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EDITORIAL

Administering surfactant without intubation – what does the laryngeal mask offer us?☆,☆☆

Administração de surfactante sem intubação – o que a máscara laríngea nos oferece?

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In our management of the preterm infant in need of respiratory support, we are currently grappling with competing priorities. Avoiding intubation at the beginning of life (other than for advanced resuscitation) appears to be a sensible proposition, both in infants ≤ 29 weeks gestation,[1] and certainly in those beyond 29 weeks. On the other hand, avoiding intubation means forgoing the usual conduit to deliver surfactant, the very drug that over the years has been our security blanket in dealing with the scourge of respiratory distress syndrome (RDS). Combining continuous positive airway pressure (CPAP) with selective surfactant delivery in a minimally-invasive protocol offers a great deal of promise for preterm infants of all gestations,[2,3] avoiding the pitfalls of mechanical ventilation no matter how expertly applied.

Simply put, what is needed is an approach where we can recognize at an early stage the infants on CPAP who have significant RDS, and selectively administer surfactant to these infants without resorting to intubation. But at present, the path toward this simple goal is beset by confusion and uncertainty. It is not yet clear which infants to select, and what to take into account. What combination of CPAP pressure level, FiO_2, and age, and for which gestations? Will it help to take an X-ray[4] or do a functional surfactant assay?[5] Having made a decision to give surfactant, the methods for delivering it are multiplying, a testament to the ingenuity of neonatologists in developing new techniques, and along with them, new acronyms.[6] But several key questions have yet to be answered: Should it be bolus surfactant instillation, or aerosolization, seemingly the least invasive method, but not yet widely available in the clinic.[7] Acknowledging the clinical availability of bolus administration, how should it be delivered? Intra-tracheal via a thin catheter inserted under direct vision, or supra-glottic via a laryngeal mask airway (LMA) or by pharyngeal deposition? Should analgesia be used, or avoided?

A study in this issue of *Jornal de Pediatria* examines how surfactant instillation by LMA compares with administration after intubation in preterm infants at 28–35 weeks gestation.[8] In a single-center randomized controlled trial (RCT), infants with RDS managed on CPAP and reaching treatment criteria (based on respiratory symptomatology and oxygen requirement) were randomized to receive surfactant via LMA or endotracheal tube (ETT). Those in the ETT group were pre-medicated with remifentanil and midazolam, and extubation occurred at an unspecified time (but some hours) after surfactant administration. Redosing of surfactant was according to specified criteria. The primary outcome was the proportion of infants in whom FiO_2 was ≤0.30 at 3 h post-intervention, assessed irrespective of whether intubated or on CPAP. This primary outcome was reached by 20 out of 26 infants in the LMA group (77%) and 17 of 22 in the ETT group (77%), with the trial stopped short of the calculated 30 infants per group

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in view of equivalence in this outcome at interim analysis. Redosing of surfactant was required in 23% and 18% of the LMA and ETT groups, respectively. Only around half of the LMA group ultimately avoided intubation, and the time of mechanical ventilation was longer in these infants than in the ETT group. The study was not powered to detect differences in other in-hospital outcomes.

The study by Barbosa et al. has the strengths of randomized controlled design, a sound research question, and application of failure and redosing criteria to help clinicians act in an unbiased manner given the lack of blinding. Weaknesses of the study include the small sample size, and the comparison of physiological indicators (e.g. FiO_2 and Silverman-Anderson score) that have different meanings in ventilated and non-ventilated infants. Additionally, the estimate of surfactant delivery to the lung (administered volume minus aspirated gastric fluid volume) is of questionable value and does not appear to have been validated. The measure assumes that any gastric fluid aspirated is undiluted surfactant, and that all the surfactant deposited in the stomach will be aspirated. Neither assumption is likely to hold, rendering the measure too imprecise to give a credible answer to the question of how much surfactant was actually delivered to the lung.

The study by Barbosa et al. adds to a body of evidence on surfactant administration by LMA that has burgeoned in the past year. It is one of two recent RCTs that have compared LMA administration with surfactant therapy after intubation.[8,9] The other was ostensibly a comparison of LMA surfactant with the intubate-surfactant-extubate (INSURE) approach, except that narcotic premedication used in the INSURE group led to difficulties with extubation, and predetermined that more infants in this group would achieve the primary outcome (need for mechanical ventilation or naloxone within 1 h).[9] In some other respects the findings were similar in these two trials, including the observation of a rather high rate of surfactant redosing after LMA administration (38% in the two studies combined). A figure of around 20% might be expected in infants of gestation $\geq$ 28 weeks, both with ETT administration or by thin catheter.[10]

Two other RCTs have compared surfactant administration by LMA with continuation of CPAP in infants $\geq$ 28 weeks[11,12]; in one case, the results as yet have only been reported in abstract form.[12] The design of these two studies was similar to others examining less invasive methods of surfactant delivery,[13,14] with the threshold for enrollment being an FiO_2 above 0.30, and the control group remaining on CPAP without surfactant therapy. Both studies concluded that surfactant seemed to be successfully administered by LMA, after which in the recent study by Roberts et al. there was a reduction in the need for intubation post-intervention.[12]

So by what yardstick should we gauge the relative merits of LMA administration, along with the other new methods of surfactant administration in the non-intubated subject? The following measures are suggested: familiarity (of the technique to the proceduralist), applicability (of the method to the target population), tolerability (the profile of unwanted effects), and capability (of the technique to deliver surfactant to the lung and optimize its distribution).

