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Update of minimally invasive surfactant therapy

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To date, preterm infants with respiratory distress syndrome (RDS) after birth have been managed with a combination of endotracheal intubation, surfactant instillation, and mechanical ventilation. It is now recognized that noninvasive ventilation (NIV) such as nasal continuous positive airway pressure (CPAP) in preterm infants is a reasonable alternative to elective intubation after birth. Recently, a meta-analysis of large controlled trials comparing conventional methods and nasal CPAP suggested that CPAP decreased the risk of the combined outcome of bronchopulmonary dysplasia or death. Since then, the use of NIV as primary therapy for preterm infants has increased, but when and how to give exogenous surfactant remains unclear. Overcoming this problem, minimally invasive surfactant therapy (MIST) allows spontaneously breathing neonates to remain on CPAP in the first week after birth. MIST has included administration of exogenous surfactant by intrapharyngeal instillation, nebulization, a laryngeal mask, and a thin catheter. In recent clinical trials, surfactant delivery via a thin catheter was found to reduce the need for subsequent endotracheal intubation and mechanical ventilation, and improves short-term respiratory outcomes. There is also growing evidence for MIST as an alternative to the INSURE (intubation-surfactant-extubation) procedure in spontaneously breathing preterm infants with RDS. In conclusion, MIST is gentle, safe, feasible, and effective in preterm infants, and is widely used for surfactant administration with noninvasive respiratory support by neonatologists. However, further studies are needed to resolve uncertainties in the MIST method, including infant selection, optimal surfactant dosage and administration method, and need for sedation.

Key words: Respiratory distress syndrome, Surfactant, Noninvasive ventilation

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Introduction

Respiratory distress syndrome (RDS) is a major cause of neonatal respiratory morbidity and mortality. For many years, neonates with RDS have been managed with a combination of tracheal intubation and surfactant replacement therapy (SRT) administered with mechanical ventilation. SRT in preterm infants has been proven effective in reducing pulmonary morbidity and mortality, and has been a major treatment in intubated preterm infants with respiratory distress after birth[1,2]. There have been many studies on the timing of surfactant administration for newborns with RDS. In the late 1990s and early 2000s, prophylactic SRT showed decreased respiratory morbidity (relative risk [RR], 0.69; 95% confidence interval [CI], 0.55–0.86) and mortality (RR, 0.84; 95% CI, 0.74–0.95), compared with delayed selective surfactant treatment for neonatal RDS[3,4], and prophylactic use of surfactant became widely accepted.

However, intubation itself may cause adverse effects and positive pressure ventilation after tracheal intubation may also increase acute lung injury in preterm infants[5]. Therefore, noninvasive ventilation such as continuous positive airway pressure (CPAP) has been introduced as a primary treatment for preterm infants with spontaneous breathing after birth for the purpose of reducing acute lung injury. CPAP treatment in preterm infants was more likely to have good short- and long-term outcomes, compared with intubation, positive pressure

ventilation, and surfactant application[6-10]. Three meta-analyses showed that primary CPAP therapy may decrease the incidence of bronchopulmonary dysplasia (BPD)[11-13]. These results led the European Association of Perinatal Medicine and the American Academy of Pediatrics to recommend use of noninvasive ventilation for primary respiratory support in preterm infants with respiratory distress [14,15]. There has been a rapid increase in the use of CPAP as primary therapy for preterm infants with respiratory distress, but whether and how to give surfactant to nonintubated infants remains unclear [16]. The intubation-surfactant-extubation (INSURE) technique was the first method to overcome the CPAP-surfactant dilemma. Verder et al.[17-19] published 2 randomized controlled trials using the INSURE method, which has subsequently been widely accepted in Scandinavia. Recently, the INSURE procedure has been reported to reduce the need for further intubation and duration of mechanical ventilation[20-22].

However, the need for sedative medication, secondary effects such as bradycardia or hypotension, and difficulty in extubation remain problems in the INSURE technique, and many neonatologists are investigating noninvasive or minimally invasive methods for surfactant administration, to avoid tracheal intubation and sedation[23,24]. Minimally invasive surfactant therapy (MIST) is also called less invasive surfactant administration. These MIST methods include intrapharyngeal surfactant instillation[25], surfactant nebulization[26], surfactant instillation via a laryngeal mask[27], and surfactant instillation via a thin endotracheal catheter[28], among which the most common method is tracheal catheterization[16,29,30]. Recent reviews updated several MIST methods based on feasibility studies, cohort studies, and clinical trials.

