

The Miracles of Surfactant: Less Invasive Surfactant Administration, Nebulization, and Carrier of Topical Drugs

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Keywords

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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.

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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) [1]. 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 [2]. 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 [2, 3]. 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 [4, 5]. 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 [6–8]. 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 [9]. However, a high proportion of extremely preterm infants initially stabilized on nCPAP still require IMV within the first 72 h of life [6–8]. 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) [10, 11]. 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 [12], is to allow appropriate timing of surfactant treatment [13] to spontaneously breathing infants with RDS without the need for intubation and ventilation [14, 15]. 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 [16, 17], (ii) reduction of intubation trauma by using small diameter catheters for bolus installation [18–20], (iii) preservation of physiological larynx and glottis function [21], and (iv) maintenance of spontaneous breathing with beneficial effects on progressive lung recruitment and aeration [22, 23], pendelluft phenomenon resolution [24], and cerebral oxygenation [25].

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 [26–28]. Systematic reviews also suggest that LISA carries benefits for health-related outcomes, that is, reduction of BPD, mortality [28], and the composite outcome of BPD or death [27, 29]. Conflicting data exist on the reduction for intracerebral hemorrhage [28, 29]. Of note, the inclusion criteria of studies and their methodological quality are subject to bias, requiring further evidence by RCTs [30, 31]. 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 [32].

Safety of LISA

In the hands of experienced users, LISA has proved to be a feasible, safe, and well-tolerated approach [33, 34]. 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 [35–37]. Improvements in catheter devices, video laryngoscopy, and avoiding the use of Magill forceps can further reduce the risk of proce-

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	<p>Risk factor for failure</p> <ul style="list-style-type: none"> – 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] <p>Surfactant dosing</p> <ul style="list-style-type: none"> – Optimum dose yet to be defined [10, 11, 43] <p>Risk of inhomogeneous surfactant distribution</p> <ul style="list-style-type: none"> – Inconsistent results of animal experiments [16, 17, 23] – Pilot clinical study in preterm infants with electrical impedance tomography: homogeneous distribution of surfactant after LISA 	<p>Determination of patient subgroups who benefit most from LISA</p> <p>Head-to-head studies comparing different surfactant doses for LISA</p> <ul style="list-style-type: none"> – Ongoing trial: OPTI-SURF (dosing groups 100–130 mg/kg and 170–200 mg/kg) [92] <p>Investigation of the role of inhomogeneous surfactant distribution in LISA failure</p>
Analgesia and sedation	<p>Clinical practice</p> <ul style="list-style-type: none"> – High variability, observational studies: 15–30% of infants receive analgesia/sedation [20, 39, 42] <p>Drugs</p> <ul style="list-style-type: none"> – Fentanyl (0.5–1 $\mu\text{g}/\text{kg}$ slow bolus infusion), morphine, ketamine, midazolam, thiopental, and propofol [39] <p>Patient comfort</p> <ul style="list-style-type: none"> – COMFORTneo scores↓ in neonates sedated, procedure less difficult to perform [40] <p>Patient safety</p> <ul style="list-style-type: none"> – Increased risk for desaturations and need for PPV; no international consensus on pretreatment [5, 8, 40, 42] 	<p>Studies with standardized protocols for pharmacological and non-pharmacological interventions including neurodevelopmental follow-up</p> <p>Ongoing trial: PROLISA – use of propofol vs. placebo for LISA (RCT) [48]</p>
LISA as part of less invasive care bundle	<p>Delayed cord clamping</p> <ul style="list-style-type: none"> – Improved cardiopulmonary adaptation, mortality risk↓, physiological SaO_2 levels in early transition redefined [45, 46] <p>nCPAP</p> <ul style="list-style-type: none"> – No consensus on nCPAP levels, mostly 5–9 cm H_2O; use of different nCPAP devices and HFNC [20] <p>Timing of LISA</p> <ul style="list-style-type: none"> – No recommendation of prophylactic SRT [55, 56] – Often quasi-prophylactic approach at GA <28 weeks [20, 37] <p>CPAP-recruitment-LISA</p> <ul style="list-style-type: none"> – Lung recruitment maneuver before surfactant improved effectiveness in INSURE approach [58] <p>Timing of caffeine</p> <ul style="list-style-type: none"> – 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] 	<p>Standardized treatment thresholds for LISA (consensus)</p> <p>Ongoing trial: OPTTIMMAL study of predefined PEEP levels (RCT) [49]</p> <p>Investigations on prophylactic vs. selective SRT including long-term pulmonary outcome</p> <p>Planned trial starts recruitment in 2021 [57]</p> <p>Investigation of the role of recruitment maneuver in LISA</p> <p>Ongoing trial: CaLI RCT: early caffeine, CPAP, and LISA vs. caffeine and CPAP [50], endpoint: Avoiding mechanical ventilation at 72 h after birth</p>
Benefit for moderate, late preterm, and term infants	<p>Challenges</p> <ul style="list-style-type: none"> – 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] 	<p>Definition of health-relevant endpoints for LISA vs. INSURE in moderate preterm and risk term newborns (ventilator-associated infections, lung function, and neurodevelopment)</p>

