



Less Invasive Surfactant Administration: A Viewpoint

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Abstract

The standard of care in treating respiratory distress syndrome in preterm infants is respiratory support with nasal continuous positive airway pressure or a combination of continuous positive airway pressure and exogenous surfactant replacement. Endotracheal intubation, the conventional method for surfactant administration, is an invasive procedure associated with procedural and mechanical ventilation complications. The INSURE (intubation, surfactant administration, and extubation soon after) technique is an accepted method aimed at reducing the short-term complications and long-term morbidities related to mechanical ventilation but does not eliminate risks associated with endotracheal intubation and mechanical ventilation. Alternative methods of surfactant delivery that can overcome the problems associated with the INSURE technique are surfactant through a laryngeal mask, surfactant through a thin intra-tracheal catheter, and aerosolized surfactant delivered using nebulizers. The three alternative methods of surfactant delivery studied in the last two decades have advantages and limitations. More than a dozen randomized controlled trials have aimed to study the benefits of the three alternative techniques of surfactant delivery compared with INSURE as the control arm, with promising results in terms of reduction in mortality, need for mechanical ventilation, and bronchopulmonary dysplasia. The need to find a less invasive surfactant administration technique is a clinically relevant problem. Before broader adoption in routine clinical practice, the most beneficial technique among the three alternative strategies should be identified. This review aims to summarize the current evidence for using the three alternative techniques of surfactant administration in neonates, compare the three techniques, highlight the knowledge gaps, and suggest future directions.

Keywords

- ▶ less invasive surfactant administration
- ▶ thin catheter technique
- ▶ aerosolized surfactant
- ▶ minimally invasive surfactant therapy
- ▶ surfactant administration through laryngeal supraglottic airway

Key Points

- The need to find a less invasive alternative method of surfactant delivery is a clinically relevant problem.
- Clinical trials that have studied alternative surfactant delivery methods have shown promising results but are inconclusive for broader adoption into clinical practice.
- Future studies should explore novel clinical trial methodologies and select clinically significant long term outcomes for comparison.

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Respiratory distress syndrome (RDS) is a disorder affecting preterm infants due to pulmonary surfactant deficiency. This condition's standard treatment is respiratory support with nasal continuous positive airway pressure (nCPAP) or a combination of CPAP and exogenous surfactant replacement.¹ Surfactant is conventionally administered through the endotracheal tube.^{2,3}

Endotracheal intubation for surfactant administration is an invasive procedure associated with procedural and mechanical ventilation complications.⁴ The availability of health care personnel skilled in the neonatal airway is a limiting factor that makes early surfactant administration difficult in resource-limited settings. Elective neonatal endotracheal intubation for surfactant administration may require premedication, like sedatives and vagolytics.⁵ Despite using premedication, the infant may poorly tolerate the procedure of direct laryngoscopy with complications of autonomic disturbances manifesting as apnea, bradycardia, hypoxemia, and systemic or intracranial hypertension.⁶

Even a short period of mechanical ventilation (<24 hours) of the developing lung (late canalicular and saccular stages) can result in volutrauma due to overdistension of the lung, barotrauma due to excessive pressure, atelectotrauma due to cyclical recruitment and de-recruitment, biotrauma due to inflammation and oxidative stress, and rheotrauma due to inappropriate airway flow.^{7,8} The long-term morbidities associated with mechanical ventilation include bronchopulmonary dysplasia and poor neurodevelopmental outcomes.⁹ INSURE (intubation, surfactant administration, and extubation soon after) is an accepted method aimed at reducing the short-term complications and long-term morbidities related to mechanical ventilation, especially in extreme (<28.0 weeks of gestational age [GA]) and very (<32.0 weeks of GA) preterm infants.¹⁰ The INSURE technique still carries several risks associated with endotracheal intubation and mechanical ventilation.

In this review, we aim to summarize the current evidence from randomized controlled trials (RCTs) and meta-analysis for using the alternative techniques of surfactant administration in neonates, compare the three well-studied techniques, highlight the knowledge gaps, and suggest future directions.

Alternative Surfactant Delivery Methods

The search for alternative methods that are less invasive than the INSURE technique began in the early 2000s. Three important alternative methods can overcome the problems associated with the INSURE technique. These are (1) surfactant through a laryngeal mask, (2) surfactant through a thin intratracheal catheter, and (3) aerosolized surfactant using nebulizers.

Laryngeal Mask-Assisted Surfactant Delivery

The success of surfactant delivery feasibility through supraglottic airway devices in preterm infants was first reported in 2004 (→Fig. 1).¹¹ Following this, eight RCTs were conducted to compare the efficacy of surfactant administration through laryngeal mask or supraglottic airway (SALSA) against nCPAP without surfactant^{12,13} or INSURE technique surfactant delivery (→Table 1).^{14–19}

The critical limitation of these trials is that they either did not report the prior sample size estimate or did not recruit enough participants to meet the calculated sample size. Six out of eight clinical trials were single-center trials which reduces the external validity of the results. Single-center trials tend to show larger treatment effects than multicenter RCTs.²⁰ The primary outcomes studied in most trials were the need for invasive mechanical ventilation (from 1 hour to 7 days) or improvement in oxygenation. However, the need for invasive mechanical ventilation cannot be automatically

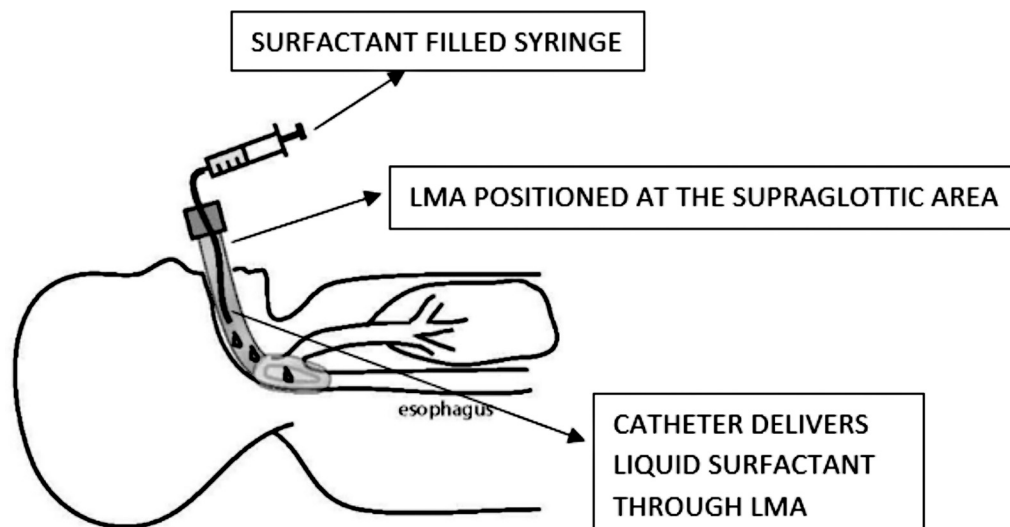


Fig. 1 Surfactant delivery through LMA with the use of a syringe and 5 Fr catheter inserted into the LMA. (Image courtesy: Dr. Satyan Lakshminrusimha, modified with permission).

