Review Article

Less invasive surfactant administration as a means to facilitate gentler transition for preterm infants? A narrative review

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Abstract: Neonatal respiratory distress syndrome (RDS) is a common challenge for those caring for preterm infants. In RDS, the underlying cause is pulmonary surfactant deficiency or inactivity. Exogenous surfactant administration is the standard treatment. Conventionally, surfactant is delivered to the lungs via an endotracheal tube, usually followed by a period of mechanical ventilation. Alternatives to endotracheal intubation and prolonged ventilation include the intubation-surfactant-extubation approach (INSURE) and the less invasive surfactant application methods (LISA) or minimally invasive surfactant treatment (MIST). In this narrative review, we summarise studies and meta-analyses regarding surfactant treatment in RDS. We also compared different modes of surfactant administration, namely the conventional method via an endotracheal tube, INSURE and LISA/MIST. Several studies have compared the conventional method of surfactant delivery to INSURE, LISA or MIST. Meta-Analyses of these studies, comparing all combinations of surfactant delivery indicate that in preterm infants, LISA may be most effective in reducing the incidence of death or bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH) and retinopathy of prematurity (ROP). We conclude that the LISA technique should be considered as part of a gentler form of supporting transition of preterm infants. To obtain the best result from LISA, it is recommended that LISA is performed by experienced neonatologists with appropriate equipment, as outlined in published guidelines. Further research is needed to assess the short- and long-term impact on neurodevelopment of infants treated with LISA.

Keywords: Less invasive surfactant administration (LISA); preterm infants; respiratory distress syndrome (RDS); continuous positive airway pressure (CPAP)

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Introduction

Neonatal respiratory distress syndrome (RDS), caused by pulmonary surfactant deficiency, is a common problem in preterm infants. Due to its impact on infants' morbidity and mortality, RDS poses significant challenges for the medical team caring for preterm infants. There is an inverse relationship between gestational age and the incidence of RDS. Exogenous surfactant administration is an evidence-based treatment of RDS and it is effective in reducing the rates of pneumothorax and intensity and duration of mechanical ventilation, along with the decreasing mortality and major neonatal morbidities (1,2). For over forty years, exogenous surfactant has been predominantly administered

as a rapid bolus, instilled through an endotracheal tube and followed by a period of mechanical ventilation (3). Whilst this method was effective in reducing oxygen and ventilatory requirements in preterm infants, as well as the rate of pneumothorax, significant other adverse events were noted. Recognised adverse events of conventional surfactant administration include significant oxygen desaturation and bradycardia during endotracheal intubation, arterial hypotension and depression of the infant's electroencephalogram related to the use of intubation drugs (4,5). Despite these not infrequently occurring adverse events, surfactant administration via an endotracheal tube had become the norm in neonatal medicine. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-2/rc).

Objective

Our main objective was to define the most optimal means of surfactant delivery to preterm infants as a means to enabling them to transition gently.

Methods

We searched and reviewed the most up-to-date literature on methods of surfactant delivery way via an endotracheal tube, INSURE and less invasive surfactant administration (LISA)/minimally invasive surfactant treatment (MIST). We used online database PubMed (National Center for Biotechnology Information, Bethesda, USA) to search literature related to surfactant treatment in RDS with LISA or without LISA from 1991 to 2020. For our search process, no restrictions were made for publication year, language, publication status or study design. We present our findings in narrative form, emphasising LISA advantages, indications, practical considerations and also potential complications.

