REVIEW ARTICLE

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Less invasive surfactant administration methods: Who, what and how

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Surfactant administration via an endotracheal tube (ETT) has been the standard of care for infants with respiratory distress syndrome for decades. As non-invasive ventilation has become commonplace in the NICU, methods for administering surfactant without use of an ETT have been developed. These methods include thin catheter techniques (LISA, MIST), aerosolization/ nebulization, and surfactant administration through laryngeal (LMA) or supraglottic airways (SALSA). This review will describe these methods and discuss considerations and implementation into clinical practice.

Journal of Perinatology (2024) 44:472–477; https://doi.org/10.1038/s41372-023-01778-2

INTRODUCTION

For infants with respiratory distress syndrome (RDS), surfactant administration via an endotracheal tube (ETT) has been the standard of care for decades. As non-invasive ventilation (NIV) has become commonplace in the NICU, methods for administering surfactant without use of an ETT have been developed. These methods include thin catheter techniques (LISA, MIST) [1], aerosolization/ nebulization, and surfactant administration through laryngeal (LMA) or supraglottic airways (SALSA). This review will describe these methods and discuss considerations and implementation into clinical practice. The clinician should note that currently the only U.S Food and Drug Administration approved device to deliver surfactant is an ETT and all methods reviewed here are considered off-label use.

DESCRIPTIONS

Thin catheter techniques

Thin catheter surfactant administration is the most well-studied of the less invasive techniques. The two most common thin catheter techniques are LISA (less invasive surfactant administration) and MIST (minimally invasive surfactant therapy). LISA, first described in 1992 by Verder [2] in a pilot study and later in 2007 by Kribs [3] in Cologne, Germany, involves use of a laryngoscope and Magill forceps to pass a 4 to 5 French feeding tube through the vocal cords into the trachea for surfactant administration. MIST (also called the Hobart technique) was described in 2011 by Dargaville [4] in Hobart, Australia. Similar to LISA, laryngoscopy is performed during MIST, but instead of a feeding tube, a 16-gauge vascular catheter is passed through the vocal cords into the trachea for surfactant administration. Magill forceps is not needed since a vascular catheter is more rigid then the feeding tube employed for LISA. These methods are frequently and collectively referred to as LISA and for brevity, this review will do the same.

Performing the LISA technique. While the infant is maintained on NIV, a small diameter catheter (feeding tube, angiocatheter or umbilical line catheter) is placed through the vocal cords by laryngoscopy. Based on the stiffness of the catheter, a Magill forceps may be needed to assist in placement of the catheter. Surfactant is then administered slowly (over 1–3 min) and the catheter is then removed. The infant continues to breathe spontaneously throughout the procedure and positive pressure breaths are not given unless the infant requires positive pressure ventilation (PPV) for hypoxemia or bradycardia.

A photo of the LISA technique is shown in Fig. 1. Video demonstrating the LISA procedure being performed in the clinical setting can be found at https://youtu.be/IYf92NN1kV0. Video demonstrating the MIST (Hobart method) procedure being performed in the clinical setting can be found at https://www.youtube.com/watch?v=ULHyMFpK5GA&pp=ygUnbGVzcyBpbnZhc2l2ZSBzdXJmYWN0Y-W50IGFkbWluaXN0cmF0aW9u.

Aerosol

Aerosolization/nebulization represents the least invasive method for surfactant administration and has been pursued for decades with the first report by Robillard [5] in 1964 and reemergence of trials in the late 1990's and early 2000's [6–9]. Technical problems with this method have been substantial and have included: attaining a particle size that makes its way to be deposited to the lungs and is not exhaled, stability, delivery over a reasonable timeframe and delivery of an appropriate dose to the lungs. Currently, the FDA has not yet approved a device for aerosolization of surfactant and clinical use has been limited to trials or expanded access to devices undergoing FDA review.