Table 1 Clinical trials for laryngeal mask-assisted surfactant delivery

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion/comments
Attridge et al ¹³ (2013)	Single-center, prospective, unblinded RCT at the University of Virginia, United States	Inclusion: 1. X-ray and clinical RDS 2. BW >1,200 g 3. <72 h old 4. On nCPAP for at least 30 min with FiO ₂ -0.30–0.60 Exclusion: 1. Pneumothorax 2. Prior surfactant or intubation 3. Congenital anomaly	Calfactant (3 mL/kg.) administered through LMA in 2–4 aliquots via a catheter with the tip midway down the airway lumen. nCPAP (comparison)	Priori SS: 183 Enrolled: 26 ITT analysis 13 (LMA) group vs. 13 (nCPAP group)	Need for mechanical ventilation	CPAP vs. LMA: 23 vs. 8% (p = 0.59)	Underpowered No significant difference detected in the primary outcome
Sadeghnia et al ¹⁴ (2014)	Dual center RCT at the Shahid Beheshti and Al-Zahra Hospitals, Iran. Randomization and Allocation: not reported	Inclusion: 1. BW ≥ 2 kg with RDS symptoms at birth or within 48 h 2. On bubble CPAP needing FiO ₂ ≥ 0.3 for > 30 min Exclusion: 1. Airway abnormalities 2. Cardiothoracic or craniofacial malformations, 3. Perinatal asphyxia 4. Air-leak syndromes	Beractant (100 mg/kg) was administered through i-gel (intervention) and by INSURE (comparison)	Priori SS: not reported. 35 (i-gel) vs. 35 (Insure)	a/A PO ₂ before and after surfactant	i-gel vs. INSURE: Before surfactant mean (SD)-0.18 (0.03) vs. 0.19 (0.04; p = 0.39) After surfactant: 0.48 (0.08) vs. 0.43 (0.08) (p = 0.014)	Surfactant administration using i-gel resulted in better oxygenation than the INSURE technique
Pinheiro et al ¹⁵ (2016)	Single-center RCT at Albany Medical Center, United States. Randomization: 1:1 ratio within two GA blocks (<33 and ≥ 33 wk) using a computerized algorithm. Allocation concealed by clerical staff in serially numbered opaque envelopes.	Inclusion: 1. GA 29 ^{0/7} –36 ^{6/7} wk 2. Diagnosis of RDS 4. 48 h of age 3. On nCPAP ≥ 5 cm H ₂ O (with or without NIPPV) 4. FiO ₂ 0.30–0.60 to maintain SpO ₂ 88 to 95% Exclusion: 1. Prior intubation or surfactant therapy 2. BW < 1 kg 3. Major malformations 4. Apgar's score ≤ 3 at 5 min 5. Pneumothorax 6. Severe RDS indicated by FiO ₂ 0.40–0.60	Calfactant 3 mL/kg/ dose administered through size 1 LMA classic using a 5 Fr catheter or ETT Premedication: Atropine (0.01 mg/kg) in the LMA group Atropine (0.01 mg/kg) and morphine (0.1 mg/kg) in INSURE group.	Priori SS: 78 (39 in each group) 30 (LMA) vs. 31 (INSURE)	Need for MV	LMA vs. INSURE: 30 vs. 77% (p ≤ 0.001)	Surfactant therapy through an LMA decreased the need for MV in newborns with moderate RDS compared with INSURE with sedation

(Continued)

Table 1 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion/comments
Barbosa et al ¹⁶ (2017)	Prospective, un-blinded single-center RCT at Maternidade Unimed-BH in Belo Horizonte, Brazil. Randomization: By table of random numbers.	Inclusion: 1. GA at birth 28–35 wk 2. BW ≥ 1 kg 3. < 8 h of age 4. On nCPAP 5. SA score > 4 or respiratory frequency > 60 bpm or $FiO_2 \geq 0.40$ 6. Clinical and X-ray diagnosis of RDS Exclusion: 1. GA > 35 wk 2. Major congenital anomalies 3. Prior intubation 4. Apgar's score < 3 at 5 min 5. Chorioamnionitis and/or ROM > 18 h	Poractant 200 mg/kg administered within 8 h of age through size 1 preoral LMA using Fr catheter ETT surfactant followed by mechanical ventilation (comparison)	Priori SS: 30 Enrolled and analyzed: 48 26 (LMA) vs. 22 (ETT) SS reduced after an interim analysis showed equivalence	Reduction of oxygen need to $FiO_2 \leq 0.30$ at 3 h after surfactant	LMA vs. ETT: 77 vs. 77% ($p = 0.977$)	LMA surfactant had equivalent supplemental oxygen need at 3 h compared with ETT surfactant
Roberts et al ¹² (2018)	Multicenter, prospective RCT All the centers were in the United States Randomization: Computer-generated random numbers stratified by study site and enrollment (28 ^{0/7} –31 ^{6/7} wk and 32 ^{0/7} –35 ^{6/7} wk) using random blocks of 2, 4, and 6. Allocation: sequentially numbered, opaque, sealed envelopes.	Inclusion: 1. GA 28 ^{0/7} –35 ^{6/7} wk 2. BW ≥ 1,250 g 3. Age ≤ 36 h 4. On noninvasive respiratory support (CPAP, NIPPV, or BiPAP) 0.40 for ≥ 30 min 6. CXR and clinical RDS. Exclusion: 1. Prior MV or surfactant administration 2. Major congenital anomalies 3. Airway abnormality 4. Respiratory distress because of non-RDS etiology 5. Apgar's score < 5 at 5 min.	Poractant alfa 200 mg/kg was administered via size 1 LMA Unique CPAP (comparison)	Priori SS estimate: 144 (72 per group) Enrolled and analyzed: 103 Enrollment was terminated after four years due to difficulty in recruitment 50 (LMA group) vs. 53 (CPAP group)	Need for invasive MV in the first 7 d of life	LMA vs. CPAP: 38 vs. 64% ($p = 0.006$)	Surfactant via LMA decreased the rate of invasive MV compared with CPAP alone in preterm infants with moderate RDS
Gharehbaghi et al ¹⁷ (2018)	Single center RCT at Al-Zahra hospital, Tabriz, Iran	Inclusion: 1. GA 33–37 wk and BW ≥ 1,800 g	Beractant 100 mg/kg was given via size 1 LMA	Priori SS estimate: not reported Enrolled and analyzed:	Reduction in patient's FiO_2 requirement	LMA vs. INSURE: FiO_2 before and after surfactant in	Surfactant via LMA is a safe and effective

