were comparable to those treated with MIST in terms of median gestation, birth weight, exposure to antenatal corticosteroids, mode of delivery and Apgar score at 5 minutes. Several potential benefits of MIST were identified. FiO2 was more rapidly weaned in surfactant-treated infants than controls in the first 72 hrs. Need for intubation <72 hrs was diminished after MIST, most notably for infants at 25–28 weeks gestation (OR 0.21, 95% CI 0.083-0.55), but with a strong trend in the same direction in the 29–32 week group (odds ratio 0.34, 95% CI 0.11-1.06). Duration of oxygen therapy was reduced in infants treated with MIST at all gestations.

The findings of the evaluation of MIST using the Hobart method, coupled with the clear evidence that CPAP failure occurs largely because of unremitting RDS and is associated with adverse outcomes, have been the genesis of the OPTIMIST-A trial. The first of a pair of clinical trials investigating MIST in preterm infants at different gestation ranges (25–28 and 29–32 weeks). The acronym is derived from Collaborative Paired Trials Investigating Minimally-Invasive Surfactant Therapy. There is considerable scientific justification for this trial, with strong data in support of: a) the poor outcome for those failing CPAP, b) the capacity to identify such infants early, c) the potential for MIST to alter the outcome in such infants and d) the potential benefits of surfactant delivery in the spontaneously breathing infant. It is thus appropriate to subject MIST to the highest level of scientific scrutiny in the form of a randomised controlled trial.

Evidence From RCTs

Efficacy

Two RCTs.[17,18] have evaluated the thin catheter intervention. Kanmaz et al.[18] compared the INSURE method with intratracheal surfactant administration using nasogastric tubing as a catheter in 200 preterm newborn infants. They described a reduction in the need for mechanical ventilation at 72 hours in the thin catheter group. The incidence of BPD was also relatively low in the intervention group. Göpel et al.[17] compared the standard method of care with surfactant administration via a thin catheter in 220 very-low-birth-weight neonates with gestational ages of less than 29 weeks and reported a reduction in the need for mechanical ventilation in the intervention group. Kanmaz et al.[18] reported a significant reduction in the incidence of BPD (P = .009) in the intervention vs control groups.

Safety

Kanmaz et al.[18] reported that bradycardia and desaturation rates were similar in both groups in their study; however, they observed that surfactant reflux during administration via a thin catheter was significantly higher than in the INSURE group (21% vs 10%; P = .002). Twelve percent of infants had severe apnea lasting 20 seconds and bradycardia (<100 beats/min) requiring positive-pressure ventilation with a T-piece device during surfactant administration via a thin catheter. Göpel et al.[17] reported episodes of bradycardia and significant desaturation in 5% of the neonates in their intervention group.

CONCLUSION

Overall, this review comprehensively summarizes the methodologic details, effectiveness, and safety of the different methods of surfactant administration while maintaining spontaneous breathing. However, the RCTs were limited in their description of the individual methods and included small samples. Observational studies had larger samples but they were not looking at the specific question of thin catheter instillation vs intubation as a method of surfactant administration. The choice of surfactant also differed between the studies, thus affecting generalizability. In addition, none of the studies evaluated early childhood neurodevelopmental outcomes.

Surfactant administration via a thin catheter may be an efficacious and potentially safe method; Further, large RCTs are required to assess the neonatal and childhood outcomes of infants treated with early stabilization by CPAP followed by selective surfactant administration by thin catheter compared with those of infants treated with

intubation as the method of surfactant administration. Further studies are also needed for other methods of minimally invasive surfactant administration.

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