Narrative discussion of our findings

As early as in 1992, Verder *et al.* described surfactant administration in spontaneously breathing premature infants with RDS by use of a 6 French (Fr) catheter whilst the infants remained on continuous positive airway pressure (CPAP). However, this ground-breaking method, described in Ugeskrift for Laeger, a Danish medical journal (6), was not widely adopted at the time. In 1997, Valls-i-Soler *et al.* described a method of surfactant administration using a 3.5 Fr catheter, introduced through the side-port of an endotracheal tube, to administer surfactant over 60 seconds whilst the baby remained ventilated (7). In Germany, Kribs *et al.* also described a new method to administer exogenous surfactant to neonates receiving continuous positive airway pressure (CPAP). Under direct laryngoscopy, the researchers inserted a thin catheter into the infants' trachea using Magill's forceps, whilst maintaining the infant on CPAP. Surfactant was infused to the lungs over several minutes. Following surfactant administration, the catheter was immediately removed (8). Kribs *et al.* tested their new method of surfactant application to spontaneously breathing preterm infants with gestational age between 26–28 weeks in a multi-centre, parallel-group, randomised controlled trial (RCT) in 12 neonatal intensive care units in Germany between 2007-10 and showed a reduced need for mechanical ventilation in infants for whom the procedure was performed (9). In 2011, Dargaville *et al.*, in preparation for a multi-centre RCT, reviewed several methods of what is now referred to as MIST in which surfactant is delivered without tracheal intubation, including nasopharyngeal instillation, administration though laryngeal mask airway, aerosolization and tracheal catheterisation with a feeding tube or vascular catheter (10). Starting in 2013, the "OPTIMIST" trial was commenced: Here, surfactant is delivered to the trachea via a small, stiff vascular catheter, without the help of Magill's forceps, to preterm neonates with RDS (gestational age 25–28 weeks) who remain on CPAP during the procedure (11). Around the same time, Herting *et al.* described a technique that allows the application of surfactant to the most immature extremely low birth weight infants whilst on CPAP. The authors were the first to coin the term "less invasive surfactant administration" (LISA) (12). Both MIST and LISA are practiced with a variety of catheters, therefore the difference between the two is largely semantic. The global use of the term LISA has been proposed (13). In the 2019 edition of the European Consensus Guidelines on the Management of Respiratory Distress Syndrome, published by Sweet *et al.*, the use of LISA is proposed as "the preferred method of surfactant delivery in spontaneously breathing babies" (14). Acknowledging the currently limited strength of evidence, Sweet *et al.* declare their recommendation for LISA as based on B2 quality of evidence (moderate quality, weak recommendation) (14). However, the authors also cautiously note that the world's largest trial on less invasive surfactant delivery, the "OPTIMIST" trial, is still ongoing and that the results will influence future meta-analysis.

Why recommend the use of LISA technique?

In Germany, Kribs *et al.* were the first to use LISA to treat infants with RDS. Their method became known as the "Cologne Method." Due to the excellent results described by Kribs *et al.* in 2007 (8), many German neonatologists started to adopt their strategy even before the results from RCTs were available (15). However, LISA became even more popular after the results of a multi-centre RCT were published in 2011. In the trial by Gopel *et al.* authors compared LISA with standard endotracheal surfactant delivery followed by mechanical ventilation and found that infants randomised to LISA required significantly fewer days on mechanical ventilation [0 days, IQR 0–3 *vs.* 2 days, IQR 0–5 (P<0.0001)] and a lower need for oxygen therapy at 28 days [30 infants (30%) *vs.* 49 infants (45%), P=0.032] compared with the standard treatment group (9).

In Turkey, Kanmaz *et al.* studied 200 preterm infants with RDS born before 31 weeks gestation. Infants enrolled in this prospective single-centre RCT in the neonatal intensive care unit were randomized to receive early surfactant treatment either via a thin catheter during spontaneous breathing or by the INSURE technique, as described by Verder *et al.* (16), in which surfactant was given via an endotracheal tube but ventilation was only temporarily provided and infants changed back to nasal CPAP as soon as they breathed spontaneously. The study showed that the incidence of moderate to severe bronchopulmonary dysplasia (BPD) among infants who survived to discharge was significantly higher in the INSURE group (20.2% *vs.* 10.3%, P=0.009), compared to the group who received surfactant by a thin catheter (17). Several other studies followed, including further German Neonatal Network (GNN) studies in the most immature infants (18), comparing conventional surfactant application as well as INSURE to LISA.