Performing the aerosol technique. Various aerosolization/nebulization devices have been investigated including a jet nebulizer, vibrating mesh, heated capillary and a pneumatically driven device. Some devices interface directly with the respiratory

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Received: 18 May 2023 Revised: 14 August 2023 Accepted: 12 September 2023
Published online: 22 September 2023

Fig. 1 MIST/LISA technique. Used with permission. Dargaville et al. OPTIMIST-A Trial Investigators. Effect of minimally invasive surfactant therapy vs sham treatment on death or bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome: The OPTIMIST—a randomized clinical trial. JAMA 2021; 326(24): 2478–2487. Copyright © 2021 American Medical Association. All rights reserved.

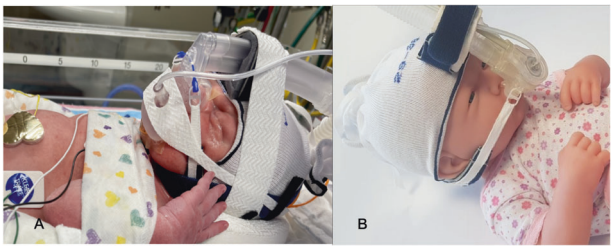

Fig. 2 Aerosol technique. A Aero-02. Photo by Scott Guthrie. Used with parent and ONY Biotech permission. **B** AeroFact. Used with permission Aerogen Pharma.

support while others are separate from the respiratory support (inserted into the mouth similar to a pacifier). Dosing of surfactant for this method is typically twice the intratracheal dose.

Photos of the aerosol technique are shown in Fig. 2.

SALSA: Surfactant administration through laryngeal (LMA) or supraglottic airways

While once reserved for the "difficult airway", the laryngeal mask airway (LMA) has transitioned from a device rarely used, to one being used for resuscitation [10, 11], short surgeries [12, 13], transport [14, 15], and medication administration [16]. Familiarity with the device in the NICU setting has increased dramatically in large part due to increased exposure through the American Academy of Pediatrics Neonatal Resuscitation Program (NRP). Since 2016, NRP guidelines now incorporate training of placement of an LMA as part of the certification program [17]. While the term LMA is more familiar to providers, LMA is a registered trademark of Teleflex Incorporated, therefore, the term supraglottic airway device (SAD) will be used in this review to encompass all supraglottic airway devices available for clinical use in neonates. Use of an SAD for administration of surfactant was first described in case reports in 2004 [18] and 2005 [19] with the first randomized, controlled trial (RCT) published in 2013 [20].

Performing the SALSA technique. The SALSA technique is performed by placing an SAD in the mouth and advancing until resistance is felt, indicating placement in the posterior pharynx. An adapter with a CO_2 detector is placed on the proximal end of the SAD and positive end-expiratory pressure (PEEP) is administered through a T-piece, anesthesia, or self-inflating bag. Surfactant is administered through a separate limb of the adapter, allowing for continuous PEEP to be delivered. Positive pressure breaths are not given unless the infant requires PPV for hypoxemia or bradycardia (Note: if a self-inflating bag is used, PPV will need to be given to deliver PEEP).

Fig. 3 SALSA technique. Photo by K. Roberts. Used with parent permission.

A photo of the SALSA technique is shown in Fig. 3. Detailed instructions on how to perform the SALSA technique are available through the following links:

- Step-by-Step instructional video: https://www.youtube.com/watch?v=Iig9l4Bgly4.
- Videos of the procedure performed in the clinical setting:
  - Video without PPV: https://youtu.be/oTnv291PwrE.
  - Video with routine PPV: https://www.youtube.com/watch?v=ioXGyfVLdyE.
- Procedure flow chart which can be downloaded and used at the bedside: https://docs.google.com/presentation/d/1Dc5vQeII79TFWr7_eWe6VMb91tr0mcG47NBRZFxgE3k/edit?usp=sharing.

CLINICAL CONSIDERATIONS

Considerations regarding the various methods include: efficacy, ability to maintain PEEP, need for positive pressure ventilation (PPV), patient population, use/need for premedication, physiologic effect on the infant, potential adverse effects and provider skill and familiarity with the device.