Different MIST methods

There are four different MIST methods, i.e., pharyngeal surfactant administration, aerosolized surfactant administration, laryngeal mask-guided surfactant administration, and surfactant administration via a thin catheter[31]. The timeline of the 4 different techniques for surfactant administration is shown in Table 1 as a modified metanarrative review by More et al.[31].

1. Surfactant Instillation into the pharynx

Intrapharyngeal surfactant instillation is the oldest approach in which a pulmonary surfactant is injected into the pharynx before the first breath and spreads at the air-fluid interface when the preterm infant starts breathing. Surfactant application into the pharynx was first applied by Enhoerning and Robertson in 1972 using a premature rabbit model, and the results showed that this procedure was effective in improving lung function in preterm rabbits[59]. In 1987, a randomized trial of intrapharyngeal instillation was first performed in humans by the Ten Centre Study Group[32]. Dambeanu et al.[33] performed a randomized multicenter clinical pilot study: intrapharyngeal surfactant instillation after birth versus routine surfactant application in preterm infants with gestational age 28–33 weeks. A feasibility and safety study of 23 preterm infants born at 27–30 weeks of gestation was done by Kattwinkel et al.[25] in 2004. In 2011, Cochrane Reviews showed that surfactant application into the pharynx before the first breath is potentially feasible, safe, and may be effective, but there were no well-designed randomized controlled trials[60]. Table 2 shows the characteristics of these human studies[25,32,33].

Table 1. The timeline of the studies of 4 different techniques of surfactant administration

Methods	Pharyngeal administration	Aerosolized administration	LMA-guided administration	Thin catheter administration
Studies	Ten Centre Study Group[32], 1987*	Jorch et al.[34], 1997	Brimacombe et al.[38], 2004†	Verder et al.[44], 1992
	Dambeanu et al.[33], 1997*	Arroe et al.[35], 1998	Trevisanuto et al.[27], 2005†	Kribs et al.[28,29,45], 2007, 2008, 2010
	Kattwinkel et al.[25], 2004	Berggren et al.[26], 2000*	Micaglio et al.[39], 2008†	Göpel et al.[46], 2011*
		Finer et al.[36], 2010	Barbosa et al.[40], 2012†	Dargaville et al.[47,48], 2011, 2013
		Minocchieri et al.[37], 2013*	Attridge et al.[41], 2013*	Mehler et al.[49], 2012
			Sadeghnia et al.[42], 2014*	Kanmaz et al.[50], 2013*
			Pinheiro et al.[43], 2016*	Klebermass-Schrehof et al.[24], 2013
				Heidarzadeh et al.[51], 2013*
				Aguar et al.[52], 2014
				Kribs et al.[53], 2015*
				Mohammadizadeh et al.[54], 2015*
				Bao et al.[55], 2015*
				Krajewski et al.[56], 2015
				Göpel et al.[57], 2015
				Canals Candela et al.[58], 2016

LMA, laryngeal mask airway.
*Prospective randomized controlled trials. †Case reports or case series.
Normal: Observational studies with or without control group.

2. Surfactant nebulization

Surfactant nebulization is an old concept that appeared to be an attractive alternative technique of surfactant application, and was called noninvasive surfactant therapy. A nebulizer is used to administer the pulmonary surfactant in aerosolized form. Administration as an aerosol is limited by many technical problems: particle size 0.5 to 2.0 mm, stability during the process of nebulization, and loss of surfactant[61]. Thus, various types of nebulizers have been studied for surfactant administration. Fok et al.[62] tested a jet nebulizer and an ultrasonic nebulizer in an animal model, and concluded that these types of nebulizers were not effective for SRT.