Table 1 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion/comments
Amini et al ¹⁸ (2019)	Randomization and Allocation: Computer-generated numbers in sealed opaque envelopes.	2. Clinical and X-ray signs of RDS Exclusion: 1. Apgar's score <4 at 5 min 2. Major congenital anomalies 3. Pneumonia 4. Pneumothorax	Of ETT After surfactant therapy, LMA and ETT were removed and infants were placed on CPAP Premedication: INSURE group only—Fentanyl (1–2 µg/kg)	50 25 (LMA) vs. 25 (INSURE)	following surfactant administration	mean (SD) = 0.60 (0.12) vs. 0.57 (0.12) and 0.42 (0.15) vs. 0.36 (0.10); (p < 0.001)	alternative to surfactant therapy via ETT
	Single-center prospective, open-label RCT conducted at Tehran University of Medical Sciences, Tehran, Iran.	Inclusion: 1. GA <37 wk 2. BW ≥ 1,200 g 3. Diagnosis of RDS in < 2 h of life 4. Need for CPAP ≥ 5 cm H ₂ O with FIO ₂ 0.30–0.60 Exclusion: 1. Prior intubation 2. Major malformations 3. mean BP < 40 mm Hg 4. Apgar's score ≤ 3 at 5 min 5. FIO ₂ need > 0.60 6. Pneumothorax 7. Apnea requiring assisted ventilation.	Poractant α 2.5 mL/kg/dose was given via size 1 LMA or via ETT by INSURE Premedication: INSURE group only—morphine (0.1 mg/kg)	Priori SS estimate: not reported Enrolled and analyzed: 60 (30 in each group) 30 (LMA) vs. 30 (INSURE)	Need for RDS-related MV	LMA vs. INSURE: 23.3 vs. 20% (p = 0.75)	Early surfactant via LMA and ETT is equally effective with no significant differences in the adverse outcomes
Gallup et al ¹⁹ (2022)	Single-center RCT conducted at Albany Medical Center, United States. Randomization and allocation: Computer-based stratified block randomization 1:1 allocation for the first half of the study, followed by 2:1 Concealment: opaque sealed envelopes	Inclusion: 1. GA 27 ^{0/7} –36 ^{6/7} wk and BW > 800 g 2. RDS needing CPAP > 5 cm H ₂ O, or NIPPV and FIO ₂ 0.30–0.60 for > 2 hours within 48 hours of birth. Exclusion: 1. Pneumothorax 2. Prior intubation 3. Major malformations 4. Apgar's score < 3 at 5 min of life or encephalopathy	Calfactant 3 mL/kg (105 mg/kg phospholipid) was given via size 1 LMA Unique or via ETT by INSURE Premedication: LMA group: atropine (0.01 mg/kg) only ETT group: Atropine and remifentanyl (2 µg/kg)	Priori SS estimate: 130 (65 in each group) Randomized and analyzed: 93 51 (LMA group) vs. 42 (ETT group)	Failure of surfactant therapy defined as 1. Need for invasive mechanical ventilation (or) doses of surfactant therapy 3. Need for FIO ₂ > 0.60 4. Need for the second dose of surfactant within 8 hours	LMA vs. INSURE: 20 vs. 29% (p = 0.311)	Surfactant therapy via LMA is noninferior to INSURE technique

Abbreviations: a/A PO₂, arterial-to-alveolar oxygen tension ratio; BW, birth weight; BP, blood pressure; CPAP, continuous positive airway pressure; ETT, endotracheal tube; FIO₂, fraction of inspired oxygen; GA, gestational age; INSURE, intubation, surfactant administration, and extubation soon after; LMA, laryngeal mask airway; MV, mechanical ventilation; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; RCT, randomized controlled trial; RDS, respiratory distress syndrome; SA, Silverman-Andersen score; SD, standard deviation; SS, sample size.

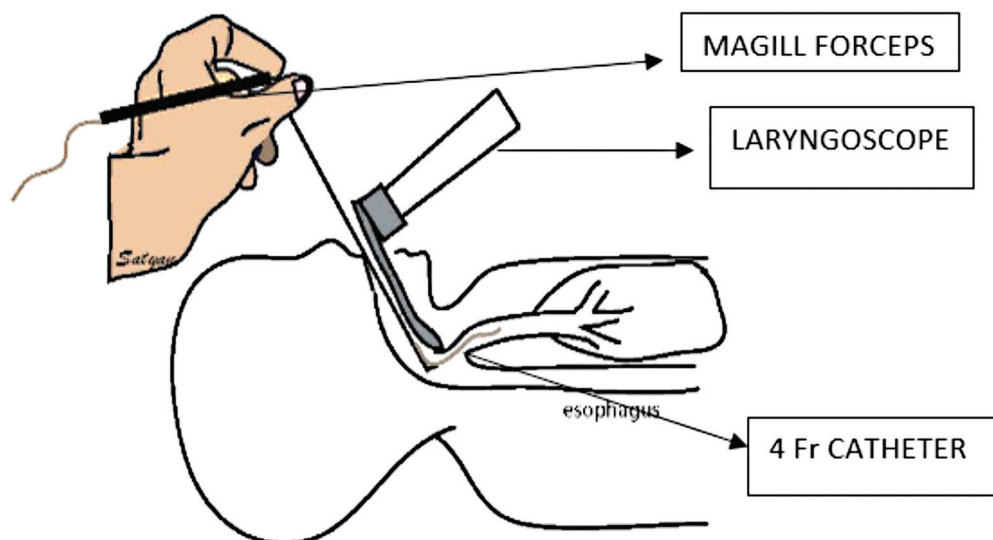


Fig. 2 Surfactant delivery through a intratracheal 4 Fr catheter inserted with the help of magill forceps and laryngoscope (Image courtesy: Dr. Satyan Lakshminrusimha, modified with permission).

construed as a failure of surfactant therapy because preterm diseases like a hemodynamically significant patent ductus arteriosus, congenital pneumonia, early pulmonary hypertension, perinatal asphyxia, and apnea of prematurity can lead to invasive mechanical ventilation or contribute to the outcome in varying proportions.

A meta-analysis including five of seven RCTs found that surfactant administration through laryngeal mask airway (LMA) reduces the need for invasive mechanical ventilation compared with nCPAP alone without any surfactant or surfactant delivery by INSURE.²¹ The meta-analysis showed that surfactant delivery via LMA is associated with a reduction in oxygen requirement compared with nCPAP alone and increased oxygen requirement compared with INSURE in 1 to 6 hours after treatment. However, this meta-analysis did not find evidence supporting SALSA for reducing mortality or short-term morbidities like pneumothorax, bronchopulmonary dysplasia, intraventricular hemorrhage, and length of hospital stay. None of the trials investigated long-term neurodevelopmental outcomes. The heterogeneity in the type of surfactant used, the type of LMA device, and the premedication use in the control arm (INSURE group) of these trials provides low-quality evidence, which limits our ability to make meaningful conclusions regarding its routine use in clinical practice

Thin Intratracheal Catheter-Assisted Surfactant Delivery

Kribs et al in 2007 demonstrated the feasibility and safety of the surfactant administration by intratracheal catheter in extremely preterm infants up to the limits of viability (23 weeks GA).²² In this study, a 0.04 Charrière catheter was clamped with Magill forceps at an angle of 120 degree and inserted into the trachea using a laryngoscope to deliver the liquid surfactant (see [Fig. 2](#)). Eight RCTs compared surfactant administration using a thin catheter, also known as less

invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST), with the standard delivery method through an endotracheal tube ([Table 2](#)).^{23–30} One RCT compared surfactant delivery by a thin catheter technique with the continuation of CPAP alone without surfactant.³¹

Six out of the nine RCTs were multicenter trials. Two studies included only very preterm infants, and three included only extremely preterm infants. Two studies included a combination of both. Six trials studied the LISA technique using a porcine surfactant, and three RCTs used a bovine surfactant. Seven trials used either a feeding tube or a vascular catheter for surfactant administration. Three trials used Magill forceps, and one used ophthalmic forceps to guide the catheter through the vocal cords. Two RCTs used a narrow-bore vascular catheter (16-gauge Angiocath, Becton Dickinson, Sandy, UT), of which one trial also used a proprietary semirigid catheter called LISAcath (Chiesi Farmaceutici SpA, Parma, Italy) for endotracheal instillation of surfactant. These catheters can be inserted endotracheally using a laryngoscope without Magill forceps by the Hobart method.³² Three studies used atropine as premedication for the procedure. One study did not use any premedication. Other studies did not report premedication use specifically.