Thin catheter technique (LISA and MIST)

Efficacy. LISA has been shown to be efficacious for the delivery of surfactant. Meta-analyses of 14 studies ($n = 1422$ infants, 23–37 weeks' gestation) comparing LISA to surfactant administration via an ETT with early extubation (INSURE technique, 12 studies) or delayed extubation (2 studies) showed decrease risk of death or bronchopulmonary dysplasia (BPD), need for intubation within 72 h, severe intraventricular hemorrhage, death during first hospitalization and BPD among survivors. There was no significant difference in risk of air leak requiring drainage [21].

LISA has also been compared to NIV without surfactant administration. In a study of 220 infants born at 26–28 weeks' gestation, infants who received LISA had decreased mechanical ventilation on day 2 or 3 after birth, decreased mechanical ventilation during their hospital stay, fewer median days on mechanical ventilation and a lower need for oxygen therapy at 28 days. There was no difference between the groups in either mortality or serious adverse events [22]. Two-year outcomes showed no differences in weight, length, or neurodevelopmental outcome (Bayley II scores) [23]. However, contrary to previous findings, a recent large, multi-site, international study of 485 infants born at 25–28 weeks gestation found that LISA did not reduce the incidence of the composite outcome of death or BPD compared to NIV without surfactant administration. The incidence

of BPD was decreased, but there was also a trend in higher mortality in the LISA group at 25–26 weeks' gestation. LISA also was not found to be protective for severe IVH in this study [24].

Ability to maintain PEEP, need for PPV. When LISA is performed, the continuous positive airway pressure (CPAP) interface remains in place. This may allow PEEP to be continuously transmitted into the lung except for the duration of time the mouth is open during laryngoscopy. However, maintenance of PEEP during surfactant administration has been questioned as Jourdain [25] and De Luca [26] found that CPAP transmission and spontaneous breathing around a LISA catheter are greatly impaired or even close to zero due to the effect on airflow and airway resistance with placement of a non-ventilable catheter in the trachea. During the procedure, spontaneous respiratory effort is maintained and used to distribute the surfactant. Positive pressure breaths are only used as needed for hypoxemia and/or bradycardia.

Patient population. LISA has been reported to be effective in a wide range of weights and gestational ages, and is often used even in the smallest infants. The German Neonatal Network (GNN) reports that approximately 54% of premature infants born at 27 weeks' gestation who receive surfactant by LISA avoid ventilation in the first 72 h after birth [27]. However, despite over a decade of experience with this technique, properly identifying the right patient is still problematic. Authors of the GNN report conclude that "There is still an urgent need to better define those babies at high risk for failing a treatment strategy that includes LISA". A report from Hungary has noted that the best indicator of LISA success is 28 weeks and around 1100 grams [28].

Physiologic and potential adverse effects on the infant, use/need for premedication. The primary disadvantage of LISA is that it requires laryngoscopy and placement of a catheter below the vocal cords. Thus, the physiologic response and potential adverse effects are similar to intubation and include bradycardia [29, 30], hypoxia [29–34], hypertension and/or hypotension [29, 30, 35–38], increased intracranial pressure [30, 35, 39, 40], mouth or pharyngeal trauma or bleeding, and vocal cord or subglottic injury [41]. Premedication with atropine, analgesic/sedative and muscle relaxant has been shown to mitigate the adverse physiologic effects of intubation and are recommended by the American Academy of Pediatrics [42] and the Canadian Pediatric Society [43] for all non-emergent intubations. However, with LISA, a muscle relaxant is contraindicated given the need for spontaneous respirations and concern has been raised about the possible complications associated with sedatives. Available literature on the use of sedation for LISA shows that it improves infant comfort and facilitates smoother procedure, but could also increase the incidence of desaturations, apnea and need for PPV. It has been suggested that a more pragmatic approach would be to individually tailor the need for premedication; an active, large preterm infant would receive a pharmacological approach while a non-pharmacological approach would be applied to a small, less active, comfortable preterm. The latter would be escalated to pharmacological measures if the infant shows signs of distress [44]. Surveys investigating use of LISA found premedication was used 48%, 94% and 6% in Europe, Canada and the United States respectively. Atropine was most frequently used with large variation in use of sedation/analgesia including fentanyl, ketamine, propofol, benzodiazepines, and sucrose [45–47].