Three feasibility studies and 2 randomized trials using surfactant nebulization in humans were published. Four of these studies used a jet nebulizer and one used a vibrating membrane aerosolization system. These trials suggested that nebulized surfactant is safe and feasible, with some evidence for clinical improvement[63]. However, many questions remained unanswered: the proper positioning of the nebulizer in the circuit, the suitable interface for noninvasive respiratory support during nebulization, the optimal surfactant preparation and dosing, and the group of preterm infants most likely to benefit from aerosolized surfactant[61]. Well-designed and appropriately powered, multicenter, randomized controlled trials are needed. However, nebulization is the preferred technique to avoid manipulation of the airways during surfactant administration. Table 3 shows the

Table 2. Clinical studies of intrapharyngeal surfactant administration

Study	Design and population	Control	Intervention	Results
Ten Centre Study Group[32], 1987	RCT; GA, 25–29 wk	Saline	43 I and 32 C: 25–26 wk; 116 I and 117 C: 27–29 wk	Mortality: 19% I vs. 30% C ($P<0.01$) Respiratory support in first 10 day: I group, 19 hr less in >30% oxygen ($P<0.05$) and 20 hr less ventilation ($P<0.05$)
Dambeanu et al.[33], 1997	RCT; GA 28–33 wk	Routine assistance	28 I and 25 C	Mortality: 42.8 I vs. 48% C ($P=NS$) IVH: high in both group Silverman score significantly reduced in 1st 24 hr
Kattwinkel et al.[25], 2004	Nonrandomized feasibility study; GA 27–30 wk; BW 560–1,804 g		N=23 Infasurf CPAP of 10 cmH$_2$O by mask → 6 cmH$_2$O for 48 hr	VD: 13 of 15 babies weaned quickly to RA, no further surfactant or ET for RDS CS: 5 of 8 required subsequent ET soon after birth, 2 received subsequent ET surfactant

RCT, randomized controlled trial; GA, gestational age; I, intervention group; C, control group; NS, nonspecific; IVH, intraventricular hemorrhage; BW, birth weight; CPAP, continuous positive airway pressure; VD, vaginal delivery; RA, room air; ET, endotracheal; RDS, respiratory distress syndrome; CS, c-section.

Table 3. Clinical studies of aerosolized surfactant administration

Study	Design and population	Control	Intervention	Results
Jorch et al.[34], 1997	Nonrandomized multicenter pilot study; GA, 28–35 wk; On CPAP 1–7 hr of age	No	Alveofact (n=20); jet nebulizer 150 mg/kg x2, total 300 mg/kg, loading amount within 20–50 min	Significant (A-a)DO$_2$ improvement after first 150-mg/kg dose Improvement in Silvermann score Improvement in PaCO$_2$
Arroe et al.[35], 1998	Nonrandomized pilot study; GA, 23–36 wk; RDS, <3 day	No	Exosurf (n=22); jet nebulizer groups 1–4: 1, 2, 4, or 8 vial 2 tx. of 30 min, 6 hr apart	8 Patients required IMV up to 2 hr after last tx; No adverse effects; No improvement in clinical variables or (A-a)DO$_2$; Application of treatment too late
Berggren et al.[26], 2000	RCT; GA, 27–34 wk; randomized at 2–36 hr; FiO$_2$ >0.4	CPAP (3–5 cmH$_2$O) alone	Curosurf (n=34); jet nebulizer 16 C and 16 I (porcine surfactant, 480 mg)	Need for MV: 38% C vs. 31% I ($P=NS$); BPD: 12.5% C vs. 0% I ($P=NS$) No side effects noted; No beneficial effects noted
Finer et al.[36], 2010	Feasibility and safety study; GA, 28–32 wk; RDS	No	Aerosurf (n=17); vibrating membrane nebulizer; Randomized to group 1: at least 3 hr apart; group 2 at least 1 hr apart	All infants survived; 29.4% ET surfactant replacement; 23.5% RDS at 24 hr; 11.8 % BPD at 28 day; Mean FiO$_2$ 0.4 at baseline; 0.32 at 4 hr posttreatment
Minocchieri et al.[37], 2013	RCT; GA, 29–33 wk; FiO$_2$, 0.22–0.30 in first 6 hr after birth	CPAP alone	N=64; I (porcine surfactant) vs. C; vibrating membrane nebulizer	Need for intubation in the first 72 hr: RR, 0.56 (95% CI, 0.34–0.93); BPD: no difference
Segal et al., ongoing	RCT; GA 29–34 wk; ≤21 hr	CPAP alone	CPAP+Lucinactant (3 doses) (n=48)	
Sood et al., ongoing	RCT; GA, 24–36 wk; ≤24 hr	100 vs. 200	Survanta;100 vs. 200 mg phospholipid/kg (n=120)	

GA, gestational age; CPAP, continuous positive airway pressure; (A-a)DO$_2$, alveolar-arterial oxygen difference; RDS, respiratory distress syndrome; IMV, intermittent mandatory ventilation; tx, treatment; RCT, randomized controlled trial; C, control group; I, intervention group; MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; ET, endotracheal; FiO$_2$, a fraction of inspired oxygen; RR, relative risk; CI, confidence interval.

characteristics of these studies[26,34-37].

