

Effects of less invasive surfactant administration (LISA) via a gastric tube on the treatment of respiratory distress syndrome in premature infants aged 32 to 36 weeks

Guang Yang, MD^{a,b}, Mingyan Hei, MD^{a,*}, Zhimin Xue, MD^c, Yuan Zhao, MD^c, Xinhua Zhang, MD^c, Chenghu Wang, MD^c

Abstract

To explore the clinical effects of less invasive surfactant administration (LISA) via a gastric tube on the treatment of respiratory distress syndrome (RDS) in premature infants aged 32 to 36 weeks.

A total of 97 premature infants with RDS admitted to the Children's Hospital of Shanxi from February 2017 to January 2018 were randomly divided into LISA (47 cases) and (intubation-surfactant-extubation,) INSURE groups (50 cases). In the LISA group, 6F gastric tubes were inserted into the trachea through direct laryngoscopy under nasal continuous positive airway pressure (NCPAP), and pulmonary surfactant (PS) was injected. In the INSURE group, PS was injected via tracheal intubation and NCPAP was performed after extubation. The incidence of technical-related adverse events and various complications in the two groups were observed.

PS was successfully injected through gastric tube in the LISA group. There were no significant differences in reflux, asphyxia, bradycardia (<100 beats/min), apnea, FiO₂, changes in PaO₂ and PaCO₂ at 1 hour post-treatment between the groups. During the course of administration, blood pressure and SpO₂ in the LISA group were more stable, and significant differences between the 2 groups were observed. However, no significant differences in the complications and outcomes between the 2 groups occurred.

The LISA technique can be used to treat premature infants with RDS aged 32 to 36 weeks with stronger spontaneous breathing ability. Further clinical studies are required to determine the optimal strategy of LISA administration and the most profitable patient population.

Abbreviations: BPD = bronchopulmonary dysplasia, DBP = diastolic blood pressure, FiO₂ = fraction of inspired oxygen, INSURE = intubation-surfactant-extubation, IVH = intracranial hemorrhage, LISA = less invasive surfactant administration, MV = mechanical ventilation, NCPAP = nasal continuous positive airway pressure, NEC = necrotizing enterocolitis, PEEP = positive end-expiratory pressure, PNx = pneumothorax, PS = pulmonary surfactant, RDS = respiratory distress syndrome, ROP = retinopathy of premature infants, SBP = systolic blood pressure, SpO₂ = pulse oxygen saturation.

Keywords: less invasive surfactant administration, respiratory distress syndrome

1. Introduction

Neonatal respiratory distress syndrome (RDS) is a common respiratory disease in premature infants, mainly caused by the

lack of pulmonary surfactants (PS). At present, rapid extubation after tracheal intubation (intubation-surfactant-extubation, INSURE technique) and nasal continuous positive airway pressure (NCPAP) are routinely used in infants with RDS in China. However, intubation and positive pressure ventilation can cause laryngeal and tracheal damage, leading to fluctuations in blood pressure, and an increased risk of pneumothorax (PNx) and bronchopulmonary dysplasia (BPD^[1]). To combine the advantages of NCPAP and PS, Kribs et al^[2] reported a new method of PS without endotracheal intubation in 2007, referred to as less invasive surfactant administration (LISA). Subsequently, standardized postpartum respiratory management programs were established, including early high flow NCPAP and LISA technique for the treatment of infants with RDS using more moderate respiratory management models to improve the survival outcome. In recent years, clinical studies have shown that LISA technique can reduce the potential adverse effects of routine administration methods, and is feasible, safe, and effective.^[3-4] The technique can decrease the mortality rates of very preterm infants,^[5] improve lung outcomes, reduce the incidence of BPD and mechanical ventilation (MV), shorten oxygen supplementation times, and reduce the risk of death.^[6-9] However, the research populations have been focused on premature infants under 32 weeks of gestational age around

Editor: Undurti N. Das.

The authors declare no conflicts of interest

^a Neonatal Center, Beijing Children's Hospital, Capital Medical University, Beijing,

^b Department of Pediatrics, Shanxi Medical University, ^c Neonatal Internal Medicine, Children's Hospital of Shanxi, PR China.