Using the above rubric, surfactant administration by laryngeal mask has a mixed scorecard. Whilst the LMA is increasingly promoted as a tool for facilitating resuscitation,[15,16] many neonatologists and neonatal trainees have little or no familiarity with the device or its technique of insertion. Learning the essentials may be only a matter of training, but as with most neonatal procedures, full mastery of laryngeal mask placement will inevitably require some good and bad experiences. In this respect, surfactant delivery by LMA is currently trumped by tracheal catheterization, because direct laryngoscopy is familiar to any neonatal proceduralist, and the insertion of a thin catheter through the vocal cords is not dissimilar to insertion of an endotracheal tube.

The measure of applicability finds surfactant delivery by LMA in a thorny position, because as of now the method cannot realistically be used in infants <28 weeks gestation and <1.2 kg, who represent a substantial proportion (at least one-third) of all preterm infants destined to require surfactant having started life on CPAP.[17] So if an LMA is to be used to deliver surfactant in those above 1.2 kg, another method will be needed for smaller infants, and procedural competency will need to be maintained for two techniques. On the other hand, LMA placement may be easier in awake spontaneously breathing infants above 1.2 kg than direct laryngoscopy, with the tone of the pharyngeal musculature being problematic for proceduralists now accustomed to using premedication, including muscle relaxants for non-emergent intubation in more mature infants.[18] This premise has yet to be tested in a head-to-head comparison of LMA placement against thin catheter insertion; such a comparison will be important in choosing a less invasive surfactant delivery method appropriate for this patient group.

It is in relation to tolerability that LMA placement for surfactant instillation has the most promise, potentially involving less direct pressure on the anterior hypopharyngeal wall and less mucosal trauma than during standard laryngoscopy. This form of instrumentation for surfactant delivery may thus be applied with fewer side effects, and without the need for sedation. Indeed, reported rates of reflex bradycardia in the LMA studies (0–7%)[9,19,20] do appear to be lower than what is noted with tracheal catheterization (6–35%),[10,13,21] although the incidence of hypoxia does not clearly differ. Again, only by direct comparison of the methods will the relative frequency of unwanted effects be properly assessed.

The final measure to be applied is whether the LMA is capable of effective delivery and distribution of exogenous surfactant. In advance of definitive information on the fractional delivery of a surfactant dose to the lung, it can be stated that LMA administration is likely to be superior to aerosolization in this respect, given that the latter technique results in <10% pulmonary deposition of the administered surfactant in most studies.[7] Whether it is superior to simple pharyngeal deposition is unknown. Assuming correct catheter placement, tracheal catheterization assures surfactant delivery to the trachea at the first pass, but certainly does not preclude reflux back into the pharynx, as noted in up to 30% of cases,[10] and also seen in some of the LMA studies. The ultimate fate of such refluxed surfactant is indeterminate, but at least some of it will re-enter the trachea during further spontaneous inhalations.

Capability also encompasses the distribution of surfactant within the lung, and here LMA administration is again

potentially found lacking, because with an LMA, positive pressure ventilation (PPV) is needed to disperse the surfactant from the bowl of the LMA into the lung. There is mounting evidence suggesting that pulmonary distribution and/or tissue incorporation of exogenous surfactant is better when achieved by spontaneous breathing rather than application of PPV. Clinical trials comparing administration of equivalent doses of surfactant delivered by tracheal catheterization (with no PPV) or by intubation (with PPV) have all noted benefits of the former approach.[22] Beyond the lack of another explanation, the argument that these benefits are due to better surfactant distribution is strengthened by the finding of a more homogeneous increase in aeration when surfactant is delivered by spontaneous breathing[23] compared with PPV. Experimental studies in which surfactant distribution has been directly measured during spontaneous breathing are few, and the results are thus far contradictory. One study in preterm rabbits found better tissue incorporation of surfactant with spontaneous breathing,[24] whereas another in preterm lambs ($n = 4$ per group) found surfactant distribution to be somewhat worse, with greater surfactant deposition in the right upper lobe than with ETT administration.[25] The fact that an infant's respiratory effort may improve surfactant dispersion is a windfall we did not necessarily expect as this new area of surfactant research opened up. It must now be pursued to the fullest extent, with well-conducted experimental studies that provide clarity on the mechanism and extent of any benefit of spontaneous breathing in aiding surfactant distribution.

In summary, placement of an LMA potentially lends us the opportunity to administer exogenous surfactant to preterm infants beyond 1.2 kg (some of whom who may tolerate direct laryngoscopy poorly), which with the aid of PPV probably enters the lung in high proportion, but may spread less well than under conditions of spontaneous breathing. We still need to know whether the technique can become widely applicable, how much surfactant actually reaches the lung, and whether in larger studies this approach is superior to continuation of CPAP, or to alternative forms of surfactant administration, including tracheal catheterization. Only when these gaps in knowledge are filled will we fully understand what the LMA has to offer for surfactant therapy in the preterm infant.

Conflicts of interest

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