3. Surfactant instillation via laryngeal mask

In 2004, Brimacombe et al.[38] described the feasibility of using a laryngeal mask for SRT in a report of 2 cases. This was followed by several case reports and randomized trials[27,39-41]. Attridge et al.[41] compared surfactant application via laryngeal mask and CPAP alone in a randomized controlled trial including 26 neonates with respiratory distress and a birth weight more than 1,200 g. In 2 more recent reports, randomized trials of instillation of surfactant through a laryngeal mask and the INSURE technique were compared[42,43]. These 2 studies showed that there were no differences in short-term outcomes between the 2 groups. Table 4 provides an overview of

human studies to date[27,38-43].

4. Surfactant administration via a thin catheter (tracheal catheterization)

There are 2 basic methods for surfactant instillation via a thin catheter: the Cologne method and the Hobart method[45,47,52]. Other methods are variations of the above two methods. Table 5 shows the techniques of tracheal catheterization for surfactant administration [16,24,28,47,48,50,52].

Surfactant administration through tracheal catheterization was first described by Verder et al.[44], who used it as an alternative to the INSURE technique. In 2007, Kribs et al.[28] performed and published the first feasibility study using the Cologne method (Fig. 1), in which

Table 4. Clinical studies of LMA-guided surfactant administration

Study	Design and Population	Control	Intervention	Results
Brimacombe et al.[38], 2004	Case reports: GA 30 and 37 wk; BW 1,360 and 3,200 g respectively		Surfactant administered via Classic LMA	Successful uses
Trevisanuto et al.[27], 2005	Nonrandomized feasibility study; GA ≤35 wk; BW >800 g; ≤72 hr, a/APO₂ <0.20	CPAP, 5 cmH₂O	Surfactant administered via LMA without sedation or analgesia (n=8)	3 hr after surfactant instillation: mean (A-a)DO₂ increased (0.13±0.04 to 0.34±0.11; P<0.01) without complications
Micaglio et al.[39], 2008	Case reports: GA 37, 34, and 32 wk; BW 3,500, 2,050, and 1,530 g respectively		ProSeal LMA	Successful uses
Barbosa et al.[40], 2012	Case report: GA 31 wk, BW 1,335 g		ProSeal LMA	Successful use
Attridge et al.[41], 2013	RCT; BW≥1,200 g; age at inclusion, ≤72 hr; CPAP with FiO₂ 0.3 to 0.6	CPAP alone	13 I (calfactant surfactant, 3 mL/kg) and 13 C	MV need within 96 hr: RR, 1.0 (95% CI, 0.25–4.07) Reduced FiO₂ requirement for 1st 12 hr
Sadeghnia et al.[42], 2014	RCT; Mean GA 35 wk, BW>2,000 g	INSURE	35 I (Survanta, 100 mg/kg) and 35 C	Higher (A-a)DO₂ after procedure in the LMA group, no further differences
Pinheiro et al.[43], 2016	RCT; GA 27–36 wk; BW >800 g; 2–48 hr; ≥ 5 cmH₂O, FiO₂ 0.3–0.6 (n=130)	INSURE	Surfactant via LMA	Failure rate 77% in control group vs. 30% in intervention group, mainly caused by differences in early failure
Roberts et al, ongoing	RCT; GA 28–35 wk; ≤36 hr; 6 cmH₂O, FiO₂≥ 0.3 (n=144)	CPAP alone	Surfactant via LMA+CPAP	Intubation/MV in 1st 7 days

LMA, laryngeal mask airway; GA, gestational age; BW, birth weight; CPAP, continuous positive airway pressure; (A-a)DO₂, alveolar-arterial oxygen difference; RCT, randomized controlled trial; I, intervention group; C, control group; MV, mechanical ventilation; RR, relative risk; FiO₂, a fraction of inspired oxygen; INSURE, intubation, surfactant and extubation.