* Correspondence: Mingyan Hei, Neonatal Center, Beijing Children's Hospital, Capital Medical University, Nanlishi Road #56, Xicheng District, Beijing, 100045, PR China (e-mail: heimingyan@bch.com.cn).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Yang G, Hei M, Xue Z, Zhao Y, Zhang X, Wang C. Effects of less invasive surfactant administration (LISA) via a gastric tube on the treatment of respiratory distress syndrome in premature infants aged 32 to 36 weeks. *Medicine* 2020;99:9(e19216).

Received: 11 June 2019 / Received in final form: 17 January 2020 / Accepted: 20 January 2020

<http://dx.doi.org/10.1097/MD.00000000000019216>

the world. Researches on moderate-late premature infants aged 32 to 36 weeks are not frequently issued according to their defined gestational age and stronger respiratory driving force. In fact, the absence of safe airway, administration PS can have results on refluxes, which hinders the deposition of substance in the lungs that lead to serious adverse events including asphyxia. In this study, LISA technique was applied to infants with RDS aged 32 to 36 weeks and compared to traditional administration methods. Adverse events during operation were recorded in detail, while the clinical effect and safety of LISA technique in moderate and late premature infants were evaluated. The limitation of LISA technique for the selection of gestational age was further explored.

2. Materials and methods

2.1. General data

Premature infants with RDS aged 32 to 36 weeks admitted to Children's Hospital of Shanxi from February 2017 to January 2018 were included in this prospective randomized controlled study. This study was approved by the ethics committee of the Children's Hospital of Shanxi and the written informed consent signed by the family members was provided. Inclusion criteria:

- (1) Gestational age from 32 weeks 0 days to 36 weeks 6 days preterms requiring NCPAP treatment after birth in 12 hours;
- (2) RDS diagnosed by physical and chest X-ray examination;
- (3) NCPAP pressures >6 cm H₂O, and fraction of inspired oxygen (FiO₂) $>40\%$.

Exclusion criteria:

- (1) Tracheal intubation after birth;
- (2) Respiratory function effected by congenital developmental abnormalities;
- (3) Family members of infants did not agree to participate.

During process of surfactant administration, the FiO₂ was adjusted using a blender to maintain pulse oxygen saturation (SpO₂) within the range of 89% to 95%. After procedure, when FiO₂ ≥ 0.6 , pH <7.20 and/or PaCO₂ >65 mm Hg or severe apnea occurred, infants were provided MV through tracheal intubation and a repeated PS of 100mg/kg if required.

2.2. Procedures

In the LISA group, 6F gastric tube with an external diameter of 2 mm was marked to indicate desired depth of insertion (32–34 weeks: 2 cm, 34–36 weeks: 2.5 cm). While the infant was breathing via NCPAP, a direct laryngoscope was introduced to provide a glottal view. The tube was grasped with a Magill forceps and the infant was intubated up to the mark, the tube was fixed in this position, the laryngoscope and Magill forceps were removed. The infant's mouth was closed, and PS was slowly injected for 1 to 3 min. After this step, 1 ml air is going to be introduced then the gastric tube was pulled out. Infants in the INSURE group were treated with tracheal intubation and artificial positive pressure ventilation. Positive pressure ventilation continued for 3 min after PS injection and NCPAP was used post-extubation. Curosur (Casey Pharmaceutical Company, Italy) at 200 mg/kg was used as the drug standard between the groups. Two attending physicians skilled in tracheal intubations and LISA technique cooperated to complete the operation. One

attending physician was responsible for the operation, whilst the other closely monitored changes in patient condition and vital signs. If reflux, asphyxia, SpO₂ $<80\%$ lasting 20 s, bradycardia (heart rate <100 beats/min), or apnea occurred during the operation, drug injections were stopped. Once the vital signs of the infants were stable, the drug was readministered.