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.

dures-associated injuries [19, 20]. Training (e.g., manikin simulation scenarios) ahead of clinical implementation of LISA in the NICU is important for success and patient safety [38]. 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 [39–42]. 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 H₂O), and caffeine administration to promote respiratory drive in the first hours of life [43–45]. Evidence on the specific impact of each “bundle” component on LISA effectiveness is still limited [46–48].

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) [49]. 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 [50]. 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 [10] and the control group that received CPAP, rescue intubation, and surfactant treatment if needed [51]. Follow-up of the NINSAPP (Nonintubated Surfactant Application) trial [11] 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 [52]. 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 [53, 54]. Different catheters/devices for LISA have been purpose-built and evaluated [19]. However, beyond the urgent need for further data on long-term outcome on LISA, open questions remain (Table 1) [46–48, 55, 56].

Nebulization of Surfactant

Constituting a truly noninvasive approach of surfactant administration, nebulization avoids any airway manipulation at all [57–60]. Moreover, data from animal models suggest improved distribution of surfactant and minor systemic and cerebral hemodynamic side effects [61, 62]. Almost 60 years have passed since Robillard et al. [63] reported on direct aerosolization of synthetic dipalmitoyl-phosphatidylcholine into the incubators of 11 preterm infants with RDS. This very first noncontrolled study found decreasing signs of RDS in 8 of these infants. Although early subsequent studies did not show beneficial effects of dipalmitoyl-phosphatidylcholine aerosol in neonatal RDS and discouraged surfactant aerosolization [64, 65], later studies in animal and in vitro models helped to develop efficient aerosol devices and establish adequate pulmonary deposition [66–68], which reawakened interest along with stepwise implementation of CPAP and noninvasive ventilation in neonatal practice.

Preclinical and Clinical Evidence for Aerosolized Surfactant

Animal studies of aerosolized surfactant in rabbit, piglet, and lamb models of RDS have shown inconsistent results, ranging from little or no effect of surfactant nebulization to pulmonary responses, similar to the effects of intratracheally administered surfactant [62, 63, 66, 67]. Clinical data are still scarce. In total, 3 pilot studies [58, 60, 69], a phase 1 clinical study [59] and a subsequent phase 2 clinical trial [70], and 4 RCTs have been published, comprising an overall number of 909 preterm infants (Table 2) [57, 59, 71, 72]. While all studies documented feasibility and safety, inconsistent results were found concerning efficacy. Improved oxygenation and superiority to nCPAP alone was found in only one [73] of the early studies. On the contrary, a first blinded RCT in 64 infants > 29 weeks’ gestation reported that treatment with nCPAP and nebulized surfactant reduced the requirement for intubation within 72 h from 69 to 34%