Table 5. MIST techniques with tracheal intubation

Method	Study	Catheter	Magill forceps used	Dose and mode of surfactant delivery	Premedication
Cologne method	Kribs et al.[28], 2007	4- to 5-FG feeding tube	Yes	100 mg/kg Slow push, 1–3 min	Atropine, sedation, and analgesia (optional)
Hobart method	Dargaville et al.[47,48], 2011, 2013	16-G Angiocath	No	100–200 mg/kg 3–4 boluses, 15–30 sec	Sucrose
Take care method	Kanmaz et al.[50], 2012	5-FG feeding tube	No	100 mg/kg Slow bolus, 30–60 sec	None
Karolinska method	Bohlin (unpublished)[16]	5-FG X 30-cm catheter	No	Slow bolus, 30 sec	Atropine/fentanyl
SONSURE method	Aguar et al.[52], 2014	4-FG feeding tube	Yes	100 mg/kg Slow push, 1–3 min	Atropine, caffeine
LISA method (Benveniste valve)	Klebermass-Schrehof et al.[24], 2013	4-FG feeding tube	Yes	200 mg/kg Slow push, 2–5 min	Caffeine

MIST, minimally invasive surfactant therapy; SONSURE, Sonda Nasogástica Surfactante Extubación; LISA, less invasive surfactant administration.
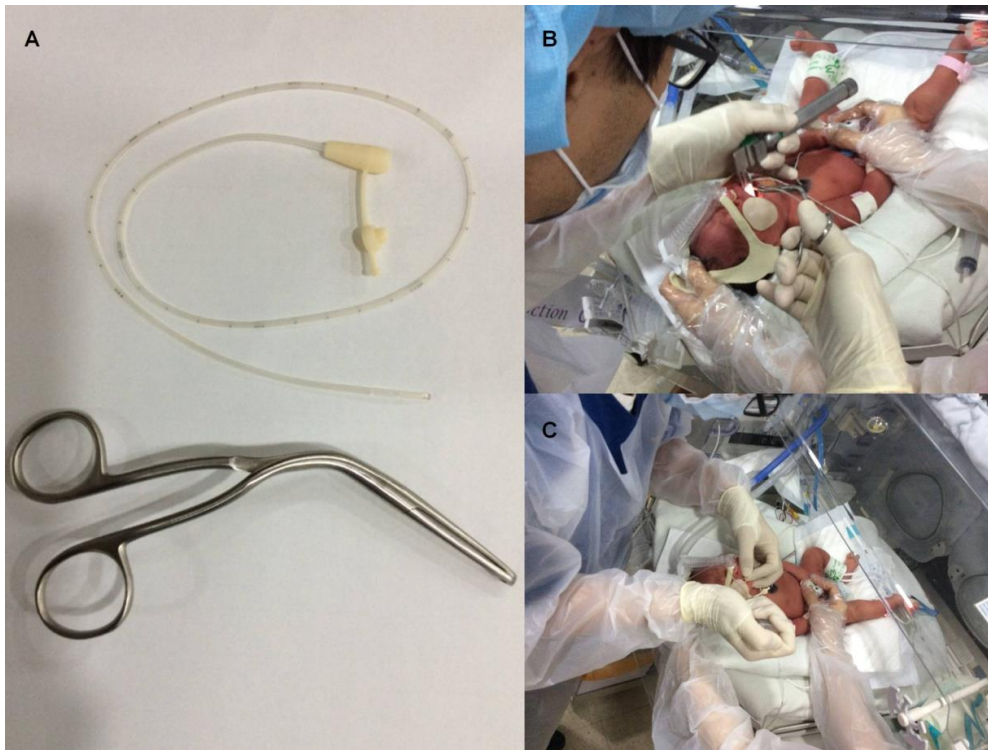
Fig. 1. Cologne method of surfactant instillation via a thin catheter. (A) Equipment used in Cologne method (feeding tube and Magill forceps). (B) Insertion of the feeding tube and (C) surfactant administration .

a 4- to 5-FG feeding tube and Magill forceps are used to introduce a thin catheter past the vocal cords. This procedure is part of a complete intervention aimed at avoidance of tracheal intubation and positive pressure ventilation during the first 72 hours after birth[29,49]. Further singlecenter and multicenter observational studies using the Cologne method have been performed.