2.3. Observed indicators

The incidences of adverse events such as reflux, asphyxia, bradycardia <100 beats/min and apnea during medication were recorded. Changes in FiO₂, SpO₂ and blood pressure were recorded every minute during administration. Changes in PaO₂ and PaCO₂ at 1 hour post-treatment, the rate of PS re-use, the rate of MV within 72 hours, and complications were recorded. Complications and outcomes included

- (1) PNX,
- (2) BPD,
- (3) necrotizing enterocolitis (NEC),
- (4) retinopathy of premature infants (ROP) $>$ stage 2,
- (5) intraventricular hemorrhage (IVH) $>$ grade III,
- (6) sepsis, and
- (7) death.

2.4. Statistical analysis

Data were analyzed according to the randomized assignments, and expressed as proportion, mean \pm standard deviation (m \pm SD) or median (interquartile range). Proportions were compared by Chi-square analysis. Continuous variables were compared by Student's *t* test or Mann–Whitney *U* test according to their distribution. A *P* value $<.05$ was considered statistically significant. Statistical analysis was carried out using the SPSS software, version 21.0 (SPSS, Chicago, IL).

3. Results

During the study period, 186 premature infants aged 32 to 36 weeks were hospitalized due to respiratory distress. Among them, 29 were intubated during resuscitation and 15 had major congenital malformations. The remaining 142 infants were initially treated with NCPAP, and 97 with RDS were included. Eligible infants were divided into LISA (47 cases) and INSURE groups (50 cases) using the random number table method (Fig. 1). There were no differences between the two groups in terms of baseline characteristics or prenatal risk factors (Table 1). No significant differences in the time from birth to PS use ($P=.49$) and frequency of administration ($P=.94$) between the 2 groups were observed. Three infants (6.4%) in LISA group and one infant (2%) in INSURE group required to reintubation before they could be correctly placed ($P=.57$). In addition, four infants in LISA group and three infants in INSURE group received MV due to aggravation of illness ($P=.80$). During the whole course of administration, there were no significant difference in the incidence of adverse events between the two group. Postnatal respiratory assistance outcomes, morbidities (PNX, BPD, NEC, ROP, IVH, and sepsis), and mortality were similar in the 2 groups (Table 2). During the operation, there was no significant difference in FiO₂ between the 2 groups (Fig. 2), but SpO₂ fluctuated slightly in the infants receiving LISA (Fig. 3). Systolic blood pressure (SBP) increased more significantly in INSURE

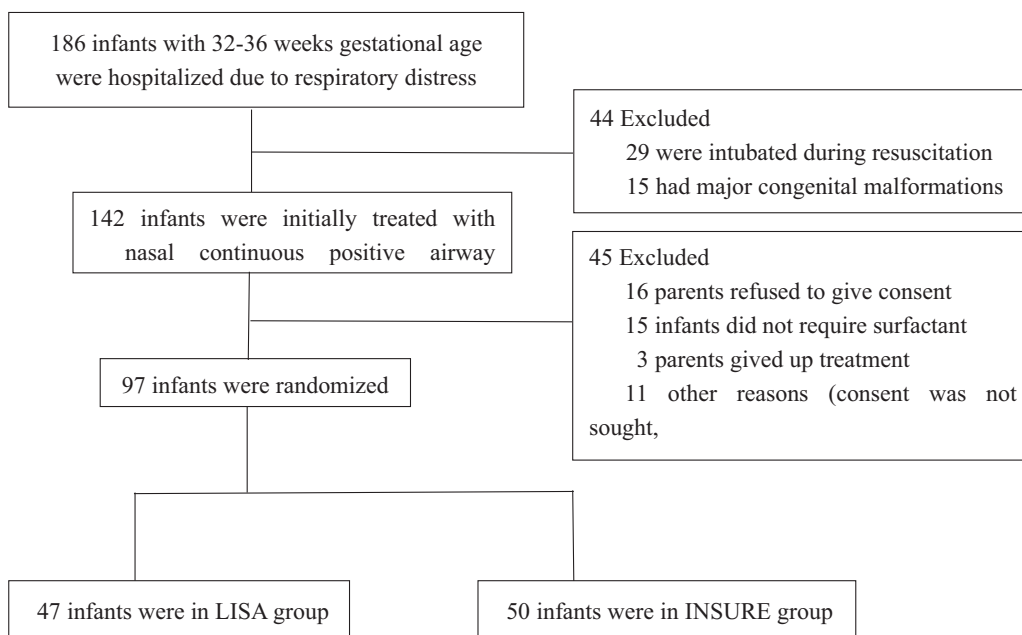


Figure 1. Trial profile.

group at 1 minutes and 3 minutes of administration (Fig. 4), and diastolic blood pressure (DBP) increased more significantly in INSURE group at 2 minutes and 4 minutes of administration (Fig. 5).

