Alternative Methods of Surfactant Administration in Preterm Infants with Respiratory Distress Syndrome: State of the Art

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ABSTRACT

For preterm infants with respiratory distress syndrome, delivery of surfactant via brief intubation (INtubate, SURfactant, Extubate; InSurE) has been the standard technique of surfactant administration. However, this method requires intubation and positive pressure ventilation. It is thought that even the short exposure to positive pressure inflations may be enough to initiate the cascade of events that lead to lung injury in the smallest neonates. In an effort to avoid tracheal intubation and positive pressure ventilation, several alternative and less invasive techniques of exogenous surfactant administration have been developed over the years. These have been investigated in clinical studies, including randomized clinical trials, and have demonstrated advantages such as a decrease in the need for mechanical ventilation and incidence of bronchopulmonary dysplasia. These newer techniques of surfactant delivery also have the benefit of being easier to perform. Surfactant delivery via pharyngeal instillation, laryngeal mask, aerosolization, and placement of a thin catheter are being actively pursued in research. We present a contemporary review of surfactant administration for respiratory distress syndrome via these alternative methods in the hope of guiding physicians in their choices for surfactant application in the neonatal intensive care unit.

Keywords: Surfactant, preterm, respiratory distress syndrome, less invasive surfactant administration, laryngeal mask, aerosol, pharyngeal instillation, nebulized.

INTRODUCTION

It is now recommended that premature infants who do not require advanced resuscitation should receive non-invasive forms of respiratory support, both in the delivery room and beyond.[1] However, without an endotracheal tube (ETT), the usual conduit for administration of exogenous surfactant is lacking, thus raising the dilemma of how to administer surfactant to infants on non-invasive ventilation (NIV) who exhibit signs of respiratory distress syndrome (RDS), for whom surfactant is of potential benefit.[2-4] Until recently, surfactant delivery via a brief intubation (INtubate, SURfactant, Extubate; InSurE) has been the usual method of surfactant administration in this context. However, this method requires intubation and positive pressure ventilation (PPV). Even brief exposure to a few large volume artificial breaths is thought to be enough to initiate the cascade of events which can lead to lung injury, thus increasing the risk of bronchopulmonary dysplasia (BPD). This concern has led to an ongoing discussion about the potential hazardous effects of the InSurE procedure and the quest for development of less invasive techniques of exogenous surfactant administration to avoid tracheal intubation and PPV.

Surfactant delivery via pharyngeal instillation, laryngeal mask, aerosolization, and placing a thin catheter are being actively pursued in research. The goal of this review is to present a contemporary picture of surfactant administration for preterm infants with RDS from experts in the alternative techniques. It is our hope that this will assist clinicians as they contemplate the increasing variety of ways surfactant can be administered in the neonatal intensive care unit (NICU).

Pharyngeal Instillation
One of the oldest methods of surfactant administration is pharyngeal instillation, in which surfactant is deposited into the pharynx with a flexible short tube attached to a syringe prior to the first breath. Surfactant then spreads at the air–fluid interface when the premature infant begins breathing. A portion of the total amount of surfactant administered is inhaled, while the remainder is harmlessly swallowed.[5,6]

In 1972, Enhöerning and Robertson used a premature rabbit model to evaluate the efficacy of surfactant injection into the pharynx and found this method to be beneficial in improving lung function.[7] In 1987, the Ten Centre Study Group conducted the first randomized controlled trial (RCT) of intrapharyngeal instillation of surfactant in premature infants of gestational age 25-29 weeks, finding a lower mortality and shorter duration of respiratory support in the first 10 days of life.[8] Kattwinkel et al.[9] performed a feasibility and safety study in 23 premature infants born at 27-30 weeks of gestation and found that nasopharyngeal surfactant instillation at birth appeared to be relatively simple and safe to perform, particularly for vaginal births. A Cochrane review of pharyngeal surfactant instillation in 2011 found that there were no data from RCT or quasi-randomized trials that evaluated the effect of intrapartum instillation of pharyngeal surfactant before the first breath on morbidity and mortality in preterm infants at risk of RDS. Evidence from animal and observational human studies suggest that pharyngeal instillation of surfactant before the first breath is potentially safe, feasible, and may be effective.[10] Recently, in a small group of premature infants born <25 weeks of gestation, oropharyngeal surfactant administration with sustained inflation soon after birth was shown to decrease the need for intubation in the delivery room.[11] However, the findings of a European multicentre RCT (EudraCT 2016-004198-41) reported to date only in abstract form do not indicate a benefit of pharyngeal surfactant instillation in the delivery room for preterm infants <29 weeks' gestation, with no difference in the rate of intubation by 5 days or in the incidence of death or BPD.[12]