In 2011, Dargaville et al.[47,48] modified this procedure without using a Magill forceps and called it the Hobart method. Dargaville et al.[47,48] evaluated 2 observational studies using the Hobart method for instillation of surfactant via an angiocatheter. The above 2 observational studies demonstrated rapid and sustained improvement in oxygenation and reduction in duration of oxygen supplementation and need for early mechanical ventilation, but there were no differences in overall duration of ventilation and incidence of BPD. A large, randomized controlled trial of MIST using the Hobart method in preterm infants (the OPTIMIST-A trial) is underway[64]. The OPTIMIST-A trial is a multicenter, randomized controlled trial of surfactant application via a vascular catheter in preterm infants on CPAP, born at 25 to 28 weeks of gestation. Inclusion criteria are age less than 6 hours after birth and need for CPAP with a fraction of inspired oxygen (FiO_2) no less than 0.3. The intervention group receives surfactant (poractant alfa, 200 mg/kg) via the Hobart method, and the control group remains on CPAP.

All feasibility and cohort studies on surfactant administration via a thin catheter are shown in Table 6, and the 7 randomized controlled trials are shown in Table 7.

Problems to be solved in the future

1. Infant selection

Not all preterm infants on CPAP show good results with MIST. Many preterm infants with mild RDS are well managed with CPAP alone. On the contrary, some infants with moderate to severe RDS start on CPAP, but should ideally receive prophylactic or early rescue surfactant replacement to gain the most advantage[65]. However, infants with significant RDS must be treated to obtain the best effect with MIST. As a clinical predictive tool, FiO_2 thresholds of 0.30 and 0.40 were used in the AMV trial and Take Care study, respectively[46,50]. The possible role of a functional surfactant assay such as the stable microbubble test of gastric aspirate is an important area for future investigation[16].

2. The MIST technique

Although there are many studies about each of the MIST techniques, there is no study comparing the various methods. All MIST should be conducted by clinicians with proper training and experience to reduce the failure rate and perform the procedure successfully. The development of a suitable surfactant and a method for surfactant aerosolization are required. A purpose-built surfactant ad-

Table 6. Clinical studies of surfactant administration via thin catheter: cohort and feasibility studies

Author	Design and population	Control	Intervention	Results
Verder et al.[44], 1992	Nonrandomized feasibility study;	ET instillation	MIST	Successful uses
Kribs et al.[28], 2007	Nonrandomized feasibility study; ELBW infants with GA, 23–27 wk	ET instillation (n=34)	MIST, $FiO_2>0.4$: 100 mg/kg surfactant (n=29)	BPD: 14% I vs. 15% C (P=NS) Mortality: 12% I vs. 35% C (P=0.025)
Kribs et al.[29], 2008	Retrospective cohort study, ELBW	Historical control (n=51, period 0)	Period 1–4 (n= 196)	Decrease CPAP failure from 46% to 25% Survival increased significantly between periods 0 and 1 from 76% to 90% and survival without BPD rose from 65% to 80%.
Kribs et al.[45], 2010	Prospective cohort study; VLBW infants or GA, <31 wk	ET instillation (n=1,222)	MIST (n=319)	MV in first 72 hr: 29% I vs. 53% C (P<0.001); BPD: 11% I vs. 18% C (P=0.004)
Dargaville et al.[47], 2011	Nonrandomized feasibility study, GA 25–34 wk	CPAP, ET instillation (n=173)	MIST (n=25)	Lower FiO_2 after MIST (pre-MIST: 0.39±0.092 (mean±SD); 4 hr: 0.26±0.093; P<0.01
Mehler et al.[49], 2012	Prospective cohort study; ELBW infants or GA, <26 wk	Historical control (n=44)	MIST (n=164)	MV 51% I vs. 72% C (P<0.05); Overall mortality 20% I vs. 39% C; BPD 18% I vs. 37% C, IVH> II 10% I vs. 33% C.
Dargaville et al.[48], 2013	Nonrandomized study (historical controls); GA, 25–34 wk, age, <24 hr	Routine CPAP and ET Instillation (n=41: GA, 25–28 wk; 56: GA, 29–34 wk)	MIST (n=38: GA, 25–28 wk; 23: GA, 29–34 wk)	MV at 72 hr, GA, 25-28 wk: OR, 0.21 (95% CI, 0.08-0.55); MV at 72 hr, GA, 29–34 wk: OR 0.34 (95% CI, 0.11–1.0); BPD: 29% I vs. 29% C (P=0.85)
Klebermass-Schrehof et al.[24], 2013	Nonrandomized study (historical controls); GA, 23–27 wk, at birth	CPAP, ET Instillation (n=182)	MIST (n=224)	MV need at 3 day: 23% I vs. 52% C (P<0.001); BPD: 16% I vs. 12% C P=NS); death or CLD 40% I vs. 51% (P=0.03)
Aguar et al.[52], 2014	Prospective cohort study, GA 24^{+0}–35^{+6} wk, at birth	INSURE method (n= 31)	MIST (n=45)	MV within 72 hr: 34% I vs. 26% C (P=0.44); a second dose of surfactant: 35% I vs. 6.5% C (P<0.0001).
Krajewski et al.[56], 2015	Prospective cohort study, preterm infants	INSURE method (n=26)	MIST (n=26)	BPD 15.4% I vs. 40% C (P<0.05), MV 3.9% I vs. 11.7% C (P<0.05).
Göpel et al.[57], 2015	Prospective cohort study (German Neonatal Network), GA <32 wk	CPAP, ET instillation (n= 1,103)	MIST (n=1,103)	MV: 41% I vs. 62% C (P<0.001); BPD: 12% I vs. 18% C (P=0.001); BPD or death:14% vs. 21% (P<0.001).
Canals Candela et al.[58], 2016	Prospective cohort study	CPAP, ET instillation (n= 28)	MIST (n=19)	ET intubation within 72 hr 42% I vs. 54% C (P< 0.05).