In 2016, Isayama *et al.* published an instructive systematic review and network-analysis in the JOURNAL of the American Medical Association (JAMA) (19). The authors compared seven ventilation strategies for preterm infants: CPAP alone, INSURE, LISA, non-invasive intermittent positive pressure ventilation, nebulized surfactant administration, surfactant administration via laryngeal mask airway, and mechanical ventilation. With respect to the primary outcome (LISA compared with mechanical ventilation and nasal CPAP alone), results from 21 trials which included 4,987 infants and 1,160 infants with BPD, showed that LISA was associated with the least likelihood of BPD at postmenstrual age (PMA) 36 weeks (19). Taken on its own, the GNN study showed similar result: LISA significantly reduced the incidence of BPD compared with endotracheal tube surfactant administration [OR 0.55 (95% CI: 0.49–0.62), P<0.001] (20). Another systematic review and meta-analysis included 6 RCTs, enrolling a total of 895 premature infants with RDS, showed that the use of LISA technique reduced the composite outcome of death or BPD at PMA 36 weeks [risk ratio (RR) =0.75 (95% CI 0.59 to 0.94), P=0.01] and BPD among survivors [RR=0.72 (0.53 to 0.97), P=0.03] (21). A complex meta-Analysis showed similar results: The authors reviewed evidence for spontaneously breathing preterm infants with RDS treated with LISA or its variations compared to INSURE, LISA significantly decreased the risks of BPD or death [RR =0.63 (0.44–0.92); number needed to treat (NNT) =11] and early CPAP failure [RR =0.71 (0.53–0.96); NNT =11] (22). A 5-year single-centre retrospective study showed surfactant treatment in premature infants born at 25 0/7 to 29 6/7 weeks of gestation. Here, the incidence of moderate to severe BPD among infants treated with INSURE was significantly higher than the LISA treated group (21.9% *vs.* 12.2%, P=0.01) (23). Others showed how in a subgroup of the COIN-Trial (24), infants with very low birth weight (VLBWI) who were not subjected to invasive ventilation at birth were found to have higher lung compliance and reduced elastic work of breathing, documented by lung function testing at term equivalent age (25,26). Correspondingly, the results from the GNN trials by Herting *et al.* and Gopel *et al.* (27,28) demonstrated LISA effectiveness in relation to gestational age: LISA prevented mechanical ventilation in the first 72 hours and LISA was more effective as gestational age increased. The incidence of BPD was lower in preterm infants having surfactant administered by LISA compared with standard technique.

LISA and brain injury

Recently, a piglet RDS model was used to investigate the effect of INSURE and LISA on lung mechanics and cerebral oxygenation (29). This animal study indicated that the LISA group had higher rates of atelectasis, alveolar inflammation and total lung injury than the INSURE group. At same time, oxygen saturation and cerebral tissue oxygen indices did not significantly decrease during surfactant administration in the LISA group (29). Likewise, near-infrared spectroscopy (NIRS) was used to measure regional cerebral tissue oxygenation saturation ($rcSO_2$) in preterm infants born at gestation 26-31weeks compared those

who had LISA to those with CPAP only during the first 120 hours of life (30). This observational study indicated that there was no significant difference in $rcSO_2$ values between the two groups (30). The aforementioned study by Kribs *et al.* showed that the group who received LISA via a thin catheter had significantly reduced severe intraventricular haemorrhage (IVH), cystic periventricular leukomalacia (PVL) indexes at 36 weeks' gestational age (18). Likewise, reports from a single-centre practice-change towards LISA for extremely premature infants born at gestation 23–27 weeks showed how the LISA group, compared to historical controls and to data from the Vermont-Oxford Neonatal Network (VONN), had significantly less IVH (28.1 *vs.* 45.9%), severe IVH (13.1 *vs.* 23.9%) and cystic PVL (1.2 *vs.* 5.6%) (31). Similarly, a Spanish single-center, retrospective longitudinal study comparing preterm infants treated with LISA and INSURE found no difference in terms of neurological complications at 24 months post-menstrual age (32). Similar outcomes were shown by Hartel *et al.*: LISA reduced the rate of grade II–IV intra-ventricular haemorrhage [OR 0.55 (95% CI: 0.48–0.64), P<0.001] in premature infants compared to mechanical ventilation (20). It remains to be speculated whether LISA helps to improve cognitive function through the avoidance of prolonged intermittent hypoxaemia, which, in extremely preterm infants, has been shown to be associated with cognitive, language and motor impairment at 18 months' corrected age (33).