4. Discussion

An increasing number of infants with RDS receive NCPAP immediately after birth. However, the use of tracheal intubation for PS replacement therapy is increasingly questioned. The objective of LISA is to reduce the failure rates of NCPAP and avoid MV.^[10] The use of LISA with spontaneous breathing has benefits to the preterm compared to under positive pressure ventilation giving PS, which caused by the uniform distribution of PS in the lung and improvements in pulmonary compliance.^[11]

In this randomized controlled study, we confirmed that LISA could be successfully used in premature infants with large body

weights and strong spontaneous breathing ability. No serious adverse events occurred and changes in FiO₂, SpO₂, and blood pressure during administration were recorded and compared in detail. The older the gestational age and the stronger the

Table 1

Comparison of general data in the two groups of infants.

	LISA (n=47)	INSURE (n=50)	P value
Gestational age (weeks), mean (SD)	33.7 (1.0)	34.1 (1.3)	.14
Birth weight (grams), mean (SD)	2106 (315)	2219 (314)	.08
Multiple births, n (%)	8 (17.0)	6 (12.0)	.48
Male, n (%)	27 (57.4)	26 (52.0)	.60
Caesarean section, n (%)	19 (40.4)	22 (44.0)	.72
Antenatal hormone use, n (%)	13 (27.7)	11 (22.0)	.52
1 min Apgar score	6.4 (0.9)	6.5 (1.2)	.67
5 min Apgar score	8.4 (0.7)	8.6 (0.6)	.11
FiO ₂ before administration	0.43 (0.1)	0.44 (0.1)	.65
PEEP before administration	6.5 (0.8)	6.3 (0.9)	.07
PaO ₂ before administration	43.1 (2.6)	43.4 (3.1)	.74
PaCO ₂ before administration	61.8 (1.8)	61.3 (1.8)	.50
SBP before administration	58.7 (7.0)	60.1 (6.0)	.90
DBP before administration	36.7 (4.0)	36.4 (3.0)	.62

Table 2

Comparison of the observed indicators in the 2 groups of infants.

	LISA (n=47)	INSURE (n=50)	P value
Time from birth to PS use (hours)	5.4 (2.1)	5.7 (2.6)	.49
Two dose surfactant, n (%)	3 (6.4)	2 (4.0)	.94
second time catheterization, n (%)	3 (6.4)	1 (2.0)	.57
PaO ₂ at 1 h post-treatment	77.1 (5.1)	76.6 (5.9)	.86
PaCO ₂ at 1 h post-treatment	46.9 (6.5)	47.2 (4.7)	.82
Adverse events during administration, n (%)			
Reflux	6 (12.8)	3 (6.0)	.25
Bradycardia	3 (6.4)	5 (10.0)	.52
Apnea	4 (8.5)	2 (4.0)	.36
Respiratory support			
Number of MV cases 72 h after birth, n (%)	4 (8.5)	3 (6.0)	.80
MV days	3.1 (0.2)	3.3 (0.2)	.27
Number of cases using NCPAP, n (%)	47 (100)	50 (100)	
NCPAP time days	2.9 (0.5)	3.0 (0.4)	.37
MV+NCPAP days	6.3 (0.4)	6.4 (0.3)	.92
Oxygen days*	1.9 (0.9)	2.1 (0.7)	.25
Serious complications, n (%)			
PNX	2 (4.3)	3 (6.0)	.70
BPD	1 (2.1)	0	.30
NEC	0	1 (2.0)	.33
ROP	0	0	
IVH	0	0	
Sepsis	1 (2.1)	2 (4.0)	.60
Death	0	0	

BPD=bronchopulmonary dysplasia, IVH=intracranial hemorrhage. MV=mechanical ventilation, NCPAP=nasal continuous positive airway pressure, NEC=necrotizing enterocolitis, PNX=pneumothorax, PS=pulmonary surfactant, ROP=retinopathy of premature infants.