Provider skill and familiarity. Because of the need for visualization of the vocal cords, LISA requires a level of expertise similar to that of intubation. In addition, because a small diameter catheter is used, a Magill forceps may be needed to assist in placement of the catheter through the vocal cords. Most clinicians in the US have little or no experience using a Magill forceps, which may add to the complexity of the learning process and mastery of the procedure. Thus, the application of LISA will primarily be limited by the skill of the clinician and most likely reserved to the NICU setting.

Aerosol

Efficacy and patient population. Because of the obstacles associated with aerosolization of surfactant (detailed earlier), studies of efficacy have shown mixed results. A single center study in 2000 showed no difference in either oxygenation indices or CPAP failure rates [7]. However, two studies published in 2019, a pilot and a phase 1 trial, did show reduction in CPAP failure rates [48, 49].

The first randomized, multi-center, phase 3 trial of aerosolized surfactant (AERO-02 trial) was reported in 2020 [50]. They found the intubation rate in the group that received aerosolized surfactant ($n = 230$) was 26% compared to 50% in the usual care group (care determined by providers, $n = 227$). Respiratory outcomes up to 28 days of age were no different between groups. The mean gestational age was 33 weeks, thus indicating a relatively older population was treated and most likely had mild to moderate RDS. It is unclear whether aerosolized surfactant is beneficial for extremely low birth weight infants as only 11 infants who received treatment in the study were 23–26 weeks' gestation. Amongst this subset, aerosolization resulted in a failure rate equivalent to control [50]. Hojnicki [51] recently reported results from the aerosolized calfactant expanded access program where institutions from the AERO-02 trial were allowed to continue use of the device. Information from 380 infants in the expanded access program were combined with the previously reported AERO-02 trial data and evaluated to identify predictors of success and avoidance of intubation. The predictors of successful treatment were a gestational age ≥31 weeks, a respiratory severity score of <1.9 and <2 previous aerosol treatments.

Gaertner [52] reviewed nine studies encompassing 1095 infants and concluded that aerosolized surfactant was most effective in reducing rate of intubation during the first 72 h of life in infants ≥28 weeks' gestation. A subsequent study published in 2022 investigating aerosolized poractant in infants 28–32 weeks' gestation was stopped early due to supposed futility [53]. Post hoc analysis of the data, however, favored treatment for infants ≥31 weeks' gestation.

While aerosolized surfactant will have a role in the NICU, there is minimal data on its use in the extremely low birth weight population and what little data is available shows it is ineffective in this population. Aerosolization does appear to be beneficial for an older subset of babies and will be useful for surfactant replacement in this group and in settings where advanced skills (i.e. laryngoscopy) are not available or a truly minimal approach is required.

Physiologic and potential adverse effects on the infant, use/need for premedication, provider skill and familiarity. Because laryngoscopy and instrumentation of the airway is not needed, no technical skills are required for aerosolization. Comfort and physiologic stability of the infant during administration is also optimized and premedication is not needed. Because this technique is minimally-invasive, it may result in earlier administration of surfactant to a large subset of neonates with mild to moderate RDS, wherein the past, their treatment has been contingent upon a worsening of symptoms. Earlier treatment could be advantageous by preventing the morbidities that may occur with worsening RDS. Other benefits include continuous delivery of PEEP, as the interface delivering CPAP remains in place, and routine use of PPV is not needed with this method. A disadvantage may be the duration of time required to administer the surfactant (30–90 min).

Despite the challenges, clinicians remain hopeful as aerosolization would be the most minimally invasive method. At this time, there is no device that is FDA approved to aerosolize/nebulize

surfactant. Several trials are ongoing, and it is expected that this technology will be available within a few years.