ET, endotracheal; MIST, minimally invasive surfactant therapy, ELBW, extremely low birth weight; GA, gestational age; FiO_2, a fraction of inspired oxygen; BPD, bronchopulmonary dysplasia; I, intervention; C, control; NS, nonspecific; CPAP, continuous positive airway pressure; VLBW, very low birth weight; FiO_2, a fraction of inspired oxygen; SD, standard deviation; MV, mechanical ventilation; IVH, intraventricular hemorrhage; OR, odds ratio; CI, confidence interval; CLD, chronic lung disease; INSURE, intubation, surfactant and extubation.

ministration apparatus such as a laryngeal mask or tracheal catheter should be developed and tested to avoid off-label use of medical devices. Finally, the introduction of a video laryngoscope should be considered in order to determine the exact location of application and to verify success of the MIST technique[16].

3. Premedication

Premedications used in MIST techniques include oral sucrose, atropine, opioids, ketamine, propofol, caffeine, morphine, fentanyl, muscle relaxants, and lidocaine spray[16,66]. According to a European survey published in 2017, 52% of neonatologists did not use any form of premedication for MIST[66]. In general, administration of narcotic agents in the INSURE method is common, but the avoidance of narcotics does not seem to have been associated with any short-term deleterious effects[67]. In the MIST technique, spontaneous breathing plays a major role in the distribution of pulmonary surfactant, so the reduction of breathing effort by narcotics may be

disadvantageous for preterm infants[50].

4. Dose and preparation

The dosage of surfactant in spontaneously breathing infants should be considered, because MIST has to be performed relatively rapidly and reflux of surfactant is seen frequently[16]. Published studies recommend a surfactant dosage of either 100 or 200 mg/kg, but 200 mg/kg is recommended for a more prolonged effect[30]. Further studies are needed to determine the optimal surfactant dose and to verify that administration of a relatively large volume (4–5 mL/kg) is safe and effective for MIST[16].

5. Safety

Short-term adverse effects such as cough, nausea, vomiting, reflux, apnea, bradycardia, and desaturation are common[61,66]. Moreover, the need for positive pressure ventilation via facial mask, retrial or failure, unilateral surfactant deposition, mucosal bleeding, lung

Table 7. Clinical studies of surfactant administration via thin catheter: randomized controlled trial