All the clinical trials that studied the LISA technique have reported the prior sample size estimation except one study. Six studies enrolled enough participants to meet the sample size. Two studies did not fulfill the sample size requirement. Six of the nine clinical trials evaluated the need for invasive mechanical ventilation as the primary outcome. Five of them specifically looked at the need for invasive mechanical ventilation within 72 hours. Three studies had bronchopulmonary dysplasia at 36 weeks as their primary outcome. Of the three studies, one evaluated death or bronchopulmonary dysplasia (BPD) at 36 weeks as a composite outcome, and another studied survival without BPD and death as two different outcomes.

Table 2 Clinical trials for thin intratracheal catheter-assisted surfactant delivery

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion
Göpel et al ²³ (2011)	Multicenter unblinded RCT at 12 NICUs (level 3) in Germany Randomization: RITA (v1.2) 1:1 ratio with variable block sizes Allocation: sequentially numbered, sealed, opaque envelopes stratified by center and multiple birth statuses	Inclusion: 1. GA 26–28 ^{6/7} wk 2. BW < 1.5 kg Exclusion: 1. Lethal malformations 2. Surfactant without intubation before enrollment Enrolled all infants, irrespective of their respiratory status	Infants on CPAP with a $FiO_2 > 0.30$ received surfactant (100 mg/kg) using 2.5–5 Fr catheter placed in the trachea using Magill forceps and laryngoscope Standard treatment included Surfactant via ETT followed by MV Sedation and analgesia were used at the discretion of each neonatologist. Atropine (5 µg/kg) was optional	Priori SS estimate: 105 in each group Enrolled and analyzed: 220 108 (Thin catheter group) vs. 112 (standard treatment group)	Need for MV or $pCO_2 > 65$ mm Hg or $FiO_2 > 0.60$, or both, for more than 2 h between 25 and 72 h of age	Thin catheter vs. Standard treatment: 28 vs. 46% ($p = 0.008$)	Surfactant via thin catheter reduces the need for MV
Kanmaz et al ²⁵ (2013)	Single-center RCT conducted in the NICU of Zekai Tahir Burak Maternity Teaching Hospital, Turkey Randomization and Allocation: location: Sequentially numbered sealed opaque envelopes stratified by GA	Inclusion GA < 32 wk with RDS by clinical, chest X-ray and blood gas parameters on nCPAP with ≥ 0.4 FiO_2 in the first 2 h of life Exclusion 1. Major congenital anomalies 2. Need for PPV or intubation in the delivery room 3. Infants not resuscitated by trial investigators	A 5F catheter was inserted beyond the vocal cords and porcine surfactant 100 mg/kg was administered in the intervention group (comparison) No premedication	Priori SS estimate: 100 in each group Enrolled and analyzed: 200 100 (thin catheter group) vs. 100 (INSURE group)	Need for invasive MV in the first 72 h of life	Thin catheter vs. INSURE: 30 vs. 45% ($p = 0.02$)	Surfactant via thin catheter reduces the need and duration of MV in very low birth weight infants
Mirnia et al ²⁴ (2013)	Multicenter RCT conducted in the NICU of three university hospitals in Tabriz, Isfahan and Mashhad, Iran	Inclusion GA 27–32 wk on nCPAP needed $FiO_2 > 30\%$ for establishing $SpO_2 > 85\%$ and needed surfactant Exclusion 1. 5 min Apgar score < 6 2. Congenital	5F feeding tube was guided through 1–2 cm below the vocal cords and poractant α 200 mg/kg was given over 1–3 min INSURE group: Same dose of surfactant	Priori SS estimate – not reported Enrolled and analyzed – 136 66 (thin endotracheal catheter (TEC) group) V. 70 (INSURE group)	Primary outcome not identified Need for MV at 72 h Mortality BPD	TEC vs. INSURE: 19 vs. 22% ($p = 0.6$) 9.3 vs. 15.7% ($p = 0.01$) 7.5% vs. 7.1% ($p = 0.9$)	TEC was effective in treating RDS Mortality was significantly decreased in the TEC group

(Continued)

Table 2 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion
Bao et al ²⁷ (2015)	Single-center RCT in the Women's Hospital NICUs, Zhejiang University, China	malformations and congenital heart disease Inclusion 1. GA 28–32 wk 2. Signs of RDS needing nCPAP ≥ 7 cm H ₂ O and $\text{FI}_2 \geq 0.3$ (28 ^{0/7} –29 ^{0/7} wk gestation) or ≥ 0.35 (30 ^{0/7} –32 ^{0/7} wk) to maintain SpO_2 at 85–95% Exclusion 1. Prior intubation 2. Congenital anomalies affecting respiratory function.	through ETT Premedication: Atropine 5 $\mu\text{g}/\text{kg}$ before intubation 16G, 130 mm Angio-cath, BD, Sandy, Utah, United States, was marked at 1.5 cm (28–29 wk) or 2 cm (30–32 wk) and using direct laryngoscopy the catheter was inserted beyond the vocal cords surfactant was given at a standard dose over 3–5 min. Infants were continued on nCPAP throughout the procedure. INSURE group - Surfactant via ETT	Priori SS estimate - 60 infants in each group. Enrolled and analyzed: 90 47(LISA group) vs. 43 (INSURE group)	Need for intubation and MV within 72 h.	LISA vs. INSURE: 17 vs. 23.3% ($p = 0.44$)	LISA in spontaneously breathing infants on nCPAP is an alternative for surfactant therapy avoiding
Mohammadi Zadeh et al ²⁸ (2015)	RCT at 2 NICUs in the tertiary care hospitals affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. Randomization and Allocation: Using cards provided in consecutively numbered, opaque, and sealed envelopes	Inclusion GA < 34 wk and BW 1–1.8 kg with signs of RDS within the first h of life and need for surfactant after 30 min of nCPAP Exclusion 1. Maternal chorioamnionitis 2. Apgar's score ≤ 4 at 5 min 3. Congenital anomalies 4. Invasive MV at birth 5. Need for MV for more than a few minutes after Surfactant	4F feeding tube marked 1.5 cm above the tip was inserted using Magill forceps and laryngoscope, and poractant alfa was injected into the trachea over 1–3 min. nCPAP was continued during and after the procedure In the ETT group, the same dose of surfactant was administered using INSURE technique. Premedication: intravenous atropine (0.025 mg/kg)	Priori SS estimate: 34 Enrolled and analyzed: 38 19 (CATH group) 19 vs. (ET group)	Need for MV within 72 h of birth.	CATH vs. INSURE: 10.5 vs. 15.8% ($p = 0.99$)	Surfactant administration via a thin intratracheal catheter has similar feasibility, efficacy, and safety as INSURE technique