LISA and retinopathy of prematurity (ROP)

ROP is considered a common cause of blindness in children globally (34). Lower gestational age, low birth weight and high oxygen concentration supplement are strong risk factors for the development of ROP (35). Sepsis, IVH, blood transfusion, genetic factors, surfactant administration have been reported as risk factors for ROP development (36,37). RDS has been reported to associate with increased risk of ROP development (38). Prolonged mechanical ventilation is also a known risk factor for any stage of ROP (39), so as BPD with prolonged oxygen exposure (40,41). Treatment of BPD with corticosteroid has been shown to relate to any stage and ≥ stage 3 ROP (42). A large cohort study by GNN which included 7,533 very low birth weight infants (VLBWI) of gestational age 22 0/7 to 28 6/7 weeks showed that LISA was associated with reduced risk of ROP development [OR 0.62 (95% CI: 0.45–0.85), P<0.001] (20). This was postulated to be due to decreased mechanical ventilation use and less BPD development as a result as LISA.

LISA as part of an approach to facilitating a smoother fetal-to-neonatal transition

Herting *et al.* emphasized that LISA is not only a technical procedure for surfactant delivery but also a part of the concept of gentle transition for preterm infants, who benefit from their own spontaneous breathing (28). It is therefore important to recognise that LISA is a complex concept which requires a skilled, multi-professional perinatal team, especially highly dedicated pediatricians/neonatologists, specialists nurses, and other allied health care professional who are well versed in the care of very preterm infants. Safely performing LISA also requires repeated teaching and training.

How to perform LISA?

Whilst it is noted that centres experienced in providing LISA report its successful application to preterm infants of all gestational ages, starting from 22 weeks to term infants, it is strongly recommended that (I) centres should have bespoke local guidelines, which take the local level of experience into account and (II) to define different gestational age thresholds at which to perform LISA (13). In general, infants with clinical signs of RDS <6 h of age who require CPAP ≥6 cmH_2 and FiO_2 ≥0.30 to maintain age-appropriate peripheral oxygen saturations (SpO_2) could be offered LISA, if a practitioner competent in providing LISA is available. Infants with very lower gestational age who suffer from severe RDS with a high oxygen requirement [FiO_2 >0.45 (lower gestations) and >0.60 (more mature infants)] might rather be considered for endotracheal surfactant, followed by brief volume-targeted ventilatory support and timely extubation. However, in accordance to the European Consensus on Treatment of RDS, these pragmatically chosen thresholds will need more clinical studies to verify (14).

Recently, a practical guide on how to perform LISA, in whom, where and when, was published by Vento *et al.* (13). The authors extended their review on which infants should receive early surfactant administration as soon as possible by LISA in the neonatal intensive care unit (NICU), or in and near the delivery room. For the technique, the authors suggest that infants should be stabilised on CPAP and this form of respiratory support should be maintained

during direct laryngoscopy and surfactant delivery in spontaneously breathing infants. The availability of bespoke LISA catheters was positively received in several European countries (43). Irrespective of catheter used, the recommended depth of insertion of the catheter tip should be 1.5 cm beyond the vocal cords for babies <27 weeks gestation and 2 cm for more mature babies (13). Use of an appropriate-sized syringe to deliver surfactant via the thin catheter is advised, authors suggest to use a 2.5 mL syringe and leave the top part inflated with air to aide evacuation of all surfactant into the giving catheter in one sweep. Surfactant should be given by one bolus but in small aliquots, spaced out over 30 s to 3 min. It is mandatory to monitor oxygen saturations throughout the procedure and to increase the inspired oxygen concentration and the level of CPAP pressure when necessary (13).