SALSA

Efficacy. SALSA has been shown to be efficacious for the delivery of surfactant. First described by Brimacombe [18] ($n = 2$, 30 and 37 weeks' gestation) in 2004 and Trevisanuto [19] ($n = 8$, 28–35 weeks' gestation) in 2005, all infants showed clinical improvement without complications. A meta-analysis published in 2021 including six randomized, controlled trials (RCT) with 357 newborns found that surfactant delivery by SAD when compared to CPAP alone or the InSurE (Intubation, surfactant administration, extubation) procedure was associated with decreased FiO2 requirement, decreased intubation, and decreased mechanical ventilation. There were no significant differences between groups for death, BPD, or pneumothorax [54]. However, these studies were not designed to detect a difference in BPD. Since publication of the meta-analysis, an additional RCT comparing SALSA to INSURE in 93 infants born at 27-36 weeks' gestation found that need for mechanical ventilation, efficacy in decreasing fraction of inspired oxygen, number of surfactant doses administered, time to wean off all respiratory support, rates of adverse events, and outcomes including pneumothorax and BPD diagnosis did not differ between groups [55]. It is important to note that equal efficacy was obtained with surfactant being administered above the glottis with the SALSA technique compared to intra-tracheal with the INSURE technique. Currently there are no completed studies comparing LISA and SALSA. The Australian-New Zealand Clinical Trial Registry notes that the SURFSUP trial, a non-inferiority trial of MIST to SALSA is currently enrolling [56]. This trial will also collect provider and patient data to help determine the ease of each procedure.

Physiologic and potential adverse effects on the infant, use/need for premedication. The key advantage of SALSA is that a catheter or device does not need to pass through the vocal cords. Therefore, laryngoscopy is not required and the adverse physiologic effects and potential adverse events associated with laryngoscopy and subglottic injury are avoided. In addition, because the SAD rests in the posterior pharynx, surfactant is administered above the vocal cords, thereby eliminating the possibility of unilateral surfactant administration and/or the increased risk of pneumothorax as seen with ETT or LISA if the device is advanced too far into the "right main stem".

SALSA can be performed without premedication or with minimal premedication (atropine, sucrose solution, and/or lorazepam). In a study comparing physiologic effects during SAD placement to ETT placement, heart rate and oxygen saturation were maintained close to baseline in both groups despite very different degrees of premedication, as SAD placement utilized atropine and 24% sucrose solution while ETT placement utilized atropine, fentanyl, and rocuronium [57].

Ability to maintain PEEP, need for PPV. PEEP can be delivered continuously throughout the SALSA procedure if an adapter is used with a T-piece or anesthesia bag. If an adapter is not used, the PEEP device is intermittently disconnected from the SAD to administer the surfactant aliquots. SALSA does not require a catheter through the vocal cords so airflow and airway resistance are not altered. PEEP is delivered directly from the posterior pharynx to the trachea, reducing or eliminating PEEP being directed into the esophagus and stomach. PPV does not need to be routinely given. If positive pressure breaths are needed for hypoxemia or bradycardia, PPV is given through the T-piece or anesthesia bag already attached to the SAD.

Patient population. Presently, commercially available SAD are not sized appropriately for infant <1250 g. Development of SADs that fit the smallest of infants are needed. Despite the size limitation, SALSA is appropriate for a large number of infants since approximately 2/3 of infants with RDS in the United States weigh >1250 g [58].

Provider skill and familiarity. Since the SAD rests in the posterior pharynx, placement requires minimal technical skill and is relatively fast and easy. Despite the ease of placement, clinician comfort with the device is an obstacle, as many clinicians have little or no experience with placing an SAD outside of NRP training on a manikin. In the Roberts trial [59], where clinicians (neonatologists, fellows, and neonatal nurse practitioners) had little to no experience with the device and were trained on a manikin prior to insertion, the SAD was successfully placed in <35 s on the first attempt in the majority of patients and clinicians stated they felt comfortable with the procedure after two experiences. This suggests that with proper exposure and training, clinicians may find the SALSA procedure to be fast, easy, and an effective tool to treat RDS. This success rate and comfort level is noteworthy, as opportunities to obtain or maintain competence in endotracheal intubation and laryngoscopy are becoming more scare. In addition, the high first-attempt success rate minimizes the risk of potential adverse events, as intubation literature has shown that higher number of attempts is associated with increasing risk, with each additional attempt doubling the odds of an adverse event [60].