Table 2 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion
Kribs et al ²⁶ (2015)	Multicenter, randomized clinical parallel-group study conducted at 13 level III NICUs in Germany Randomization and Allocation: 1:1 ratio with variable block sizes using serially numbered opaque, sealed envelopes	Inclusion 1. GA 23 ^{0/7} –26 ^{6/7} wk 2. Spontaneous breathing, age 10 to 120 min Exclusion 1. Prenatally diagnosed severe underlying disease 2. Primary cardiopulmonary failure 3. Enrolled in any other interventional trial	A laryngoscope and a Magill forceps were used to intubate a 4F catheter up to the 1.5 cm mark. After removing the laryngoscope 100 mg/kg of porcine surfactant was instilled over 30 to 120 seconds. CPAP was continued after the intervention. In the control group, infants were intubated, MV was initiated, and surfactant was given via ET. MV was weaned as soon as possible according to the center's standard practice.	Priori SS estimate: 87 infants in each group Enrolled and analyzed: 211 107 (LISA group) vs. 104 (ETT group)	Survival without BPD Death	LISA vs. ETT: 67.3 vs. 58.7% (<i>p</i> = 0.20) 9.3 vs. 11.5% (<i>p</i> = 0.59)	Surfactant via LISA technique was not superior to surfactant via ETT, followed by MV concerning survival without BPD in extremely preterm infants (23–26 wk).
Halim et al ²⁹ (2019)	Single-center RCT in the NICU of Pakistan Institute of Medical Sciences, Islamabad, Pakistan Randomization and Allocation: Random numbers using a web-based randomization tool	Inclusion 1. GA <34 wk 2. Clinical and radiological evidence of RDS treated with CPAP Exclusion 1. Major congenital malformations 2. Intubation at birth	6F nasogastric tube was inserted 1–2 cm past the vocal cords under direct visualization using a laryngoscope. 100 mg/kg of beractant was administered while CPAP was continued. INSURE Surfactant (Comparison): Premedication: not reported	Priori SS estimate: 43 infants in each group Enrolled and analyzed: 100 50 (LISA group) vs. 50 (INSURE group)	Need for invasive mechanical ventilation	LISA vs. INSURE: 30 vs. 60% (<i>p</i> = 0.003)	LISA technique was more effective than INSURE in preventing the need for invasive mechanical ventilation
Han et al ³⁰ (2020)	Multicenter RCT at eight level III NICUs in Beijing, Tianjin, and Hebei province, China Randomization and Allocation: Sequentially numbered opaque sealed	Inclusion 1. GA <31 ^{6/7} wk 2. On NCPAP 3. Signs of respiratory distress with $FiO_2 > 0.4$ for $SpO_2 > 85\%$ 4. Surfactant need within 6 h of life Exclusion	5F gastric tube was inserted 1 cm past the vocal cords using a 10 cm ophthalmic forceps and laryngoscope. 70–100 mg/kg of calf pulmonary surfactant was administered while continuing CPAP.	Priori SS estimate: 130 infants in each group Enrolled and analyzed: 298 151 (MISA group) vs. 147 (EISA group)	Development of bronchopulmonary dysplasia (MV or CPAP or $FiO_2 > 0.3$ at 36 wk CGA)	MISA V. EISA: 19.2 vs. 25.9% (<i>p</i> = 0.17)	Minimally invasive surfactant administration was not superior to endotracheal surfactant delivery concerning a reduction in BPD

(Continued)

Table 2 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/ sample size	Primary outcome	Results	Conclusion
Dargaville et al ³¹ (2021)	<p>envelopes were used for the 1:1 assignment</p> <p>Multicenter RCT at 33 tertiary-level NICUs in 11 countries</p> <p>Randomization and Allocation: Permuted block randomization with stratification using a computer-generated code linked to a corresponding opaque sealed envelope</p> <p>1:1 group assignment</p> <p>Blinding: A screen was used to blind clinicians and parents</p>	<ol style="list-style-type: none"> 1. Delivery room intubation 2. Major congenital malformations 3. Death or transfer 4. Enrolled in other studies 5. Repeat dose of surfactant via ETT in first 72 h <p>Inclusion:</p> <ol style="list-style-type: none"> 1. GA 25^{0/7}–28^{6/7} wk 2. Inborn at a study center and admitted to the NICU 3. On CPAP/ NIPPV without prior intubation with a CPAP level of 5–8 cm H₂O and requiring FIO₂ of ≥0.30 within the first 6 h of life <p>Exclusion:</p> <ol style="list-style-type: none"> 1. Serious congenital anomaly 2. Imminent need for intubation 	INSURE Surfactant (comparison) Premedication: none	Priori SS estimate: 606 Enrolled and analyzed: 485 241 (MIST group) vs. 244 (control group)	Composite of death prior to 36 wk PMA or BPD assessed at 36 wk (oxygen requirement)	MIST vs. CPAP 43.6 vs. 49.6% (RR, 0.87; 95% CI, 0.74–1.03, <i>p</i> = 0.1)	MIST technique of surfactant delivery did not cause a statistically significant reduction in the composite outcome of death or bronchopulmonary dysplasia.

Abbreviations: BW, birth weight; BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; EISA, endotracheal intubation surfactant administration; ETT, endotracheal tube; FIO₂, fraction of inspired oxygen; GA, gestational age; INSURE, intubate-surfactant-exubate; LISA, less invasive surfactant administration; MISA, minimally invasive surfactant administration; MIST, minimally invasive surfactant therapy; MV, mechanical ventilation; NICU, neonatal intensive care unit; NIPPV, nasal intermittent positive pressure ventilation; PMA, postmenstrual age; PPV, positive pressure ventilation; RCT, randomized controlled trial; RDS, respiratory distress syndrome; RITA, randomization in treatment arms; RR, relative risk; SS, sample size; TEC, thin endotracheal catheter.

Subsequently, a meta-analysis of six out of nine trials showed that in preterm infants receiving nCPAP as the respiratory support, the intratracheal catheter technique for surfactant delivery compared with endotracheal intubation was beneficial in terms of reduction in the composite outcome of death or BPD at 36 weeks, BPD at 36 weeks among survivors, and the need for mechanical ventilation with a trend toward lower rates of air leaks.³³

Noninvasive Surfactant Delivery by Aerosolization

Early attempts to study surfactant delivery by aerosolization through a jet nebulizer in an RCT showed no difference in the arterial/alveolar PO₂ and the need for mechanical ventilation.³⁴ The authors of this study felt that the failure of effective aerosolized surfactant delivery could be the reason for their negative results. Finer et al showed the feasibility and safety of aerosolized delivery of Aerosurf, a peptide-containing synthetic surfactant by nCPAP, to preterm infants at risk for RDS using a clinically approved vibrating membrane nebulizer called Aeroneb Pro.³⁵ Following this, an RCT using aerosolized surfactant (poractant alfa) through a new-generation vibrating membrane nebulizer called eFlow neonatal showed that early postnatal administration of nebulized surfactant might reduce the need for intubation in preterm infants with mild RDS (–Table 3).³⁶

Among the two strata of preterm infants (29.0–31.6 and 32.0–33.6 weeks of GA) studied in this trial, the nebulized surfactant aided the successful establishment of noninvasive support in the 32.0 to 33.6 weeks of group alone. This study's results were limited by the single-center enrollment and small sample size ($n = 32/\text{group}$). A recently published multicenter pragmatic RCT including 457 infants (23–41 weeks of GA) used a modified Solarys nebulizer to deliver aerosolized surfactant into the mouth (–Fig. 3).³⁷ The study has reported an approximately 50% reduction in the need for subsequent intubation for liquid surfactant administration. This difference was not consistent among infants born at various GA strata, especially extreme preterm infants. A single-center phase 2 trial investigated four dosing schedules of beractant α delivered using two nebulizers, compared the data between three gestational strata, and found that aerosolized surfactant therapy is feasible without serious adverse outcomes.³⁸

A multicenter RCT enrolled spontaneously breathing preterm infants (28.0–32.6 weeks of GA) with mild-to-moderate RDS to investigate the safety, tolerability, and efficacy of nebulized poractant alfa, a porcine surfactant in comparison with nCPAP alone.³⁹ After the interim evaluation of the first 120 randomized neonates, the trial was terminated prematurely because the nebulized surfactant was found to have negligible efficacy in the study population. The authors analyzed the randomized infants and found that the nebulized surfactant did not reduce the likelihood of intubation within 72 hours of life compared with CPAP alone. Although the trial was conceptualized based on robust preclinical data, it could not be translated to clinical efficacy. The authors speculate that significant surfactant aerosol loss due to a leak

at the nasal interface leading to decreased deposition in the lungs could be a reason for the loss of efficacy.