A significant limitation of pharyngeal instillation is that it is not possible to control or accurately measure the proportion of instilled surfactant that ultimately is deposited in the lung. Although pharyngeal surfactant deposition is less invasive than intubation or inserting a feeding tube or a vascular catheter into the trachea, other less invasive techniques may have advantages over this method.

Surfactant Administration Through Laryngeal or Supraglottic Airways
Originally developed in 1981 for adult patients undergoing surgery, the laryngeal mask airway (LMA) is now available in sizes

appropriate for neonates down to 1250 g. Laryngeal mask airways are a specific trademarked device which are within the general category of supraglottic airway devices (SADs). Several companies manufacture SADs, with variations on the shape of the device and cuff characteristics. In this review, SAD will be used when referring to this piece of equipment. In addition to multiple options for SADs, surfactant administered through an SAD can be performed with a variety of other equipment based on what is available or preferred at a given institution. In 2019, the acronym *SALSA: Surfactant Administration through Laryngeal or Supraglottic Airways* was coined to encompass various iterations of the procedure. For the remainder of this review, the term SALSA will be used when referring to this method of surfactant delivery.

The use of SAD in the NICU setting was originally reserved for the "difficult airway" but has since transitioned from a device rarely used to one that has gained familiarity and is now being used for resuscitation, short surgeries, transport, and medication administration.[13-20] Use of an SAD for surfactant administration in neonates was first described in 2004 by Brimacombe et al.[21] (n = 2, 30 and 37 weeks' gestation) and in 2005 by Trevisanuto et al.[22] (n = 8, 28-35 weeks' gestation). In these case reports, all infants showed clinical improvement without complications. Since that time, animal studies have shown surfactant administration via an SAD to have equal efficacy in improvement in PaO_2 levels when compared to the gold standard of administration via an ETT,[23] and that administration through an SAD has equal efficacy when given with and without PPV.[24] Human RCTs have shown the device to be effective in improving respiratory status and avoidance of mechanical ventilation (MV) when compared to continuous positive airway pressure (CPAP) alone or InSurE (Table 1).[21,22,25-34]

A recent meta-analysis including 6 RCTs with 357 newborns found that surfactant delivery by SAD, when compared to CPAP alone or the InSurE procedure, was associated with decreased FiO_2 requirement, decreased intubation, and decreased MV.[35] In addition to being superior to CPAP alone or the InSurE procedure in terms of respiratory status, key advantages of SALSA include the ease, short duration, and physiologic stability during placement; the ability to place the device without the need for laryngoscopy or premedication; and ability to maintain functional residual capacity (FRC) during the procedure.

Because the device can be placed in the posterior pharynx without the need for visualization of the vocal cords, placement does not require laryngoscopy, thereby requiring minimal technical skill and rendering the procedure relatively fast and easy. In the trial of Roberts et al.,[36] the SAD was successfully placed in <35 seconds on the first attempt in the majority of patients with minimal change in heart rate or oxygen saturation. Clinicians (neonatologists, fellows, and neonatal nurse practitioners) had little to no experience with the device and after training on a manikin stated they felt comfortable with the procedure after only 2 experiences.