The use of medication for procedures requiring direct laryngoscopy is a matter of ongoing debate. The location for such interventions in the setting of preterm stabilisation, whether laryngoscopy is performed on delivery suite or the NICU, adds another level of complexity. In preparation for the LISA procedure on the NICU, a dose of caffeine citrate (20 mg/kg, intravenously or orally) should be given to preterm infants <30 weeks gestation and birth weights <1,250 gram, to enhance respiratory drive (13). Equally, Atropine may be given to decrease the incidence or bradycardia during LISA (13,44). Whether or not LISA should be carried out with or without analgesia/sedation is the topic of heated discussion, as the current state of evidence remains inadequate to make firm recommendations. As an alternative to pharmacological agents, oral sucrose might be considered as a form of non-pharmacological analgesia. Whilst sucrose clearly is not a true analgesic, its administration has been described to enhance the tolerability of the LISA procedure (44). In summary, the choice of premedication should be based on the difference of GA and also include a balance between the perceived benefits and risks (13).

The introduction of LISA and its impact on care was assessed in a two-centre audit by Roberts *et al.* (44). The authors found that clear local guidance, specifying the indications for LISA and the procedure itself was of benefit. Using experienced clinicians compared to paediatric trainees for the LISA procedure resulted in greater success and better physiological stability of the infants. Further, the use of Atropine significantly reduced the incidence of bradycardia (44). This study highlights for one that the LISA method can be rapidly adopted with good results, and secondly that it is required for LISA to be performed in a gentle way by experienced operators as to minimise interference with the spontaneously breathing preterm infant. Therefore, training up staff members to be appropriate LISA operators, to familiarise whole support team to create the appropriate environment and to use the most adequate equipment and a suitable local protocol are instrumental in making LISA a success (13,44).

Complications of LISA

Complications secondary to LISA were reported, including failure to insert the LISA catheter, surfactant reflux, oxygen desaturation and bradycardia and abortion of LISA and reverting to endotracheal intubation and manual ventilation. Most complications developed during the immediate procedure and only rarely are complications encountered within hours after the LISA procedure (10,44-47). However, infants who received LISA should remain under close monitoring. According to Hartel *et al.*, late complications include that VLBWI treated with LISA can have a higher focal intestinal perforation (FIP) rate (4.3%) compared to those treated with surfactant via endotracheal tube (4.0%) or without surfactant treatment (1.2%) (20). In their study, the risk of FIP was significantly higher in infants with a gestational age <26 weeks treated by LISA compared to infants who had surfactant via endotracheal tube (10.0% *vs.* 7.4%, P=0.029), this was not found in the subgroup of infants born at gestation 26–28 weeks (P=0.13). Using a multivariable logistic regression analysis, the results showed that surfactant administration with LISA was associated with an increased risk of FIP. It was postulated that CPAP may affect pre- and post-prandial intestinal blood flow velocity in preterm infants and implementation of invasive measures may play a critical role in FIP (20).

Future research

The clinical advantages of LISA to treat different gestational age with spontaneous breath preterm requires further study as well as studies in different settings, including extending the practice of LISA to low- and middle-income countries. The short-term side effects of LISA on cerebral oxygenation requires urgent study. Further, the effects of the various combinations of premedication on long-term brain development requires need more attention.