Comparison of Three Alternative Methods with INSURE

Three alternative methods of surfactant delivery studied in the last two decades have both advantages and limitations when compared with each other (–Table 4). A recent network meta-analysis compared their efficacy with INSURE.⁴⁰ Sixteen RCTs and 20 observational studies with a large sample size ($n = 13,234$) were included in the analysis. The primary outcomes analyzed were mortality ($n = 12,155$), the need for mechanical ventilation ($n = 5,961$), and BPD ($n = 10,993$). The sample's median GA and birth weights were 29 weeks 6 days (interquartile range [IQR]: 28 weeks 1 days–31 weeks) and 1,289 g (IQR: 1,040.8–1,622.5). Compared with the INSURE method, surfactant delivery via a thin catheter alone and not SALSA or nebulization showed a significant decrease in mortality, need for mechanical ventilation (MV), and BPD. The significance of the difference in mortality and BPD seen with the thin catheter method was lost when RCTs alone were included for analysis. The main limitations of this study are the pooling of the results from RCTs and observational studies, the exclusion of three RCTs involving SALSA as the intervention,^{17–19} two RCTs studying thin catheter technique,^{29,31} and one RCT comparing nebulized surfactant with usual care,³⁷ and lack of adequate representation of extremely preterm infants (<28 weeks) in the sample.

Conclusion

The need to find a LISA technique is a clinically relevant problem. The three alternative methods, namely surfactant delivery through (1) laryngeal mask, (2) thin intratracheal catheter, and (3) aerosolization, have shown promising results in clinical trials. Before broader adoption in routine clinical practice, we must identify the most beneficial technique among the three alternative strategies. There is no RCT comparing these three techniques. An essential challenge of conducting well-designed RCT is the recruitment of participants. A multicenter RCT with a multiarm, multistage (MAMS) design will be one way to move forward. MAMS trial design provides the benefit of a smaller sample size, shorter duration, lower cost, and a shared control arm.⁴¹

The recent RCTs, which have studied outcomes like death and BPD rather than the need for invasive mechanical ventilation, have shown that equipoise still exists between the alternative methods of surfactant delivery and nCPAP alone. So, future trials should have four arms comparing the three surfactant delivery methods simultaneously with a control arm of nCPAP without surfactant. Those trials should study the composite outcome of death or respiratory morbidity as the primary outcome and report the adverse effects of each modality of surfactant delivery, other short-term morbidities, and long-term neurodevelopmental outcomes. Such trials can be resource intensive during the initial phases, but they might have the potential to provide

Table 3 Clinical trials for surfactant delivery by aerosolization

Citation	Design	Population	Intervention/ comparison	Analysis/sample size	Outcomes	Results	Conclusion
Berggren et al ³⁴ (2000)	Multicenter RCT was conducted at six NICUs in Sweden Randomization and Allocation: Randomized using sealed envelopes	Inclusion 1. GA <36 wk 2. Age 2–36 h 3. Clinically and radiologically diagnosed progressive RDS 4. Arterial/alveolar oxygen tension ratio 0.15–0.22 5. FIO ₂ > 0.4 needed to maintain SaO ₂ 85–95%. 6. No evident lung or cardiovascular malformation Exclusion Not fulfilling the inclusion criteria	A jet nebulizer (Aiolos Karlstad, Sweden) was used to generate surfactant aerosol and was administered via the CPAP equipment into the nostril. Dose – 480 mg dry weight of poractant α CPAP alone with no aerosols (control group)	Priori SS estimate – not reported Enrolled – 34 infants Analyzed – 32 infants 16 (nebulized surfactant group) vs. 16 (CPAP group)	Need for MV	Nebulized surfactant group vs. CPAP group 37.5 vs. 31.3%	No beneficial effects of aerosolized surfactant were demonstrated in this trial with a small sample size
Minochieri et al ³⁵ (2019)	Single-center blinded RCT conducted in tertiary NICU in Western Australia Randomization and Allocation: Computer-generated block stratified randomization was used with opaque sealed sequentially numbered envelopes. Stratification was based on GA: 29 ^{0/7} –31 ^{6/7} wk and 32 ^{0/7} –33 ^{6/7} wk	Inclusion 1. GA 29 ^{0/7} –33 ^{6/7} wk 2. Age < 4 h 3. Clinical signs of mild-to-moderate RDS requiring CPAP 5–8 cm H ₂ O 4. FIO ₂ requirement 0.22–0.30 to maintain SpO ₂ 86–94% Exclusion 1. Prior intubation or surfactant 2. Known pneumothorax 3. Cardiorespiratory instability 4. Cardiothoracic malformation 5. Chromosomal aberrations.	A customized vibrating membrane nebulizer (eFlow neonatal nebulizer system, PARI Pharma, Starnberg) was used to administer poractant alfa 200 mg/kg body weight. Control – nasal bubble CPAP alone without surfactant.	Priori SS estimate – 70 (35 patients/group) Randomized and analyzed: 64 32 in Nebulized surfactant group vs. 32 in CPAP group Intention to treat analysis	Need for intubation within the first 72 h*	Nebulized surfactant vs. CPAP alone 34.4 vs. 68.8% (RR [95% CI]: 0.526 [0.292–0.950])	Nebulized surfactant in the first 4 h of life reduced the need for intubation within the first 72 h in the study population
Cummings et al ³⁷ (2020)	Multicenter RCT conducted in 22 level three or four NICUs in the United States Randomization and Allocation: Moses-Oakford algorithm was used to generate sequential	Inclusion Cohort 1 1. Nonintubated and not received prior surfactant. 2. Age > 1 h but < 12 h of life 3. Suspected or confirmed RDS	The aerosol group received 6 mL/kg body weight of 35 mg/mL calfactant suspension, 210 mg phospholipids/kg body weight, through a modified Solarys nebulizer.	Priori SS estimate = 458 (229 patients per group) Randomized and analyzed = 457 230 in the aerosol group vs. 227 in the usual care group	Need for endotracheal intubation and liquid surfactant administration within the first 4 d	Aerosol group vs. usual care group 26 vs. 50% (p < 0.001)	Aerosolized calfactant administration reduces the need for intubation and liquid surfactant instillation in infants with mild-to-moderate RDS during the first 4 d of life