When considering the need for premedication, SALSA has the advantage of placement without laryngoscopy. When performing endotracheal intubation, the American Academy of Pediatrics[37] and the Canadian Pediatric Society[38] recommend

Table 1. Surfactant Administration Through Laryngeal or Supraglottic Airways (SALSA) Literature

Trial	Intervention vs. Control	Age/Weight	Entry Criteria	Premedication	Findings
Case reports					
Brimacombe, 2004[21]	n = 2	30 weeks; 37 weeks	FiO_2 0.50; FiO_2 0.80	None; midazolam	Improvement in respiratory function
Trevisanuto, 2005[22]	n = 8	28–35 weeks	Age < 72 hours; a/A PO_2 < .2	None	a/A PO_2 at 3 hours after surfactant increased from 0.13 to 0.34, $P < .01$
Micaglio, 2008[27]	n = 3	32, 34, 37 weeks	CPAP 5 and requiring surfactant for RDS	Lidocaine in 5% glucose solution	No complications
Barbosa, 2012[28]	n = 1	31 weeks; 1335 g	CPAP 5, FiO_2 0.50	None	Improvement on FiO_2 requirement and Silverman score at 3 and 6 hours after surfactant
Vannozzi, 2017[29]	n = 4	BW > 1.5 kg	$FiO_2 \geq 0.35$	None	Improvement on FiO_2 requirement, respiratory rate, and Silverman score at 3 hours after surfactant
Smee, 2021[30]	n = 60	≥28 weeks; BW ≥1.2 kg	Age < 48 hours; $FiO_2 \geq 0.30$	Sucrose and atropine	All infants tolerated the procedure well and clinically improved. After surfactant, 66% weaned to room air by 4 hoursand 17% required intubation. Device successfully placed on first attempt 78%, on ≤2 attempts 98%
Randomized controlled trials					
Attridge, 2013[31]	SAD (n = 13) vs CPAP alone (n=13)	BW ≥1.2 kg	Age <72 hours; FiO_2 0.30–0.60	None	FiO_2 at 1 hour 0.25 vs. 0.37, $P = 0.002$; FiO_2 at 12 hours 0.27 vs. 0.40, $P = 0.04$; Required MV 8% vs. 23%, $P = 0.59$
Sadeghnia, 2014[32]	SAD (n = 35) vs InSurE (n = 35)	BW ≥2 kg	Age < 48 hours; $FiO_2 \geq 0.30$	None	a/A PO_2 after surfactant dose 0.48 vs. 0.43, $P = .014$
Pinheiro, 2016[33]	SAD (n = 30) vs InSurE (n = 31)	29–36 weeks	Age < 48 hours; FiO_2 0.30–0.60	SAD: Atropine; InSurE: atropine and morphine	Failure requiring MV 30% vs. 77%, $P < .001$; early failure 3% vs. 67%, $P < .001$; late failure, FiO_2 decrease and adverse events similar between groups
Barbosa, 2017[34]	SAD (n = 26) vs InSurE (n = 22)	28–35 weeks; BW > 1 kg	$FiO_2 \geq 0.40$	SAD: Lidocaine gel on mask; InSurE: remifentanil and midazolam	Similar respiratory efficacy ($FiO_2 \leq 0.30$ at 3 hours post surfactant) and need for second dose of surfactant. lower Silverman–Anderson score at 3 and 6 hours after surfactant
Roberts, 2018[25]	SAD (n = 50) vs CPAP alone (n = 53)	28–35 weeks; BW ≥1250 g	Age ≤ 36 hours; FiO_2 0.30–0.40	SAD: Atropine and 24% sucrose solution	MV in first 7 days 38% vs. 64%, $P = .006$; Duration of MV, CPAP, and supplemental oxygen at 7 days of age similar between groups
Amini, 2019[26]	SAD (n = 30) vs. InSurE (n = 30)	< 37 weeks; BW ≥1200 g	Age ≤ 2 hours; FiO_2 0.30–0.60	SAD: None; InSurE: morphine	No differences in the requirement for MV, requirement for second dose surfactant, pneumothorax, IVH, duration of CPAP, and length of NICU admission

a/A PO2, arterial-to-alveolar oxygen tension ratio; BW, birth weight; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; InSurE, intubation, surfactant administration, extubation; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; SAD, supraglottic airway device.

