IJIMM, Volume 2, Issue 6, 2024 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Less Invasive Surfactant Administration, For Treatment of Respiratory Distress Syndrome in Preterm Newborns, Long-Term Outcomes and Future Directions

Rustamov Bakhtiyorjon Boboqulovich
Bukhara State Medical Institute, Subject Area: children's health, neonatology

Abstract: Surfactant replacement therapy (SRT) has long become the standard of care in the treatment of neonatal respiratory distress syndrome (RDS), significantly decreasing acute pulmonary morbidity and mortality in preterm infants. For decades, this beneficial replacement therapy has been administered via endotracheal tube. Despite significantly improving the outcome of RDS, however, the burden of bronchopulmonary dysplasia remains, in particular, in very immature preterm infants. Acknowledging the direct relationship between exposure to and duration of invasive mechanical ventilation and chronic lung disease, the latter has been gradually replaced by noninvasive ventilation strategies in neonatal RDS. This replacement is strongly related to the demand for similarly noninvasive modes of surfactant administration. Alternative techniques in spontaneously breathing infants have evolved, including less invasive techniques using thin catheters (less invasive surfactant administration and minimally invasive surfactant treatment) as well as nebulization of surfactant, although the latter is not ready for clinical application yet. In addition, given their therapeutic delivery to the lungs and subsequent alveolar distribution, surfactant preparations represent an attractive vehicle for pulmonary deposition of drugs in preterm infants. Further improvement of SRT and expansion of the field of application of lung surfactant may hold additional benefits, especially in the treatment of the most immature preterm infants.

Keywords: Surfactant, Respiratory distress syndrome, Less invasive surfactant administration, preterm newborns.

Introduction

Research for more than 3 decades has convincingly established surfactant replacement therapy (SRT) as highly effective treatment for newborn infants with respiratory distress syndrome (RDS). The lung physiology dynamically changes after SRT, historically performed via endotracheal tube in mechanically ventilated infants, with rapid improvements in pulmonary gas exchange, reduced work of breathing, and decreased risk of interstitial pulmonary edema, pneumothorax and mortality. In concert with further advances in perinatal medicine (e.g., use of antenatal steroids and prenatal transport of women at risk of preterm delivery to tertiary level care centers), SRT has particularly improved the survival of the smallest babies with gestational ages between 22 and 28 weeks. Correspondingly, SRT has changed the nature of RDS-associated long-term pulmonary morbidities such as bronchopulmonary dysplasia (BPD), while the incidence of BPD remains high, that is, up to 50% infants <29 weeks' gestation. Current approaches to prevent the lifetime burden of BPD are limited by its multifactorial etiology and the biological heterogeneity of affected infants. Translational studies reveal inflammation, apoptosis, disturbed alveolarization, airway remodeling, and angiogenesis as underlying, potentially malleable mechanisms of BPD development. Most of these pathophysiological pathways are associated with exposure to and duration of invasive mechanical ventilation (IMV), even for a brief period of time, as required for the INtubation-SURfactant-Extubation (INSURE) approach. To minimize the risk of ventilation-induced injury, the use of nasal continuous positive airway pressure (nCPAP) has become the favored strategy for early respiratory management of preterm infants. Efficient nCPAP is key to maintain the functional residual capacity of the immature lung; to promote the endogenous surfactant production, which typically takes place on the second or third day of life;

and to provide adequate and stable oxygen delivery to vital organs. However, a high proportion of extremely preterm infants initially stabilized on nCPAP still require IMV within the first 72 h of life. The notion that surfactant deficiency might be the crucial risk factor for CPAP failure has led researchers to investigate less invasive modes of surfactant administration to spontaneously breathing infants. Most extensively studied are thin catheter administration techniques, for example, less invasive surfactant administration (LISA) or minimally invasive surfactant treatment (MIST), which have been shown to be both feasible and effective in reducing need for IMV in several randomized controlled trials (RCT). While thin catheter techniques (referenced in this review as LISA) have gained popularity in neonatal intensive care units (NICUs) across the world, noninvasive surfactant nebulization techniques remain in the province of research. Recent studies on surfactant as a carrier of topical drugs, for example, anti-inflammatory compounds, hold promise for more specific therapeutic strategies of RDS and BPD based on individualized risk patterns of preterm infants. We will review the current evidence for the "miracles" of surfactant, their challenges, and future directions of research.