*Inhalation of oxygen using a mask or by nasal catheters during hospitalization.

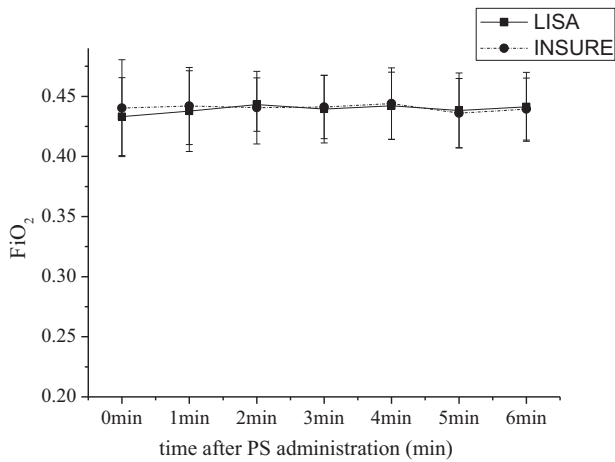


Figure 2. Here, 0min indicates the start of PS administration. There was no significant difference in FiO₂ between the 2 groups. FiO₂=fraction of inspired oxygen, INSURE=intubation-surfactant-extubation, LISA=less invasive surfactant administration, PS=pulmonary surfactant.

spontaneous breathing, the greater the risk of reflux in the absence of a safe airway.^[12] In previous studies, the gestational age using LISA technique was less than 32 weeks, which still remained a challenge. At the start of the study, reflux was the most common adverse effects due to our lack of clinical experience in LISA. After perfecting the LISA technique, the incidence of reflux was significantly lower. Compared to traditional administration methods, no differences in the incidence of reflux between the 2 groups were observed. We believe that although reflux is related to gestational age and spontaneous breathing, in fact, our research illustrates that depth of gastric tube insertion and the time of administration play more important role than above. The operator have concerns on that position of the gastric tube might lead to an uneven administration of the drugs in both lungs caused by over intubated, on the other hand, lower position can have side effects as reflux. Previous studies assessed the depth of intubation on the basis of gestational age, without no consideration of birth weight. We found that the depth of intubation and birth weight were closely

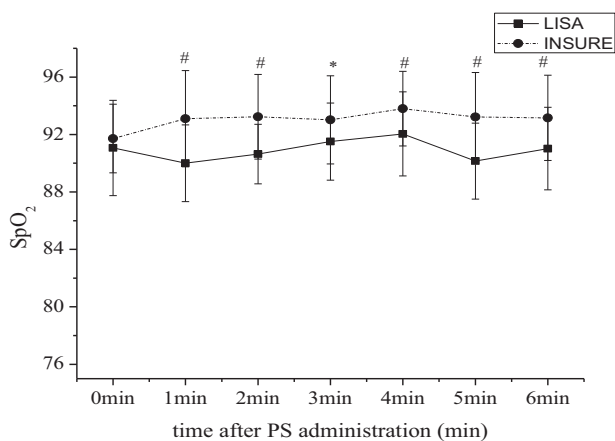


Figure 3. The SpO₂ in INSURE group was higher than that in LISA group during the whole course of administration. SpO₂, pulse oxygen saturation. [#]P<.01, ^{*}P<.05.