Table 2. Clinical studies of nebulization of surfactant in preterm infants with mild-to-moderate RDS

Study [ref.]	Design	Study cohort (GA, N age in h)	Patients	Surfactant/dosage/nebulizer/mode of NIV	Control	Results
Jorch et al. [69]	Nonrandomized multicenter pilot study	28–36 weeks, 1–7 h	20	Natural bovine surfactant (Alveofact [®]), 2 × 150 mg/kg, jet nebulizer, pharyngeal bubble CPAP	No	A-aO ₂ ↓ and PaCO ₂ ↓, improvement in Silverman score, most improvements after initial 150 mg/kg surfactant
Arroe et al. [70]	Nonrandomized pilot study	23–36 weeks, <72 h	22	Synthetic surfactant (Exosurf [®]), 108 or 216 or 432 mg phospholipids, jet nebulizer, nCPAP	No	No adverse effects, no improvement in clinical variables including A-aO ₂ , 8 patients required IMV within 2 h after intervention
Berggren et al. [57]	Unblinded RCT	27–34 weeks, <48 h	34	Natural porcine surfactant (Curosurf [®]), 480 mg, jet nebulizer, nCPAP	nCPAP alone	No adverse effects, no differences in the need for IMV/duration of CPAP, no differences in BPD, PDA, air leak
Finer et al. [58]	Feasibility and safety pilot study	28–32 weeks, <1 h	17	Synthetic surfactant (Aerosurf [®]), max. 72 mg, retreatment: group 1 at 3 h, group 2 at 1 h, vibrating membrane nebulizer, nCPAP	No	All infants survived; transient desaturations, no bradycardia, persistent RDS at 24 h: 23.5%; IMV to d28: 29.4%, BPD at d28: 11.8%
Minocchieri et al. [59]	Unblinded RCT	29–33 weeks, <6 h	64	Natural porcine surfactant (Curosurf [®]), 100 mg/kg, retreatment after 12 h, vibrating membrane nebulizer, bubble nCPAP	Bubble nCPAP alone	Need for IMV within 72 h: RR 0.53 (95% CI 0.292–0.950), but significant effects only at 32 ⁰ –33 ⁶ weeks, no differences in BPD, no major adverse effects
Sood et al. [60]	Unblinded phase 1 clinical study	24–36 weeks, ≤24 h	17	Modified bovine surfactant (Survanta [®]), 100 vs. 200 mg phospholipids, jet nebulizer, NIV	100 vs. 200 mg	No adverse effects, 2/17 infants required IMV within 2 h after intervention, 13/17 infants received 2 doses
Cummings et al. [72]	Unblinded multicenter study	24–36 weeks, <12 h	457	Natural calf surfactant (Calfactant [®]), 210 mg phospholipids/kg, jet nebulizer with modified pacifier interface, NIV	Standard care for RDS	Need for IMV within 96 h: RR 0.51 (95% CI 0.41–0.63), no differences in respiratory support d3, d7, and d28; no differences in other secondary outcomes
Sood et al. [71]	Randomized phase 2 clinical trial	24–36 weeks, ≤24 h	149	Modified bovine surfactant (Survanta [®]), 4 dosing schedules (100/200 mg, 2 dilutions), jet versus vibrating membrane nebulizer, NIV	No	Surfactant reflux, desaturation no differences between dosing schedules, ns, no serious adverse events, 15/149 infants required IMV within 2 h after intervention
Bianco et al. [73]	Unblinded multicenter RCT	28–32 weeks	129	Natural porcine surfactant (Curosurf [®]), 200 mg/kg vs. 400 mg/kg phospholipids, vibrating membrane nebulizer, nCPAP	nCPAP alone	No safety concerns, no reduction in likelihood of respiratory failure within first 72 h, trial stopped was early for limited effect of the intervention

