Respiratory Report: Minimally Invasive Surfactant Therapy (MIST) Questions and Controversies

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I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

Surfactant replacement therapy has been the gold standard for the treatment of respiratory distress syndrome (RDS) for decades. Traditionally infants requiring surfactant have been intubated and surfactant instilled via the endotracheal tube (ETT), and then the infant was manually ventilated via resuscitation bag. In the "good old days" this was done without pre-medication, however rapid sequence induction (RSI) has become the standard of care for intubation in all but the most emergent situations.

Sometime in the mid to late 1990's word out of Germany of a new technique of giving surfactant emerged. Rather than intubating the baby, surfactant was given by performing laryngoscopy and passing a feeding tube (or another suitable catheter) through the vocal cords into the trachea while the baby was receiving CPAP. The surfactant was trickled into the lungs with the baby breathing spontaneously, and no manual ventilation was performed at all.

I gave surfactant this way the first time in the late 1990s. Using a feeding tube I found it fairly easy to perform the procedure, but did note that once the surfactant hit the carina the baby had a propensity to become bradycardic, hence quite a bit of stimulation was required during the procedure, but the end result was a reduction in FiO_2 to 0.21 and additional dosing was not required.

In recent years, MIST or less invasive surfactant administration (LISA) has become all the rage with many centres now routinely using this approach. In the unit I practice in, we have had variable results and have resorted to using a 5Fr umbilical catheter to administer surfactant as safety changes made to feeding tubes make them incompatible with standard syringes, and we found the multi-access catheter (MAC) is too flimsy to facilitate easy placement. As well, atropine is now given prior to the procedure to mitigate vagal response.

That manual ventilation (handbagging) is less than ideal has been know now for some time. Even the most experienced clinicians invariably give higher pressure (with attending higher volume) than they think, and it has been surmised that even handbagging to assess ETT placement is a set up for chronic lung disease. (CLD). With that in mind, the concept of delivering surfactant without the risk of barotrauma and volutrauma associated with manual ventilation sounds like a great idea. Who doesn't want to reduce the risk of CLD? However, with RSI being the accepted standard for ETT placement, this raises questions regarding neuroprotection and mitigation of discomfort during laryngoscopy which, of course, must be performed in order to place whatever catheter one uses properly through and below the vocal cords.

Dr. K. Barrington notes that laryngoscopy and intubation have not generally been separately evaluated in studies of physiological responses in the neonate during intubation and that laryngoscopy itself produces several physiologically undesirable effects.(1) How then, does MIST/LISA compare with the traditional method of surfactant administration? The discomfort of laryngoscopy is still present as are vagal responses, and the risk of cerebral hypertension from the baby coughing and struggling still exist. Given this, one might expect that neurological sequelae might be more prevalent in the former patients. This has certainly been at the forefront of my thoughts on the subject.

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There are ways to give surfactant via ETT that do not involve handbagging. Dr. J Pillow (Australia) advocates giving surfactant while the baby is being mechanically ventilated rather than handbagging it in. (2) One must be careful not to contaminate the flow sensor (if present) and adjustments to pressure and inspiratory time must be made to compensate for the higher viscosity of surfactant, but since the pressure is limited by the ventilator the risk of over-distention is reduced. This is my preferred method of giving surfactant to an intubated baby.

This brings us back to the babies receiving MIST/LISA. What evidence do we have to support the safety and efficacy of this new practice? As it turns out, a study out of Germany seems to indicate that the practice is not only safe, outcomes are improved across the board when compared to traditional installation via ETT.

There is a notable exception to these findings: a sub-group prone to focal intestinal perforation (FIP) (those of less than 26 weeks gestational age). Those who remember my column on non-invasive ventilation (NIV) will recall that I do not believe infants of less than 25 weeks gestational age are good candidates for NIV. There may be many reasons for the increase in FIP, but the increased rate was of statistical significance. The authors postulate that, with this subset of patients, the air in the intestines stretches the intestinal membrane such that sheer forces are increased and microtears form, similar to what may happen with conventional ventilation and conducting airways producing air leak.

The German study does not mention (as far as I could find) the use of any adjuncts such as atropine to reduce vagal effects. It also does not go into detail regarding the use of RSI for intubation, something that could affect results, but it is a large study with compelling data worth further investigation. (3)

"A solution in search of a problem" is a common sentiment among some of my colleagues and I must admit having similar feelings myself. After all, the rate of CLD in our post 27-week group of

infants is low and decreases rapidly to zero by 30 weeks, so the question of how much benefit there is versus how much more discomfort there is for the patient is, I think, valid. In addition, several colleagues have indicated that placing the catheter while maintaining NIV is at best awkward, and at worse far more difficult than intubation, and a quantity of surfactant ends up being swallowed, although smaller volume dosing may reduce this. Still, particularly in units struggling with high CLD rates in their later gestation patients, MIST/LISA may well be an improvement over traditional practice and may improve not just pulmonary outcomes, but others as well.

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While neonatology has a long history of things that we thought were great (chest physio and dexamethasone come to mind), those struggling with the question of safety and efficacy of MIST/LIST can take some solace in knowing that current evidence suggests the practice appears safe, at least for now. What is needed is further investigation comparing outcomes using routine RSI for intubation and surfactant delivery of atropine and MIST/LISA. As is the case with non-invasive ventilation, I suspect the key to success is in the selection of proper patients.

Another factor to consider in very premature patients being managed with NIV is FiO_2. Until anti-oxidant production and supplementation are established, the premature infant has no protection from free radicals and is therefore very susceptible to oxidative stress. There seems to be great variance in clinical practice when it comes to just how high a safe FiO_2 is. I firmly believe less is best.

This is my seventh submission to Neonatology Today, and I am honoured to share stories, experience, and up and coming practice with you, dear readers. I welcome questions, suggestions, and ideas for future columns.

Be well all, and enjoy the summer!

References:

1 https://www.cps.ca/en/documents/position/endotracheal-intubation-newborn
2 personal communication
3 https://www.nature.com/articles/s41598-018-26437-x

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