the use of an anti-cholinergic, analgesia/sedative, and muscle relaxant, and the European consensus guidelines[1] state that "It is considered good practice to avoid discomfort during elective intubation by using a sedative or analgesic such as fentanyl, propofol, or midazolam." Similar to traditional intubation, the InSurE and less invasive surfactant administration (LISA) procedures require laryngoscopy. For the LISA procedure, the European consensus guideline[1] states that "Laryngoscopy is undoubtedly uncomfortable, but when attempting LISA there is a better chance of achieving a success

without sedation." The European guideline[1] also states that "Using low-dose sedation prior to laryngoscopy for the LISA procedure is technically feasible, will make the baby less uncomfortable but will increase the risk of CPAP failure. At present, there is no clear answer about whether to sedate routinely for LISA, and individual neonatologists must decide for themselves." In contrast, clinical studies investigating the use of an SAD have used minimal premedication, varying from no premedication to the use of atropine and/or sucrose solution for the procedure.

Another advantage of SALSA is the ability to continuously deliver positive end-expiratory pressure (PEEP) throughout the procedure. This allows for maintenance of FRC and the addition of PPV breaths if the clinician believes that PPV breaths improve alveolar recruitment and enhance surfactant distribution. Furthermore, PPV breaths are readily available if needed for hypoxemia or bradycardia, which can be induced by surfactant administration.

SALSA also has application beyond the high-resource NICU setting. The technique requires minimal technical skill, is easily adapted to be performed with equipment that is readily available, and does not require a mechanical ventilator. Therefore, community hospitals and nurseries in low- and middle-income countries that have the ability to deliver CPAP and have surfactant available can benefit from this technique.

Current obstacles to widespread application of this technique include the need for an appropriately sized SAD to be used in the smallest infants and clinician familiarity with the use of an SAD. Currently available commercial devices primarily fit infants greater than 1250 grams. While just over half of preterm infants receiving surfactant are >1250 grams (51.4% in Australian and New Zealand tertiary units[39]), infants <1250 grams are at high risk of developing BPD, would benefit greatly from avoidance of MV, and more frequently require repeat surfactant dosing. Clinician familiarity is also an obstacle, as many clinicians have little or no experience with placing an SAD. However, with exposure and training, clinicians may find the SALSA procedure to be fast, easy, and effective.

As previously mentioned, the SALSA technique can be performed with a variety of equipment, based on what is available or preferred at a given institution. The most basic SALSA technique requires only an SAD and a syringe containing surfactant. Variations on the technique include SADs of difference shapes and cuff characteristics, use of an adapter to allow for continuous PEEP throughout the procedure, use of a CO_2 detector, variations in the catheter through which surfactant is delivered (cut feeding tube, vascular catheter, multi-purpose catheter, and in-line suction catheter), and whether or not a ventilation device is used (T-piece resuscitator, anesthesia bag, or self-inflating bag).

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=Iig9l4BgIy4, video of the procedure performed in the clinical setting: https://www.youtube.com/watch?v=ioXGyfVLdyE, and a procedural flow chart which can be downloaded and used at the bedside:

https://documentcloud.adobe.com/link/track?uri=urn:aaid:scds:US:83001e7d-4044-4ee3-807b-0e01c9691a80. Of note, the SALSA procedure is considered off-label use since surfactant is only approved for delivery through an ETT, and SADs do not have European Conformity or U.S. Food and Drug Administration (FDA) approval for the delivery of medications.