A-aO₂, alveolar-arterial gradient; BPD, bronchopulmonary dysplasia; IMV, invasive mechanical ventilation; nCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; PaCO₂, partial pressure of carbon dioxide; PDA, patent ductus arteriosus; RCT, randomized controlled trial.

compared to nCPAP alone [59]. Recently, Cummings et al. [71] published the largest RCT to date, comparing nebulization to intubation and subsequent surfactant in 457 neonates with RDS. This multicenter trial confirmed feasibility and safety of the intervention in infants on CPAP, high-flow nasal cannula, and noninvasive ventilation using a modified nebulizer with pacifier interface [71]. A reduction in need for intubation and intratracheal surfactant from about 50% to about 25% was reported, with a number needed to treat of 5 [71]. However, lack of blinding and missing definitions of treatment failure implicated a high risk of bias [74]. Of note, in both RCTs, benefit of nebulization was limited to moderately preterm infants born beyond 31 weeks' gestation [59, 71]. A phase 2 clinical trial including 149 preterm infants with RDS recently reported feasibility of 4 dosing schedules of aerosolized surfactant, absence of serious adverse events, and reduced need for intubation within 72 h [70]. Given that aerosol groups were compared to historical controls, however, conclusion about efficacy is limited [70]. Very recently, a multicenter RCT in 129 infants with mild-to-moderate RDS compared nCPAP with 2 different dosing regimens of nebulized surfactant with nCPAP alone [72]. The authors found no reduction in the likelihood of respiratory failure within the first 72 h of life, and the trial was stopped early due to limited effect of the intervention [72]. It is of interest that the same study group had demonstrated efficacy of aerosolized surfactant in preclinical settings before [68].

Factors Determining Pulmonary Delivery and Efficacy

Difficulties in pulmonary deposition and distribution of aerosolized surfactant arise from particle size, dose, and stability of formulation during nebulization, nebulizer-dependent recovery rates, and loss of surfactant to the device, oropharynx, esophagus, and exhaled air [75]. Different types of nebulizers have been tested [70, 75]. While jet nebulizers often result in pulmonary deposition of <1–5% of aerosols, evolution of vibrating membrane nebulizers has improved aerosolization with deposition rates of ≥20% reported in animal and in vitro models, and pulmonary responses potentially similar to intratracheal surfactant in terms of oxygenation and lung mechanics [67, 68].

Aerosolization of Synthetic Surfactant Preparations

Few synthetic surfactants have been subject to nebulization in animal and in vitro models [76, 77]. Synthetic formulations differ from natural surfactants with standardized and potentially optimized composition, production of higher quantities, and increased resistance

against inactivation [78]. The feasibility of nebulization of synthetic surfactant has been confirmed in rabbit and lamb models of RDS [76, 77]. However, intervention was not superior to nCPAP, most likely due to limited pulmonary aerosol delivery [76]. Subsequent studies of high-concentration powder aerosolization aim to generate concentrated surfactant aerosols [77, 79]. Aerosolized synthetic surfactants have not been subjected to clinical trials apart from 2 pilot studies conducted 10 and more than 20 years ago, respectively, testing a peptide- and a non-peptide-containing synthetic surfactant in 39 infants in total [58, 69]. Although the administration was shown to be feasible and safe, due to lack of control groups, conclusions regarding the efficacy cannot be drawn.

Surfactant as a Vehicle for Topical Drugs

Thirty years ago, animal experimental data showed for the first time that pulmonary surfactant, due to the unique spreading properties, could act as a vehicle for intratracheal delivery of the topical drug pentamidine [80]. Subsequent in vitro experiments and animal studies provided further evidence for a tentative role of pulmonary surfactant as carrier for antimicrobial agents with the aim of treating mainly adult patients with severe pneumonia [81, 82]; however, this fascinating idea has not been pursued in humans.