IMPLEMENTION INTO CLINICAL PRACTICE

Thin catheter technique

Due to the success experienced in Germany, LISA now has broad European acceptance. Current United Kingdom [61] and European consensus guidelines [62] recommend LISA due to its minimally invasive nature and potential impact on care. Surfactant administration with this method has received an indication throughout European Union countries by the National Authorization Procedure and specially designed LISA catheters have received European Conformity approval. A survey of European neonatologists found that 52% were using LISA, with 41% using LISA on a routine basis [45]. The Canadian Pediatric Society [63] also recommend use of LISA and a recent survey of Canadian NICUs were 96% of the respondents were Level 3-3+ NICUs found that 61% used LISA at their institution (50% routine, 12% sometimes) [46]. In the United States, LISA continues to slowly gain acceptance. A survey of US neonatologist where 97% of the respondents worked at Level 3–4 NICUs found that 18% used LISA at their institution (4% routine, 4% sometimes, 7% research) [47]. Several quality improvement reports have been published demonstrating that LISA can be implemented into clinical practice [64, 65].

SALSA

As SALSA gains familiarity, it is becoming more widely implemented. For the first time, SALSA has been recognized as a recommended mode of surfactant delivery by consensus statement. The 2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome [62] stated that "Laryngeal mask surfactant may be used for more mature infants >1.0 kg."

There is increased realization that because SALSA requires minimal skill for placement, this simplified technique for administering surfactant is ideal for application not only in high- level NICU settings, but also in lower-level NICU and community hospital settings. A recent quality improvement initiative in a community hospital based NICU reported a 40% reduction in intubation and mechanical ventilation after the implementation of the SALSA technique [66]. In a community hospital with the capability to provide CPAP, the addition of SALSA may result in improvement in respiratory status and avoid the need for transfer to a higher level of care.

In addition to application in developed countries, SALSA may also be ideal for low- and middle-income countries (LMIC) [67, 68]. In 2018, Azerbaijan, a middle-income country, launched an initiative sponsored by the Ministry of Health to teach neonatal clinicians how to use the SAD to deliver Ministry-supplied surfactant [69]. Jordan has also reported their experience with SALSA. SALSA has also been introduced to India as part of a quality improvement project and early experience on the subcontinent has been reported [70, 71].

Surfactant administration as part of a care bundle

As clinicians consider implementation of the techniques discussed above, it is imperative that they view less-invasive surfactant administration as one step in a bundle of care. This bundle includes delayed cord clamping allowing for fetal transition, early CPAP, making sure the baby is allowed and encouraged to breathe, early administration of caffeine for those below a certain gestational age, and early skin to skin contact. Each of these things individually demonstrate a beneficial effect and it should be recognized that less-invasive surfactant administration should not be practiced in isolation.

CONCLUSION

The ability to deliver surfactant in a minimally invasive way is an important tool to optimize success with NIV and in doing so, limit harm associated with mechanical ventilation. All methods reviewed have been shown to reduce the need for mechanical ventilation and have significant potential to be integrated into clinical practice. Most likely the future of surfactant administration will not be a single method to use every time, but rather, a method should be applied for a specific patient and in a specific setting. Future studies should be designed to help define this practice.

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AUTHOR CONTRIBUTIONS

SG and KR contributed equally to the design, drafting, revising, and final approval of the manuscript.

COMPETING INTERESTS

Guthrie and Roberts are paid consultants for ONY Biotech.

CONSENT FOR PUBLICATION

Signed consent obtained from parent/guardian.

ADDITIONAL INFORMATION

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