Less Invasive Surfactant Administration. The Scientific Concept of LISA

The physiological rationale of LISA, initially developed in Denmark in 1992, is to allow appropriate timing of surfactant treatment to spontaneously breathing infants with RDS without the need for intubation and ventilation. Animal research and pilot clinical trials determined the theoretical advantages of LISA compared to standard SRT, specifically: (i) avoidance of lung injury induced by positive pressure ventilation, (ii) reduction of intubation trauma by using small diameter catheters for bolus installation, (iii) preservation of physiological larynx and glottis function, and (iv) maintenance of spontaneous breathing with beneficial effects on progressive lung recruitment and aeration, pendelluft phenomenon resolution, and cerebral oxygenation.

Clinical Evidence for LISA Effectiveness

There is compelling evidence from RCTs and meta-analyses that LISA compared to standard SRT or INSURE reduces the need for IMV, particularly in the first 72 h after birth. Systematic reviews also suggest that LISA carries benefits for health-related outcomes, that is, reduction of BPD, mortality, and the composite outcome of BPD or death. Conflicting data exist on the reduction for intracerebral hemorrhage. Of note, the inclusion criteria of studies and their methodological quality are subject to bias, requiring further evidence by RCTs. In line with this, the first adequately powered RCT to study the effect of surfactant administration to spontaneously breathing infants on the composite outcome of mortality or BPD (OPTI-MIST trial, $n = 606$ infants) has recently finished recruitment.

Safety of LISA

In the hands of experienced users, LISA has proved to be a feasible, safe, and well-tolerated approach. Beyond surfactant reflux and repeated attempts to insert the catheter into the trachea, adverse side effects such as gagging, bradycardia, desaturations, apnea and decreases in regional cerebral oxygenation may occur in 5–40%. These events are most often related to direct laryngoscopy and usually manageable with a brief period of noninvasive positive pressure ventilation and slowing the rate of surfactant administration. Improvements in catheter devices, video laryngoscopy, and avoiding the use of Magill forceps can further reduce the risk of procedure-associated injuries. Training (e.g., manikin simulation scenarios) ahead of clinical implementation of LISA in the NICU is important for success and patient safety. NICU guidelines are essential as high-risk infants who would previously have been intubated are now being managed to support spontaneous breathing at a much earlier and more vulnerable stage than ever before. To enhance acceptance among healthcare professionals, LISA should not be considered as a single strategy but rather as part of a "less intensive support bundle," including delayed cord clamping, nCPAP for initial stabilization (even with high PEEP levels of ≥8 cm H_20), and caffeine administration to promote respiratory drive in the first hours of life. Evidence on the specific impact of each "bundle" component on LISA effectiveness is still limited.

Retrospective chart reviews suggest that LISA-treated infants benefit from having less exposure to discomforting procedures early in life (e.g., blood tests, chest X-rays, transfusions, and antibiotic

treatments). In this context, it will be of great value to determine whether the primary LISA approach reduces the rate of multiple re-intubations and ventilation episodes, particularly in the most vulnerable infants. In a large observational study of the German Neonatal Network (GNN) including 7,533 preterm infants ≤28 weeks of age, LISA was associated with decreased risk for short-term outcomes such as mortality, BPD, clinical sepsis, pneumonia, intracerebral hemorrhage grades II–IV, surgery for persistent ductus arteriosus, and retinopathy requiring treatment. The only potential adverse effect of LISA was a slight increase in focal intestinal perforation in a subset of infants born at 23–24 weeks. Whether "protective" or earlier intubation of extremely preterm infants with significant abdominal distension on CPAP reduces focal intestinal perforation requires further investigation. With regard to long-term outcome, no statistically significant differences in somatic or neurodevelopmental outcomes at 2 years were found between the LISA intervention group in the AMV (Avoidance of Mechanical Ventilation) trial and the control group that received CPAP, rescue intubation, and surfactant treatment if needed. Follow-up of the NINSAPP (Nonintubated Surfactant Application) trial also found no difference between LISA intervention and standard intubation infants at 2 years, apart from higher mental developmental index values for LISA in the subgroup of 25–26 weeks' gestation. Unpublished GNN data support the contention that the spontaneous breathing concept facilitated by nCPAP and LISA is of advantage for lung function of preterm children at early school age. Given the current evidence on effectiveness and safety of LISA, recent guidelines for SRT mention LISA as the preferred mode for surfactant delivery in preterm infants spontaneously breathing on CPAP. Different catheters/devices for LISA have been purpose-built and evaluated. However, beyond the urgent need for further data on long-term outcome on LISA, open questions remain (Table 1).