In the mid-1990s, it became evident that in a considerable number of very immature preterm infants, RDS was not only caused by a primary surfactant deficiency but also complicated by a complex and multifactorial pathogenesis of an injurious inflammatory sequence in the airways and lung tissue with the consequent increased risk of BPD [83, 84]. Fetal exposure to chorioamnionitis has been convincingly shown to initiate an inflammatory reaction in the immature lung, which can be aggravated by postnatal insults such as traumatic stabilization techniques, oxygen toxicity, initiation of mechanical ventilation, pulmonary and systemic infections, and others factors [85, 86]. Systemic corticosteroids downregulated airway and tissue inflammation and improved pulmonary outcome [87, 88]; however, with early postnatal steroids, the rate of adverse neurodevelopmental outcome is increased, and this strategy is no longer indicated [88].

Clinical Evidence for a Potential Role of Pulmonary Surfactant as a Carrier of Topical Drugs

Use of natural surfactant as a vehicle for the topical anti-inflammatory drug budesonide in preterm infants

with RDS was first reported by Yeh et al. [89]. The combination of early postnatal intratracheal instillation of budesonide and surfactant improved the combined outcome of death and BPD in a small pilot trial [88] and similarly pulmonary long-term outcome without causing adverse effects [90]. In a subsequent RCT in 3 centers that included 265 VLBW infants with severe RDS, intratracheal administration of budesonide with surfactant significantly decreased the incidence of BPD or death compared with surfactant alone (42 vs. 66%, $p < 0.001$) [91]. After the intervention, concentrations of pro-inflammatory cytokines in tracheal aspirate fluid were much lower in the budesonide/surfactant group.

Since this study included only infants with severe RDS, there are several open questions that need to be addressed in future trials: how does the administration of budesonide/surfactant affect pulmonary and long-term outcome of very immature infants with mild RDS and those preterm infants with fetal exposure to chorioamnionitis? Will the surfactant administration technique such as less invasive strategies, the timing and duration of surfactant instillation or the dose of exogenous surfactant, for example, OPTI-SURF study [92], interfere with the anti-inflammatory effects of budesonide? Most importantly, these results need to be confirmed in a large, properly powered RCT. The results of the OPTIMIST trial are eagerly awaited and will be presented within the year 2021 [32].

A recently published observational cohort comparison reported that budesonide/surfactant did not change the overall incidence of BPD or death but reduced the severity of BPD and facilitated an earlier extubation [93]. Similarly, in a small dose-escalating trial of budesonide with surfactant, respiratory outcome of extremely low gestational age infants did not differ from historical controls. Interestingly, budesonide was detected in the blood of all infants with a half-life of 3.44 h, and tracheal aspirate fluid cytokine levels decreased in those babies with elevated concentrations prior to treatment [94].

Biophysical and Chemical Stability

Biophysical and chemical stability of surfactant/budesonide has been evaluated in a number of experimental studies confirming pulmonary and systemic anti-inflammatory effects of this strategy in adult rabbits [95], mechanically ventilated preterm lambs [96], and rats [97]. In preterm neonatal rabbits, the combined administration attenuated hyperoxia-induced lung injury [98]. Moreover, pulmonary distribution of 2 natural surfactant preparations was recently tested, and both were shown to be effective vehicles for budesonide delivery [99].

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.

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Conflict of Interest Statement

C.H. has received honoraria for presentations and travel support from Chiesi Farmaceutici, a surfactant producer. C.H. served as advisor for Draeger Medical, a company producing incubators, monitors, and ventilators. C.P.S. has a consultancy agreement with Chiesi Farmaceutici S.p.A. (Parma, Italy). Both University Hospitals in Würzburg and Leipzig are participants in the German Neonatal Network.

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Author Contributions

C.H., K.G., and C.P.S. equally contributed to the manuscript, being responsible for conception, design, drafting, and writing of this manuscript.

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