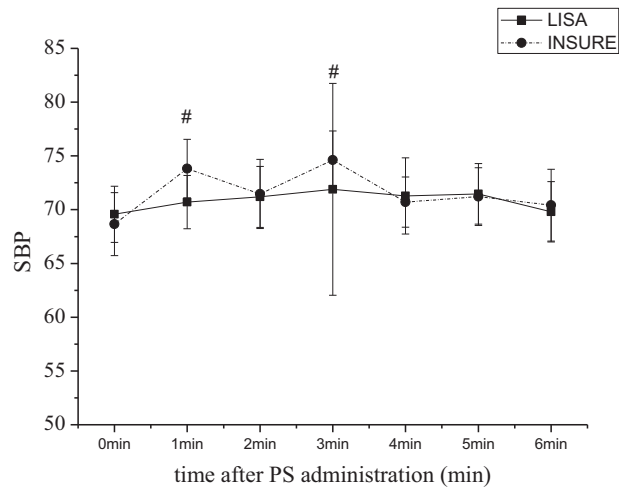


Figure 4. The SBP increased significantly in INSURE group at 1 and 3 minutes of administration, and there was significant difference between the 2 groups. SBP=systolic blood pressure. [#]P<.01.

related (birth weight ≤ 1.5 kg: 2 cm, birth weight 1.5–2 kg: 2.5 cm, birth weight 2–2.5 kg: 3 cm, birth weight ≥ 2.5 kg: 3.5 cm), which was more reasonable. According to our research, the optimal time to administer PS is 1 min, because over or less 1 min can increase the risk of reflux. The operator can use a stethoscope to monitor breathing, in which symmetrical vesicle sounds from both lungs were noted, suggesting an appropriate intubation position. If the bilateral vesicle sounds were asymmetrical, the depth of intubation was not ideal and required adjustments. LISA training is therefore necessary for an optimal outcome and gestational age should not limit the use of LISA technology.

Tracheal intubation can damage the airway mucosa, increasing the probability of infection.^[13] The texture of the gastric tube is soft, and damage to the vocal cords or trachea during intubation is unlikely. The diameter of the gastric tube is relatively narrow and easier to pass through the glottis, increasing the comfort of infants during the operation process. The fluctuated of blood

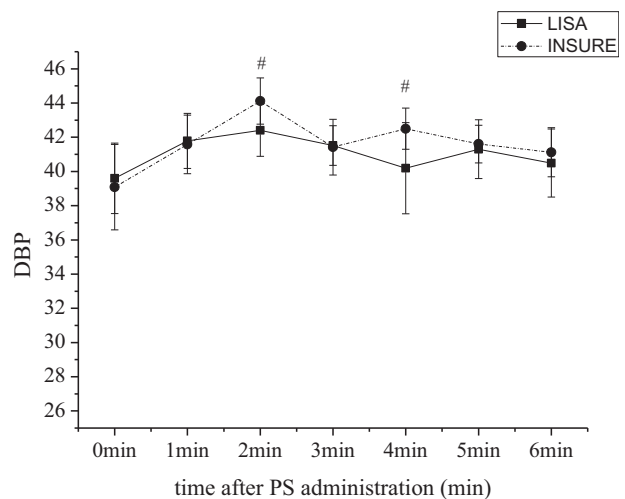


Figure 5. The DBP in INSURE group increased significantly at 2 and 4 minutes of administration, there was significant difference between the 2 groups. DBP=diastolic blood pressure. [#]P<.01.

pressure in INSURE group during the procedure have effects on cerebral perfusion,^[14] eventually increasing the risk of intracranial hemorrhage.^[15] During the course of administration, INSURE group maintained high levels of SpO₂, which were directly relating to the pressure of the operator's resuscitating airbag. The greater the pinching pressure of the airbag, the higher level of oxygen gas transported to the lungs, which can cause barotrauma injuries to the lung tissue. LISA technique could maintain NCPAP during the operation, SpO₂ was stabilized, and pressure to the lungs from operator was not required. This significantly reduced pulmonary barotrauma and severe IVH, improving the treatment outcome.^[16–17] A total of 7 cases (4 in the LISA group and 3 in the INSURE group) were treated with NCPAP combined with PS after birth, and received MV due to progressive increases in FiO₂ and/or PaCO₂ retention. Severe RDS required MV, and most neonatologists did not use LISA for treatment.^[18] As such, LISA is not a “one-size-fits-all” solution for RDS, but is more suitable for infants with mild to moderate RDS.