Table 1. LISA failure, open questions and future directions of research on LISA

Issue to be addressed	What is known? (study [ref.])	Future research (study [ref.])
LISA failure	Risk factor for failure – GA <28 weeks, highest $FiO_2 \geq 0.5$, absence of ACS, surfactant dose <200 mg/kg body weight of poractant alfa, CRP >10 mg/L, muscular fatigue, insufficient respiratory drive, or cardiovascular instability [41] Surfactant dosing – Optimum dose yet to be defined [10, 11, 43] Risk of inhomogeneous surfactant distribution – Inconsistent results of animal experiments [16, 17, 23] – Pilot clinical study in preterm infants with electrical impedance tomography: homogeneous distribution of surfactant after LISA	Determination of patient subgroups who benefit most from LISA Head-to-head studies comparing different surfactant doses for LISA – Ongoing trial: OPTI-SURF (dosing groups 100–130 mg/kg and 170–200 mg/kg) [92] Investigation of the role of inhomogeneous surfactant distribution in LISA failure
Analgesia and sedation	Clinical practice – High variability, observational studies: 15–30% of infants receive analgesia/sedation [20, 39, 42] Drugs – Fentanyl (0.5–1 µg/kg slow bolus infusion), morphine, ketamine, midazolam, thiopental, and propofol [39] Patient comfort – COMFORTneo scores↓ in neonates sedated, procedure less difficult to perform [40] Patient safety – Increased risk for desaturations and need for PPV; no international consensus on pretreatment [5, 8, 40, 42]	Studies with standardized protocols for pharmacological and non-pharmacological interventions including neurodevelopmental follow-up Ongoing trial: PROLISA – use of propofol vs. placebo for LISA (RCT) [48]
LISA as part of less invasive care bundle	Delayed cord clamping – Improved cardiopulmonary adaptation, mortality risk↓, physiological SaO_2 levels in early transition redefined [45, 46] nCPAP – No consensus on nCPAP levels, mostly 5–9 cm H_2O; use of different nCPAP devices and HFNC [20] Timing of LISA – No recommendation of prophylactic SRT [55, 56] Often quasi-prophylactic approach at GA <28 weeks [20, 37] CPAP-recruitment-LISA – Lung recruitment maneuver before surfactant improved effectiveness in INSURE approach [58] Timing of caffeine – Evidence for caffeine use in extremely preterm infants beyond the indications of the CAP trial is low [40, 44, 47] – Often early caffeine administration in the delivery room [20]	Standardized treatment thresholds for LISA (consensus) Ongoing trial: OPTTIMMAL study of predefined PEEP levels (RCT) [49] Investigations on prophylactic vs. selective SRT including long-term pulmonary outcome Planned trial starts recruitment in 2021 [57] Investigation of the role of recruitment maneuver in LISA Ongoing trial: CaLI RCT: early caffeine, CPAP, and LISA vs. caffeine and CPAP [50], endpoint: Avoiding mechanical ventilation at 72 h after birth
Benefit for moderate, late preterm, and term infants	Challenges – Infants are more vigorous with higher GA, risk of underdosing surfactant [33, 42, 43] – Compared with INSURE, benefits of LISA not yet determined (given a low risk of BPD) [20]	Definition of health-relevant endpoints for LISA vs. INSURE in moderate preterm and risk term newborns (ventilator-associated infections, lung function, and neurodevelopment)

ACS, antenatal corticosteroids; BPD, bronchopulmonary dysplasia; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; GA, gestational age; HFNC, high-flow nasal cannula; INSURE, intubate-surfactant-extubate mode of surfactant delivery; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; RCT, randomized controlled trial; SaO_2, oxygen saturation; SRT, surfactant replacement therapy.