Thin Catheter Surfactant Administration

The alternative of using a thin catheter to deliver surfactant to the trachea rather than an ETT was first reported by Verder et al.[40] in 1992 in a pilot study. However, it was rediscovered and used by Kribs et al.[41] in 2007. Kribs et al.[41] administered exogenous surfactant to spontaneously breathing preterm babies through a flexible catheter. A recent survey demonstrated that the utilization rate of LISA with thin catheter administration in Turkey[42] (81.6%) was one of the highest reported to date in the literature, just after the rate reported from Spain (89%).[43] In a recent large-scale survey of 37 European countries,[44] the mean utilization rate was 52.5% while previous studies reported lower rates. Surveys from different European countries show that thin catheter use rates have increased since 2015.[45] On the contrary, LISA usage in the United States and UK have been found to be 15% and 18.7% in new surveys.[46,47]

The procedure, now known as the Cologne method, is performed without or with less need for analgesia or sedatives compared with InSurE, and the babies receive continuous support with nasal CPAP. Besides laryngoscopy, the introduction of the flexible catheter in the trachea often requires the use of a Magill forceps. Dargaville et al.[48] further developed an alternative technique (the Hobart method (https://www.youtube.com/watch?v=wAkNATfH9S0)) in which a semi-rigid 16G vascular catheter is inserted through the vocal cords without the need for Magill forceps. Further to these reports, many techniques have been described in which different types of catheters (feeding tube, umbilical catheters, vascular catheters, specifically designed catheters such as SurfCath®, LISAcath®, etc.) have been used for intra-tracheal surfactant delivery. The reports have also shown variation in terms of dosage, duration and type of surfactant administration, use of forceps, number of surfactant aliquots, and type of non-invasive respiratory support. Of the many acronyms associated with these methods, such as minimally invasive surfactant treatment (MIST), surfactant without an ETT (SurE), minimally invasive surfactant administration (MISA), and less invasive surfactant administration techniques (LIST), in this review, we will refer to these methods collectively as LISA, which is known and commonly accepted worldwide.

Several improvements in neonatal outcomes have been noted with LISA. Göpel et al.[49] conducted a multicenter RCT in Germany, examining whether, compared to continuation of CPAP, selective use of LISA was associated with a reduction in need for MV in preterm infants at 26-28 weeks' gestation. In this first reported RCT, they found a reduction in need for intubation on day 2 or 3 of life from 46% to 28% with LISA. In 2013, Kanmaz et al.[2] published another randomized controlled study, in which LISA using the "Take Care" method (https://www.youtube.com/watch?v=q9nt3lSuRHI) was compared with conventional surfactant delivery via InSurE. A similar reduction in the need for MV <72 hours was noted in the LISA group, as well

as a decrease in the rate of BPD.[2] Kribs et al.[50] investigated in 2015 the impact of the LISA technique on survival and BPD in extremely preterm infants <27 weeks' gestation. They found an association between LISA and survival without major complications but no significant reduction in the rate of BPD or total survival. In a large non-randomized observational study of the German Neonatal Network including 7533 preterm infants ≤28 weeks of age, LISA was associated with decreased risk for short-term outcomes such as mortality, BPD, clinical sepsis, pneumonia, intracerebral hemorrhage grades II-IV, surgery for persistent ductus arteriosus, and retinopathy requiring treatment.[51]

Presently, there is convincing evidence from RCTs and meta-analyses that LISA compared to surfactant delivery via ETT reduces the need for MV, particularly in the first 72 hours after birth.[52-55] Systematic reviews also suggest that LISA carries benefits for health-related outcomes, including reduction in the incidence of BPD, mortality, and the composite outcome of death or BPD.[52,54] Recently, a Cochrane analysis including 16 studies and 2164 neonates was published on surfactant therapy via LISA in preterm infants.[56] The analysis of the studies comparing LISA with surfactant administration with ETT revealed significant decrease in the need for intubation within 72 hours (relative risk (RR) 0.63, 95% CI 0.54 to 0.74), in risk of the composite outcome of death or BPD at 36 weeks' postmenstrual age (RR 0.59, 95% CI 0.48 to 0.73), severe intraventricular hemorrhage (IVH) (RR 0.63, 95% CI 0.42 to 0.96), death during first hospitalization (RR 0.63, 95% CI 0.47 to 0.84), and BPD among survivors (RR 0.57, 95% CI 0.45 to 0.74). It should be kept in mind that the studies included in this meta-analysis had variable inclusion criteria and methodological approaches, and that further evidence from adequately powered RCTs is required to confirm whether LISA provides benefits over standard surfactant replacement therapy via ETT or over continuation of CPAP.[56,57] An adequately powered multicenter RCT (the OPTIMIST-A trial, ACTRN12611000916943) studying the effect of surfactant administration via LISA compared with continuation of CPAP on the composite outcome of death or BPD has recently finished recruitment, unfortunately before reaching the recruitment target due to curtailment of research activity during the COVID-19 pandemic. The results of this multicenter blinded RCT of LISA versus continuation of CPAP in preterm infants 25-28 weeks' gestation have only been reported in abstract form as of this time. The incidence of BPD in survivors was lower after LISA (RR 0.83, 95% CI 0.70 to 0.98). The need for intubation <72 hours and the incidence of pneumothorax were halved, and median duration of respiratory support was reduced by 6 days in the LISA group.[58]