LISA caused fewer traumas when combined with NCPAP and the compliance of infants was good, and the treatment effect improved. At the same time, non-use or low dose analgesics and/or sedatives may be a potential advantage of LISA.^[19–20] The LISA technology is relatively simple and can be quickly mastered. Applying LISA in NCPAP is feasibility in moderate and late premature infants with RDS and spontaneous breathing. Further clinical studies are required to determine the optimal strategy for LISA technique and the patient groups most likely to benefit.

Author contributions

Conceptualization: Guang Yang, Zhimin Xue.

Data curation: Guang Yang.

Formal analysis: Guang Yang, Mingyan Hei, Zhimin Xue, Yuan Zhao, Xinhua Zhang, Chenghu Wang.

Investigation: Mingyan Hei, Yuan Zhao, Xinhua Zhang, Chenghu Wang.

Validation: Mingyan Hei, Zhimin Xue, Yuan Zhao, Xinhua Zhang, Chenghu Wang.

Writing – original draft: Guang Yang.

Writing – review & editing: Guang Yang, Mingyan Hei.

References

- Natarajan G, Pappas A, Shankaran S, et al. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev* 2012;88:509–15.
- Kribs A, Pillekamp F, Hünseler C, et al. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age \leq 27 weeks). *Paediatr Anaesth* 2007;17:364–9.
- Aguar M, Cernada M, Brugada M, et al. Minimally invasive surfactant therapy with a gastric tube is as effective as the intubation, surfactant, and extubation technique in preterm babies. *Acta Paediatr* 2014;103:e229–33.
- Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013;131:e502–9.
- Klebermass-Schrehof K, Wald M, Schwindt J, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. *Neonatology* 2013;103:252–8.
- Dargaville PA, Aiyappan A, Cornelius A, et al. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F243–248.
- van der Burg PS, de Jongh FH, Miedema M, et al. Effect of minimally invasive surfactant therapy on lung volume and ventilation in preterm infants. *J Pediatr* 2016;170:67–72.
- Göpel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011;378:1627–34.
- Göpel W, Kribs A, Härtel C, et al. Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. *Acta Paediatr* 2015;104:241–6.
- Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946–55.
- Bohlin K, Bouhafs RKL, Jarstrand C, et al. Spontaneous breathing or mechanical ventilation alters lung compliance and tissue association of exogenous surfactant in preterm newborn rabbits. *Pediatr Res* 2005;57(5 Pt 1):624–30.
- Lista G, Bresesti I, Fabbri L. Is less invasive surfactant administration necessary or “only” helpful or just a fashion? *Am J Perinatol* 2018; 35:530–3.
- Vannozi I, Ciantelli M, Moscuzza F, et al. Catheter and laryngeal mask endotracheal surfactant therapy: the CALMEST approach as a novel MIST technique. *J Matern Fetal Neonatal Med* 2016;1–8.
- Shim GH. Update of minimally invasive surfactant therapy. *Korean J Pediatr* 2017;60:273–81.
- Mehler K, Oberthuer A, Haertel C, et al. Use of analgesic and sedative drugs in VLBW infants in German NICUs from 2003–2010. *Eur J Pediatr* 2013;172:1633–9.
- Kribs A. How best to administer surfactant to VLBW infants? *Arch Dis Child Fetal Neonatal Ed* 2011;96:F238–240.
- Aldana-Aguirre JC, Pinto M, Featherstone RM, et al. 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:F17–23.
- Dargaville PA. Innovation in surfactant therapy I: surfactant lavage and surfactant administration by fluid bolus using minimally invasive techniques. *Neonatology* 2012;101:326–36.
- Zwicker JG, Miller SP, Grunau RE, et al. Smaller cerebellar growth and poorer neurodevelopmental outcomes in? Very preterm infants exposed to neonatal morphine. *J Pediatr* 2016;172:81–7e2.
- Langhammer K, Roth B, Kribs A, et al. Treatment and outcome data of very low birth weight infants treated with less invasive surfactant administration in comparison to intubation and mechanical ventilation in the clinical setting of a cross-sectional observational multicenter study. *Eur J Pediatr* 2018;177:1207–17.