Table 3 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/sample size	Outcomes	Results	Conclusion
Sood et al ³⁸ (2021)	Single-center Phase II RCT at a level III NICU in the United States and Computer-generated stratified block randomization assigned patients to 4 groups at a 1:1:1:1 ratio	requiring nCPAP, HFNC, or NIV. Cohort 2 1. Age <24 h 2. Received liquid surfactant by 1 h of age 3. Extubated to nasal respiratory support Exclusion 1. Congenital anomaly 2. Hypotension with metabolic acidosis (base deficit > 10 meq/L) 3. Hypoxemia (SpO ₂ <88%) or hypercapnia (paCO ₂ ≥ 60 mm Hg) 4. Grade 3 or 4 IVH or acute hypoxic-ischemic encephalopathy	Usual care group – determined as appropriate by the physician	Intention to treat analysis	Four primary outcomes: 1. Safety A. Surfactant reflux 2. Feasibility 3. Impact of different dosing schedules 4. Efficacy defined as the need for intubation within 72 h of aerosolized surfactant	Dose I vs. Dose II vs. Dose III vs. Dose IV: 8 vs. 21% vs. 11 vs. 13% (p < 0.05) Data for primary outcomes 2 and 3 compared between three GA strata Study was not powered for efficacy. Efficacy was compared with historical controls	Aerosolized surfactant therapy is feasible without any serious adverse outcomes. Short-term efficacy was better than historical controls

(Continued)

Table 3 (Continued)

Citation	Design	Population	Intervention/ comparison	Analysis/sample size	Outcomes	Results	Conclusion
Dani et al ³⁹ (2022)	Multicenter, open-label, RCT was conducted in 34 centers in six European countries. Randomization and Allocation: Computer-based balanced block randomization scheme	Inclusion 1. GA 28 ^{0/7} –32 ^{6/7} 2. mild to moderate RDS 3. On nCPAP 5–8 cm H ₂ O with FIO ₂ 0.25–0.40 Exclusion: 1. Intubation within 1 h after birth 2. Surfactant use before study 3. RDS not secondary to surfactant deficiency 4. Severe asphyxia 5. Major congenital abnormalities 6. PROM (>21 d) 7. Air leak 8. IVH ≥ grade III 9. Hemodynamic instability	A vibrating membrane nebulizer (investigational eFlow Neos, PARI Pharma GmbH) was connected close to the patient between the nasal prongs and the connection of the ventilator circuit to deliver poractant α in two doses - 200 mg/kg (group 1) and 400 mg/kg (group 2) Group 3: CPAP only without surfactant	Priori SS estimate: 252 (84 infants in each group) Randomized and analyzed: 126 42 (group 1) vs. 41 (group 2) vs. 43 (group 3)	Respiratory failure within 72 h	Group 1 vs. Group 3: 57 vs. 58% (p = 0.926) Group 2 vs. group 3: 49 vs. 58% (p = 0.39)	Nebulized surfactant did not decrease the likelihood of respiratory failure within the first 72 h of life compared with CPAP alone

Abbreviations: CI, confidence interval; FIO₂, fraction of inspired oxygen; GA, gestational age; HFNC, high-flow nasal cannula; IVH, intraventricular hemorrhage; MV, mechanical ventilation; nCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PROM, prolonged rupture of membranes; RCT, randomized controlled trial; RDS, respiratory distress syndrome; RR, relative risk; SS, sample size.

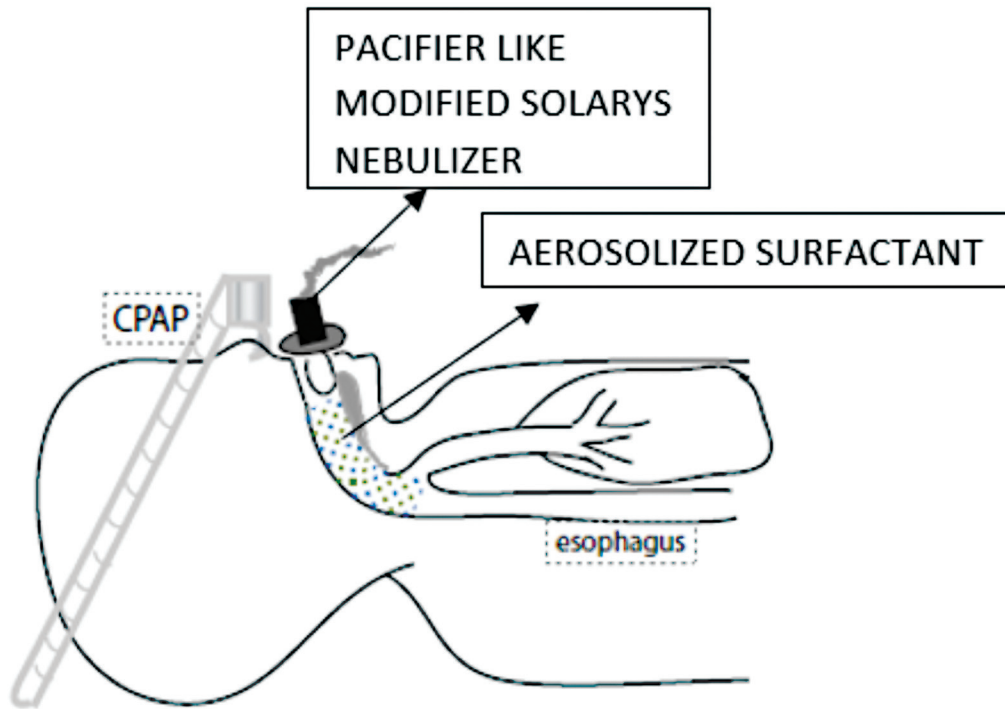


Fig. 3 Aerosolized surfactant delivered with the help of a modified Solarys nebulizer resembling a pacifier (Image courtesy: Dr. Satyan Lakshminrusimha, modified with permission).

Alternative methods of surfactant delivery	Laryngeal mask	Thin catheter	Aerosolization
Advantages	<ol style="list-style-type: none"> 1. Avoids complications due to direct laryngoscopy 2. Availability of the device in the NICU 3. Familiarity with the use of the device among NICU providers. 4. Ability to treat apnea/hypoxemia (potential complication of surfactant administration) with PPV - potential complication of surfactant administration 	<ol style="list-style-type: none"> 1. Can be used in the extremely preterm infants 2. Avoids PPV for surfactant administration 3. Reduces the need for intubation and mechanical ventilation in preterm infants 4. Some evidence for a reduction in BPD/mortality 	<ol style="list-style-type: none"> 1. Truly a noninvasive strategy for surfactant delivery 2. Allows concurrent use of CPAP 3. Avoids direct laryngoscopy and PPV 4. Some evidence for the reduced need for intubation and mechanical ventilation 5. No premedication is required
Disadvantages	<ol style="list-style-type: none"> 1. Interruption of CPAP during the procedure 2. Need for PPV to disperse the surfactant through the lungs. 3. Cannot be used in extremely preterm infants 4. Lack of evidence for a reduction in BPD 	<ol style="list-style-type: none"> 1. Need direct laryngoscopy with the associated risks 2. Need availability and use of Magill forceps 3. Need training and providers with advanced skills. 4. May need premedication 5. Lack of evidence regarding the long-term neurodevelopmental outcome 	<ol style="list-style-type: none"> 1. Optimal dose of surfactant for the nebulization route is unknown 2. Deposition of a significant fraction of the aerosolized dose in the upper airways 3. Lack of an effective nebulizer to aerosolize surfactant 4. Lack of evidence for use in severe RDS 5. Data on the effect on BPD and NDO is unavailable

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; NDO, neurodevelopmental outcome; NICU, neonatal intensive care unit; PPV, positive pressure ventilation; RDS, respiratory distress syndrome.

definitive data to make recommendations for standardized surfactant delivery techniques.