The long-term effects of LISA method have been studied in 2 recent reports. Neurodevelopmental outcomes at 2 years were reported to be similar between the LISA and control groups in the Avoidance of Mechanical Ventilation trial.[49,59] Mehler et al.[60] reported higher mental developmental index values at 2 years of age in a subgroup of infants 25-26 weeks' gestation included in the Nonintubated Surfactant Application (NINSAPP) trial.[50]

Current evidence confirms that LISA is a safe, feasible, and an effective method to deliver surfactant. Several guidelines

have suggested LISA to be the preferred mode of surfactant administration in preterm infants spontaneously breathing on CPAP.[1,3,61,62] There remains some skepticism regarding its physiopathological rationale, with the emerging clinical evidence not matched by preclinical data regarding the mechanisms of surfactant distribution within the lung after LISA.[57] This method of surfactant delivery is often performed without any PPV, and hence, the dispersal of surfactant from the trachea is facilitated by spontaneous breathing. What evidence there is does appear to indicate that surfactant delivery under conditions of spontaneous breathing has beneficial effects with regard to lung recruitment and aeration compared with surfactant delivery aided by PPV.[63-68] Further carefully designed laboratory studies are needed to understand the mechanisms of surfactant distribution aided by spontaneous breathing. The other putative advantages of LISA—avoidance of lung injury induced by PPV, minimization of intubation trauma by use of a narrow-bore catheter, preservation of glottic function—also deserve further investigation and confirmation.

From a clinical perspective, future studies should focus on identifying patient subgroups most likely to benefit from LISA, optimum surfactant dosage, the role of inhomogeneous surfactant distribution in cases where LISA fails to produce a surfactant response, optimal protocols for pharmacological and non-pharmacological sedation/analgesia during LISA, lung recruitment before LISA, treatment thresholds, and the role of prophylactic LISA.[69-73]

Surfactant Administration by Aerosol

The delivery of surfactant by aerosol has the potential to be the most non-invasive way to deliver surfactant, as minimal technical skill and no manipulation of the airway is required for this method. In the current era of NIV, aerosolized surfactant has an increased appeal as this may avoid the pitfalls of laryngoscopy,[74,75] a common element of the InSurE[40] and LISA techniques.[2,48,49,76] The ability to create a functional aerosolization device which is easy to use in the clinical setting has, however, been a significant obstacle to the success of this method and its translation into clinical practice.

Shortly after the cause of RDS was identified and the search for effective treatments had begun, Robillard et al.[77] reported in 1964 the administration of a synthetic preparation of L-α-lecithin by microaerosol to 11 infants with birth weights ranging from 680 to 3120 g. The study substance was aerosolized directly into the incubator in the hopes that the infant would inhale it and symptoms would improve. Eight infants showed improvement and survived to discharge, but over the next 55 years, the difficulties in aerosolization of a complex substance like surfactant would result in limited progress in this area with only 6 published studies.[78-83] Only 2 of these were prospective RCTs.[78,79] In one RCT, no difference was observed[74] and in the other, there was a reduction in the nasal CPAP failure rate.[79]