Trial	Intubation vs. control	Gestation range	Entry criteria	Primary outcomes	Other findings
Göpel et al.[46], 2011	MIST (n=108) vs. CPAP followed by ET instillation (n=112)	26–28 wk or VLBW	Age <12 hr FiO$_2$>30%	Intubation days 2–3	MV days 2–3 28% vs 46% (NNT: 6, 95% CI: 3–20, P=0.008); intubation at any time: 33% vs 73% (P<0.001); median days on MV: 0 vs 2; Oxygen at 28 days: 30% vs 45% (P=0.032)
Kanmaz et al.[50], 2013	MIST (n=100) vs. INSURE (n=100)	<32 wk	Age<72 hr FiO^2>40%	Intubation <72 hr	MV within 72 hr: 30% vs. 45% (P=0.02); MV at any time: 40% vs. 49% (P=0.08); BPD: 10% vs. 20% (P=0.009)
Heidarzadeh et al.[51], 2013	MIST (n=38) vs. INSURE (n=42)	≤32 wk	Immediately after birth	Feasibility, description of outcomes	Lower rate of NEC and shorter duration of CPAP and hospital stay in the intervention group, no further differences
Kribs, et al.[53], 2015	MIST (n=104) vs. CPAP, ET instillation (n=107)	23–26 wk	Age<2 hr FiO^2≥0.30 or Silverman score ≥5	Survival without BPD at 36-wk GA	Survival without BPD 67.3% vs. 58.7% (P=0.20); intubation: 74.8% vs. 99.0% (P=0.04); pneumothorax: 4.8% vs. 12.6% (P=0.02); Severe IVH: 10.3% vs. 22.1% (P=0.02); survival without major complications: 50.5% vs. 35.6% (P=0.02).
Mohammadizadeh et al.[54], 2015	MIST (n=19) vs. INSURE (n=19)	≤34 wk	Age<1 hr FiO$_2$≥0.30 or Silverman score ≥5	Need for MV and duration of oxygen therapy	No difference in need for MV, but duration of surfactant therapy significantly shorter in intervention group
Bao et al.[55], 2015	MIST (n=47) vs. INSURE (n=43)	28–32 wk	Age<2 hr nCPAP≥7 cmH$_2$O and FiO$_2$≥0.3 (28^{+0}–29^{+6} wk or ≥0.35 (30^{+0}–32^{+6} wk)	Feasibility, rate of MV in the first 72 hr, duration of MV, CPAP, and oxygen requirement, neonatal morbidities	No differences in rate of MV in the first 72 hr, duration of oxygen and neonatal morbidities, duration of MV and CPAP significantly less in the intervention group
Dargaville, et al.[64], ongoing	Hobart	25–28 wk	Less than 6 hr after birth FiO$_2$>30%	BPD or mortality	

MIST, minimally invasive surfactant therapy; CPAP, continuous positive airway pressure; ET, endotracheal; VLBW, very low birth weight; FiO$_2$, a fraction of inspired oxygen; MV, mechanical ventilation; NNT, number need to treat; CI, confidence interval; INSURE, intubation, surfactant and extubation; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; GA, gestational age; IVH, intraventricular hemorrhage; nCPAP, nasal CPAP.

bleeding, gastric deposition, and airway obstruction may occur during or after the MIST procedure[61,66]. Some studies suggested that the MIST technique may be associated with increased risk of necrotizing enterocolitis or spontaneous intestinal perforation, but additional large-scale, randomized controlled trials are needed to confirm the above association[53,57].

There have been 2 long-term follow-up studies of infants treated with MIST. Porath et al.[67] performed a 6-year follow-up of a feasibility cohort study. The survival rate and disability-free rate in the intervention group tended to be higher than in the control group. Teig et al.[68] also published a 36-month follow-up of infants treated with MIST. This study showed that the intervention group performed better on the Bayley Scales Mental Developmental Index and Psychomotor Developmental Index than a historical control group.

Conclusions

MIST is a method of surfactant administration without intubation in spontaneously breathing preterm infants with RDS. There are four different MIST methods, i.e., surfactant administration by intrapharyngeal instillation, aerosolization, laryngeal mask, and tracheal catheterization. There is growing evidence for surfactant instillation via a laryngeal mask as an alternative to the INSURE procedure. Several clinical studies showed an advantage of MIST via tracheal catheterization over either CPAP alone or surfactant application via INSURE technique; moreover, MIST via catheter application seems gentle, safe, feasible, and effective in preterm infants with RDS. Intrapharyngeal surfactant instillation and surfactant nebulization are less invasive, but there are few data to recommend these methods. Further studies are needed to resolve uncertainties of the MIST method, including appropriate infant selection, optimal surfactant dosage and administration method, and need for sedation.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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