Conflict of Interest
None declared.

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References

- Polin RA, Carlo WACommittee on Fetus and Newborn American Academy of Pediatrics. Surfactant replacement therapy for pre-term and term neonates with respiratory distress. *Pediatrics* 2014;133(01):156–163
- Kendig JW, Notter RH, Cox C, et al. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. *N Engl J Med* 1991;324(13):865–871
- Kendig JW, Ryan RM, Sinkin RA, et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. *Pediatrics* 1998;101(06):1006–1012
- Foglia EE, Ades A, Sawyer T, et al; NEAR4NEOS Investigators. Neonatal intubation practice and outcomes: an international registry study. *Pediatrics* 2019;143(01):e20180902
- Barrington K. Premedication for endotracheal intubation in the newborn infant. *Paediatr Child Health* 2011;16(03):159–171
- Maheshwari R, Tracy M, Badawi N, Hinder M. Neonatal endotracheal intubation: how to make it more baby friendly. *J Paediatr Child Health* 2016;52(05):480–486
- Donn SM, Sinha SK. Minimising ventilator induced lung injury in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006;91(03):F226–F230
- Mokres LM, Parai K, Hilgendorff A, et al. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice. *Am J Physiol Lung Cell Mol Physiol* 2010;298(01):L23–L35
- Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011;23(02):167–172
- Verder H, Robertson B, Greisen G, et al; Danish-Swedish Multicenter Study Group. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. *N Engl J Med* 1994;331(16):1051–1055
- Brimacombe J, Gandini D, Keller C. The laryngeal mask airway for administration of surfactant in two neonates with respiratory distress syndrome. *Paediatr Anaesth* 2004;14(02):188–190
- Roberts KD, Brown R, Lampland AL, et al. Laryngeal mask airway for surfactant administration in neonates: a randomized, controlled trial. *J Pediatr* 2018;193:40–46.e1
- Attridge JT, Stewart C, Stukenborg GJ, Kattwinkel J. Administration of rescue surfactant by laryngeal mask airway: lessons from a pilot trial. *Am J Perinatol* 2013;30(03):201–206
- Sadeghnia A, Tanhaei M, Mohammadzadeh M, Nemati M. A comparison of surfactant administration through i-gel and ET-tube in the treatment of respiratory distress syndrome in newborns weighing more than 2000 grams. *Adv Biomed Res* 2014;3:160
- Pinheiro JM, Santana-Rivas Q, Pezzano C. Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery. *J Perinatol* 2016;36(03):196–201
- Barbosa RF, Simões E Silva AC, Silva YP. A randomized controlled trial of the laryngeal mask airway for surfactant administration in neonates. *J Pediatr (Rio J)* 2017;93(04):343–350
- Gharehbaghi M, Yalda JM, Radfar R. Comparing the efficacy of surfactant administration by laryngeal mask airway and endotracheal intubation in neonatal respiratory distress syndrome. *Crescent J Med Biol Sci* 2018;5(03):222–227
- Amini E, Sheikh M, Shariat M, Dalili H, Azadi N, Nourollahi S. Surfactant administration in preterm neonates using laryngeal mask airway: a randomized clinical trial. *Acta Med Iran* 2019;57(06):348
- Gallup JA, Ndakor SM, Pezzano C, Pinheiro JMB. Randomized trial of surfactant therapy via laryngeal mask airway versus brief tracheal intubation in neonates born preterm. *J Pediatr* 2022 (e-pub ahead of print). Doi: 10.1016/j.jpeds.2022.10.009
- Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med* 2011;155(01):39–51
- Calevo MG, Veronese N, Cavallin F, Paola C, Micaglio M, Trevisanuto D. Supraglottic airway devices for surfactant treatment: systematic review and meta-analysis. *J Perinatol* 2019;39(02):173–183
- Kribs A, Pillekamp F, Hünseler C, Vierzig A, Roth B. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age ≤ 27 weeks). *Paediatr Anaesth* 2007;17(04):364–369
- Göpel W, Kribs A, Ziegler A, et al; German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011;378(9803):1627–1634
- Mirnia K, Heidarzadeh M, Hosseini Mb, Sadeghnia A, Balilla M, Ghojzadeh M. Comparison outcome of surfactant administration via tracheal catheterization during spontaneous breathing with insure. *Med J Islamic World Acad Sci* 2013;21(04):143–148
- Kanmaz HG, Erdevi O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013;131(02):e502–e509
- Kribs A, Roll C, Göpel W, et al; NINSAPP Trial Investigators. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr* 2015;169(08):723–730
- Bao Y, Zhang G, Wu M, Ma L, Zhu J. A pilot study of less invasive surfactant administration in very preterm infants in a Chinese tertiary center. *BMC Pediatr* 2015;15:21
- Mohammadzadeh M, Ardestani AG, Sadeghnia AR. Early administration of surfactant via a thin intratracheal catheter in preterm infants with respiratory distress syndrome: feasibility and outcome. *J Res Pharm Pract* 2015;4(01):31–36
- Halim A, Shirazi H, Riaz S, Gul SS, Ali W. Less invasive surfactant administration in preterm infants with respiratory distress syndrome. *J Coll Physicians Surg Pak* 2019;29(03):226–330
- Han T, Liu H, Zhang H, et al. Minimally Invasive surfactant administration for the treatment of neonatal respiratory distress syndrome: a multicenter randomized study in China. *Front Pediatr* 2020;8:182
- Dargaville PA, Kamlin COF, Orsini F, 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
- Dargaville PA, Kamlin COF, De Paoli AG, et al. The OPTIMIST-a trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25–28 weeks gestation. *BMC Pediatr* 2014;14(01):213
- Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017;102(01):F17–F23
- Berggren E, Liljedahl M, Winblad B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta Paediatr* 2000;89(04):460–464
- Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. *J Aerosol Med Pulm Drug Deliv* 2010;23(05):303–309
- Minocchieri S, Berry CA, Pillow JJ; CureNeb Study Team. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2019;104(03):F313–F319
- Cummings JJ, Gerday E, Minton S, et al; AERO-02 STUDY INVESTIGATORS. Aerosolized calfactant for newborns with respiratory distress: a randomized trial. *Pediatrics* 2020;146(05):e20193967

- 38 Sood BG, Thomas R, Delaney-Black V, Xin Y, Sharma A, Chen X. Aerosolized Beractant in neonatal respiratory distress syndrome: a randomized fixed-dose parallel-arm phase II trial. *Pulm Pharmacol Ther* 2021;66:101986
- 39 Dani C, Talosi G, Piccinno A, et al; CURONEB Study Group. A randomized, controlled trial to investigate the efficacy of nebulized poractant alfa in premature babies with respiratory distress syndrome. *J Pediatr* 2022;246:40–47.e5
- 40 Bellos I, Fitrou G, Panza R, Pandita A. Comparative efficacy of methods for surfactant administration: a network meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2021;106(05):474–487
- 41 Millen GC, Yap C. Adaptive trial designs: what are multiarm, multistage trials? *Arch Dis Child Educ Pract Ed* 2020;105(06):376–378