Conclusions and Future Directions

LISA has become the preferred mode of surfactant delivery in preterm infants spontaneously breathing on CPAP, provided that neonatologists are experienced with this technique. Beyond the urgent need for further data on long-term outcome of LISA, there are open questions that should guide future research, in particular: (i) what are the predictive markers of "LISA failure"?, (ii) how to achieve a balance between patient comfort and support of spontaneous breathing, (iii) is there a comeback for prophylactic surfactant with LISA in the delivery room?, (iv) when to start caffeine, and (v) will late preterm infants or term infants benefit from LISA? With efficacy yet to be convincingly demonstrated, up to now nebulization is not ready for clinical use. Larger, adequately powered and well-designed trials are needed, in particular in very immature preterm infants at highest risk of lung injury. Issues to be addressed include the optimum dose and formulation of surfactant and technique of nebulization, positioning of devices in the ventilation circuit, optimum time of administration, lung recruitment strategies, and redosing. Current data indicate that addition of budesonide does not alter pulmonary distribution of surfactant, underlining the potential role of exogenous surfactant as an effective vehicle for targeted delivery of topical drugs, such as budesonide. In this context, new generation synthetic surfactants may represent an attractive substitute to natural surfactants in the future, with their composition being potentially optimized for homogeneous drug deposition.

References

1. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2012(3):CD000510.
2. Humberg A, Härtel C, Rausch TK, Stichtenoth G, Jung P, Wieg C, et al. Active perinatal care of preterm infants in the German Neonatal Network. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(2):190–5.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–51.
4. Hillman NH, Moss TJ, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR, et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med* . 2007;176(6):575–81.
5. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics* . 2010;125(6):e1402–9.
6. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700–8.
7. Finer NN, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970–9.
8. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics*. 2011;128(5):e1069–76.
9. Zhong J, Lui K, Schindler T. The effect of continuous positive airway pressure on cerebral and splanchnic oxygenation in preterm infants. *Neonatology*. 2019;116(4):363–8.
10. Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet*. 2011;378(9803):1627–34.
11. Kribs A, Roll C, Göpel W, Wieg C, Groneck P, Laux R, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr*. 2015;169(8):723–30.

12. Verder H, Agertoft L, Albertsen P, Christensen NC, Curstedt T, Ebbesen F, et al. [Surfactant treatment of newborn infants with respiratory distress syndrome primarily treated with nasal continuous positive air pressure. A pilot study]. *Ugeskr Laeg*. 1992;154(31):2136–9.

13. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2012;11:CD001456.

14. Dargaville PA. CPAP, surfactant, or both for the preterm infant: resolving the dilemma. *JAMA Pediatr*. 2015;169(8):715–7.

15. Banerjee S, Fernandez R, Fox GF, Goss KCW, Mactier H, Reynolds P, et al. Surfactant replacement therapy for respiratory distress syndrome in preterm infants: United Kingdom national consensus. *Pediatr Res*. 2019;86(1):12–4.

16. Niemarkt HJ, Kuypers E, Jellema R, Ophelders D, Hütten M, Nikiforou M, et al. Effects of less-invasive surfactant administration on oxygenation, pulmonary surfactant distribution, and lung compliance in spontaneously breathing preterm lambs. *Pediatr Res*. 2014;76(2):166–70.

17. Ricci F, Bresesti I, LaVerde PAM, Salomone F, Casiraghi C, Mersanne A, et al. Surfactant lung delivery with LISA and InSurE in adult rabbits with respiratory distress. *Pediatr Res*. 2021 Jan 15. [Online ahead of print].

18. Barkhuff WD, Soll RF. Novel surfactant administration techniques: will they change outcome? *Neonatology*. 2019;115(4):411–22.

19. Vento M, Bohlin K, Herting E, Roehr CC, Dargaville PA. Surfactant administration via thin catheter: a practical guide. *Neonatology*. 2019;116(3):211–26.

20. Herting E, Härtel C, Göpel W. Less invasive surfactant administration: best practices and unanswered questions. *Curr Opin Pediatr*. 2020;32(2):228–34.

21. Crawshaw JR, Kitchen MJ, Binder-Heschl C, Thio M, Wallace MJ, Kerr LT, et al. Laryngeal closure impedes non-invasive ventilation at birth. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(2):F112–9.

22. Bohlin K, Bouhafs RK, Jarstrand C, Curstedt T, Blennow M, Robertson B. 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.

23. van der Burg PS, de Jongh FH, Miedema M, Frerichs I, van Kaam AH. Effect of minimally invasive surfactant therapy on lung volume and ventilation in preterm infants. *J Pediatr* . 2016;170:67–72.