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The success of aerosol delivery is thought to depend on multiple factors. These include the type of surfactant used, the method of aerosolization or nebulization, the lung recruitment strategy employed, the age at administration, and RDS severity.[84] In the examination of these factors, animal models have demonstrated improved gas exchange similar to what is seen with bolus endotracheal instillation and have suggested that aerosol delivery has the benefit of more homogenous distribution since uninterrupted, spontaneous breathing continues.[85-88] One recent multicenter RCT reported the use of a Solarys nebulizer modified to resemble a pacifier.[84] A video demonstrating the use of the device on a patient receiving aerosolized surfactant can be viewed at this link https://drive.google.com/file/d/1uV-w6htP08ueysWVapGeine7mYNMdl9u/view?usp=sharing. This device can be combined with any type of non-invasive respiratory support to deliver a continuous dose of aerosolized surfactant.

The largest study to date using aerosolized surfactant was reported in 2020 by Cummings et al.[84] The authors sought to answer whether aerosolized surfactant was effective in preventing the need for laryngoscopy for the instillation of liquid surfactant in infants 23 weeks' gestational age or greater with a diagnosis of RDS. To answer this, a usual care group, which received surfactant per standard practice for that participating NICU, was compared to an aerosolized calfactant group who received aerosolized calfactant per study protocol. This randomized, multicenter, phase 3 trial was conducted in 22 NICUs across the United States and enrolled a total of 457 infants. The cohort consisted of newborns who were not intubated during the first hour of life and at 1 to 12 hours of age had a confirmed or suspected diagnosis of RDS and were receiving less than 0.40 FiO_2 while on some type of non-invasive respiratory support. The results of this study found that 26% (59/230) of infants in the aerosolized calfactant group required laryngoscopy and liquid surfactant instillation versus 50% (113/227) in the usual care group (RR 0.48, 95% CI 0.36 to 0.62). There were no differences in either group in the development of pulmonary air leaks, BPD, or changes in respiratory support during the first month of life. The mean gestational age of infants in both groups was 33 weeks. Of note, only 11 infants between 23- and 26-weeks' gestational age were enrolled. Infants in this group showed little difference in prevention of intubation by aerosolized calfactant. The greatest clinical benefit in the study was seen in infants between 27 and 36 weeks' gestational age as there was a clear reduction in the need for intubation in these age groups. These age groups also represent the greatest proportion of infants who are treated for RDS who could benefit from this non-invasive method of surfactant delivery to optimize NIV. It is also important to note that the study included infants with mild to moderate RDS ($FiO_2 < 0.40$) and infants were excluded for hypercapnea (>60 mmHg).

While the device is pending approval by the U.S. FDA, some NICUs have received FDA approval to continue using the device per the original study criteria: treatment at less than 12 hours of life and adequate NIV. To help identify babies who would benefit, a Respiratory Severity Score (RSS) is now being used. This is the multiple of PEEP by the fraction of inspired oxygen. Investigation is underway to quantify the ideal RSS to help identify the ideal candidate for this non-invasive form of surfactant delivery.

As of the writing of this report, there is currently no commercially available device that can aerosolize surfactant. The modified Solarys device as noted above is, however, currently under review by the U.S. FDA. Once FDA approval has been granted, it is expected that governmental approval will be sought after and will occur in other countries and that this device will eventually be widely available. Other devices by various manufacturers are also undergoing clinical trials. It is expected that more devices that can effectively aerosolize surfactant will eventually be available. This has the potential to improve care in NICUs where most babies who could benefit from this method (<36 weeks' gestation) receive care. Non-invasive respiratory support can be combined with non-invasive surfactant administration to avoid the hazards and difficulties of laryngoscopy and the potential need for MV. This method could also be used in nurseries or settings where nasal CPAP is available, but a skilled provider who can intubate for surfactant administration is not present. This may save a life, improve care in that facility, or prevent a transfer to a higher-level facility.