Conclusions

Less invasive surfactant administration technique has become very popular in European neonatal units over recent years and has begun to be used more widely throughout the world. Whilst the results of the to date largest, international RCT on minimally invasive surfactant therapy, the OPTIMIST-Trial, are currently awaited, several well conducted studies, including RCTs aggregated in meta-analyses, already demonstrate that the LISA technique reduces neonatal complications such as death or BPD, IVH and ROP in preterm infants; and decreased the days of mechanical ventilation and oxygen use. Good clinical practice has been described, however, large-scale comparisons of different LISA techniques require further attention. Until this data is available, it is advised that NICUs interested in taking up the LISA assess the local capability of performing LISA, formulate bespoke standard operational procedures which consider the local level of expertise. Until more data from non-European settings are available, units interested in adopting the LISA approach should orientate themselves on published evidence and guidance.

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Footnote

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References

1. Morley CJ. Surfactant treatment for premature babies--a review of clinical trials. Arch Dis Child 1991;66:445-50.
2. Hennes HM, Lee MB, Rimm AA, et al. Surfactant replacement therapy in respiratory distress syndrome. Meta-analysis of clinical trials of single-dose surfactant extracts. Am J Dis Child 1991;145:102-04.
3. Fujiwara, T, Chida, S, Watabe, Y, et al. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980;1:55-9.
4. Liechty EA, Donovan E, Purohit D, et al. Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. Pediatrics 1991;88:19-28.
5. Bell AH, Skov L, Lundstrom KE, et al. Cerebral blood flow and plasma hypoxanthine in relation to surfactant treatment. Acta Paediatr 1994;83:910-4.
6. Verder H, Agertoft L, Albertsen P, et al. Surfaktantbehandling af nyfødte med respiratorisk distress-syndrom primaert behandlet med nasalt kontinuerligt positivt luftvejstryk.. Ugeskr Laeger 1992;154:2136-9.
7. Valls-i-Soler A, Lopez-Heredia J, Fernandez-Ruanova MB, et al. A simplified surfactant dosing procedure in respiratory distress syndrome: the "side-hole" randomized study. Spanish Surfactant Collaborative Group. Acta Paediatr 1997;86:747-51.
8. Kribs A, Pillekamp F, Hunseler C, et al. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age </=27 weeks). Paediatr Anaesth 2007;17:364-9.
9. 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.
10. 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:F243-8.
11. Dargaville PA, Aiyappan A, De Paoli AG, et al. Minimally-invasive surfactant therapy in preterm infants on continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed 2013;98:F122-6.
12. Herting E. Less invasive surfactant administration (LISA) - ways to deliver surfactant in spontaneously breathing infants. Early Hum Dev 2013;89:875-80.
13. Vento M, Bohlin K, Herting E, Roehr CC, et al. Surfactant Administration via Thin Catheter: A Practical Guide. Neonatology 2019;116:211-26.
14. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2019 Update. Neonatology 2019;115:432-50.
15. Klotz D, Porcaro U, Fleck T, et al. European perspective on less invasive surfactant administration-a survey. Eur J Pediatr 2017;176:147-54.
16. Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994;331:1051-5.
17. Kanmaz HG, Erdeve O, Canpolat FE, et al. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. Pediatrics 2013;131:e502-9.
18. Kribs A, Roll C, Gopel W, et al. Nonintubated Surfactant Application vs. Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr 2015;169:723-30.
19. Isayama T, Iwami H, McDonald S, et al. Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A Systematic Review and Meta-analysis. JAMA 2016;316:611-24.
20. Härtel C, Paul P, Hanke K, et al. Less invasive surfactant administration and complications of preterm birth. Sci Rep 2018;8:8333.
21. Aldana-Aguirre JC, Pinto M, Featherstone RM, et al. Less invasive surfactant administration vs. 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.
22. Rigo V, Lefebvre C, Broux I. Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. Eur J Pediatr 2016;175:1933-42.
23. Buyuktiryaki M, Alarcon-Martinez T, Simsek GK, et al. Five-year single center experience on surfactant treatment in preterm infants with respiratory distress syndrome: LISA vs. INSURE. Early Hum Dev 2019;135:32-6.
24. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700-8.
25. Roehr CC, Proquitté H, Hammer H, et al. Positive effects of early continuous positive airway pressure on pulmonary function in extremely premature infants: results of a subgroup analysis of the COIN trial. Arch Dis Child Fetal Neonatal Ed. 2011;96:F371-3.
26. Schmalisch G, Wilitzki S, Roehr CC, et al. Development of lung function in very low birth weight infants with or without bronchopulmonary dysplasia: longitudinal assessment during the first 15 months of corrected age. BMC Pediatr 2012;12:37.
27. 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.
28. Herting E, Hartel C, Gopel W. Less invasive surfactant administration (LISA): chances and limitations. Arch Dis Child Fetal Neonatal Ed 2019;104:F655-9.
29. Rey-Santano C, Mielgo VE, Gomez-Solaetxe MA, et al. Cerebral oxygenation associated with INSURE vs. LISA procedures in surfactant-deficient newborn piglet RDS model. Pediatr Pulmonol 2019;54:644-54.
30. Hanke K, Rausch TK, Paul P, et al. The effect of less invasive surfactant administration on cerebral oxygenation in preterm infants. Acta Paediatr 2020;109:291-9.
31. 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.
32. Marquez IE, Sanchez L M, Ramos-Navarro C. Long-term outcomes of preterm infants treated with less invasive surfactant technique (LISA). J Matern Fetal Neonatal Med 2019;12:1-6.
33. Poets CF, Roberts RS, Schmidt B, et al. Association Between Intermittent Hypoxemia or Bradycardia and Late Death or Disability in Extremely Preterm Infants. JAMA 2015;314:595-603.

34. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008;84:77-82.
35. Schaffer DB, Palmer EA, Plotsky DF, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology 1993;100:230-7.
36. Wheatley CM, Dickinson JL, Mackey DA, et al. Retinopathy of prematurity: recent advances in our understanding. Arch Dis Child Fetal Neonatal Ed 2002;87:F78-82.
37. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
38. Araz-Ersan B, Kir N, Akarcay K, et al. Epidemiological analysis of retinopathy of prematurity in a referral centre in Turkey. Br J Ophthalmol 2013;97:15-7.
39. Ying GS, Quinn GE, Wade KC, et al. Predictors for the development of referral-warranted retinopathy of prematurity in the telemedicine approaches to evaluating acute-phase retinopathy of prematurity (e-ROP) study. JAMA Ophthalmol 2015;133:304-11.
40. Park SH, Yum HR, Kim S, et al. Retinopathy of prematurity in Korean infants with birthweight greater than 1500 g. Br J Ophthalmol 2016;100:834-8.
41. Kim SJ, Port AD, Swan R, et al. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol 2018;63:618-37.
42. Movsas TZ, Spitzer AR, Gewolb IH. Postnatal corticosteroids and risk of retinopathy of prematurity. J AAPOS 2016;20:348-52.
43. Fabbri L, Klebermass-Schrehof K, Aguar M, et al. Five-country manikin study found that neonatologists preferred using the LISAcath rather than the Angiocath for less invasive surfactant administration. Acta Paediatr 2018;107:780-3.
44. Roberts CT, Halibullah I, Bhatia R, et al. Outcomes after Introduction of Minimally Invasive Surfactant Therapy in Two Australian Tertiary Neonatal Units. J Pediatr 2021;229:141-6.
45. Dargaville PA, Ali SKM, Jackson HD, et al. Impact of Minimally Invasive Surfactant Therapy in Preterm Infants at 29-32 Weeks Gestation. Neonatology 2018;113:7-14.
46. Beltempo M, Isayama T, Vento M, et al. Respiratory Management of Extremely Preterm Infants: An International Survey. Neonatology 2018;114:28-36.
47. Kurepa D, Perveen S, Lipener Y, et al. The use of less invasive surfactant administration (LISA) in the United States with review of the literature. J Perinatol 2019;39:426-32.

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