While there is optimism for aerosolized surfactant, there are still unanswered questions. Aerosol seems to be an effective strategy for the largest group of babies who can benefit from surfactant (27 weeks and above). It is still to be determined, however, if this method can effectively and safely deliver surfactant to the smallest babies who are at the highest risk for BPD. Future studies need to identify the optimal way to use aerosol in this group and make comparisons of this technique with other alternative methods for surfactant delivery.

Non-invasive Ventilation Modes and Caffeine
Standard nasal CPAP has been used with LISA in many studies.[2,50,89,90] During surfactant administration, spontaneous breathing and CPAP transmission is regarded as an important mechanism for promoting alveolar recruitment and surfactant diffusion.[91] However, in a resuscitation manikin, CPAP transmission around a LISA catheter during minimally invasive surfactant administration has been seen to be significantly reduced.[92] Direct in vivo measurements of tracheal pressure with a LISA catheter in situ will be necessary to fully understand whether continued CPAP application confers an advantage in this setting. Oncel et al.[93] showed that non-invasive positive–pressure ventilation (NIPPV) compared with nasal continuous positive airway pressure (nCPAP) as the initial respiratory support within minimal invasively surfactant administration approach decreased the need for invasive MV within the first 72 hours of life and reduced the surfactant requirement, whereas this result was insignificant <30 weeks. Recently, Szczapa et al.[94] evaluated the use of LISA procedure in a national cohort study, and they found no difference in the effectiveness of LISA with

Table 2. Summary of the Alternative Methods of Surfactant Administration

	Instruments	Premedication/Sedation	Advantage	Disadvantage
Pharyngeal instillation	Flexible short tube and syringe	No	Easy During delivery No need for laryngoscopy	The amount of swallowed and inhaled surfactant is unknown Scant of evidence Increased use of prophylactic surfactant
SALSA	Supraglottic airway device (SAD)	No/optional	Easy and fast PEEP through surfactant delivery No need for laryngoscopy Requires minimal skill	Cannot be performed in infants <1250 g No currently known benefit on decreasing BPD
Thin catheter	Nasogastric tube, vascular catheter, specially manufactured catheters	Yes/optional	Avoidance of PPV Easy and safe CPAP continues Decreased need for MV Decreased rate of BPD and severe IVH Long-term neurodevelopmental data available	Needs skill Needs for laryngoscopy ± Magill forceps Surfactant reflux Need for sedation at more mature gestations
Aerosol	Nebulizer	No	Easy and no skill required More homogenous distribution Non-invasive ventilation continues Comfortable No need for laryngoscopy Decrease in need for intubation	Mainly studied in cases with mild RDS Long duration of application Not enough data for infants born at 23–27 weeks No device yet approved specifically for surfactant administration

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; PEEP, positive end-expiratory pressure; PPV, positive pressure ventilation; SAD, supraglottic airway device; SALSA, surfactant administration through laryngeal or supraglottic airways.

NIPPV or bilevel positive airway pressure versus LISA with nCPAP.

Caffeine is a method for improving the effectiveness of non-invasive support success for respiratory management of premature infants. For infants at high risk of requiring MV, such as those on non-invasive respiratory support, early caffeine should be considered.[1] In some centers, infants born <1000 g receive caffeine at delivery room to stimulate breathing and prevent apnea.[66] The minimally invasive surfactant methods reviewed above when combined with early caffeine may help to maintain spontaneous breathing and decrease the need for invasive ventilation; evidence of this impact is still uncertain. The ongoing CaLI trial evaluates the effect of early caffeine, CPAP, and surfactant via the LISA method compared with caffeine and CPAP alone to avoid MV in first 72 hours.[70] The use of NIV modes and the timing of caffeine during alternative surfactant administration techniques should be investigated further.

CONCLUSION

A less invasive method for surfactant delivery is more than just a single intervention, it is a part of a complex care bundle that supports a premature infant's adaptation to extrauterine life. It should be recognized that all of the methods in this review have unique benefits and barriers which affect their potential applications (Table 2). The future of surfactant therapy in the preterm infant rests with more than one administration method, and further studies should aim to identify an optimal method

for each of the many clinical scenarios encountered in preterm newborn care.

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