Less-invasive surfactant administration for neonatal respiratory distress syndrome: a consensus guideline

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Abstract
Introduction: Less-invasive surfactant administration (LISA) is a method of surfactant delivery to preterm infants for treating respiratory distress syndrome (RDS), which can reduce the composite risk of death or bronchopulmonary dysplasia and the time on mechanical ventilation.

Methods: A systematic literature search of studies published up to April 2021 on minimally invasive catheter surfactant delivery in preterm infants with RDS was conducted. Based on these studies, with parental feedback sought via an online questionnaire, 9 UK-based specialists in neonatal respiratory disease developed their consensus for implementing LISA. Recommendations were developed following a modified, iterative Delphi process using a questionnaire employing a 9-point Likert scale and an a priori level of agreement/disagreement.

Results: Successful implementation of LISA can be achieved by training the multidisciplinary team and following locally agreed guidance. From the time of the decision to administer surfactant, LISA should take <30 min. The comfort of the baby and requirements to maintain non-invasive respiratory support are important. While many infants can be managed without requiring additional sedation/analgesia, fentanyl along with atropine may be considered. Parents should be provided with sufficient information about medication side effects and involved in treatment discussions.

Conclusion: LISA has the potential to improve outcomes for preterm infants with RDS and can be introduced as a safe and effective part of UK-based neonatal care with appropriate training.

Introduction

Respiratory distress syndrome (RDS) can affect infants of all gestational ages. It is most common in preterm infants, affecting nearly all infants born at or <28 weeks of gestation [1, 2]. Exogenous surfactant administered after intubation through the endotracheal tube and followed by mechanical ventilation (MV) has been the established, evidence-based cornerstone of RDS treatment for decades [3, 4].

MV is a major risk factor for bronchopulmonary dysplasia (BPD), and variations in surfactant application methods have been developed to minimize MV, including Intubation SURfactant Extubation (INSURE) and less-invasive surfactant administration (LISA), also referred to as minimally invasive surfactant therapy [5–10]. With LISA, the surfactant is instilled directly into the trachea via a thin/small bore catheter whilst the baby continues to receive non-invasive respiratory support [8, 9, 11]. A meta-analysis of trials comparing LISA with other methods of surfactant delivery indicated that LISA reduces the need for MV at any time during neonatal intensive care and reduces the composite risk of death or BPD without increasing the risk of pneumothorax, even in extremely preterm infants [12]. Smaller subsequent studies have also shown improved outcomes [13, 14]. A recent systematic review of randomized controlled trials (RCTs) identified that LISA resulted in significantly reduced early intubation rates and BPD compared with INSURE [15]. A recent 2-year follow-up demonstrated that premature infants treated with LISA demonstrated no significant differences in weight, length, or neurodevelopmental outcome compared with infants who received standard treatment [16]. LISA is a standard of care in many European neonatal units [17–19] with good safety [16]; in the United Kingdom, the uptake of LISA is still gaining momentum [20, 21].

Recent evidence-based consensus guidelines on the use of surfactant for RDS [4, 22] recommend LISA for breathing infants with RDS. This manuscript aims to provide practical guidance to UK neonatal teams who are considering or are in the process of implementing LISA. Our recommendations are based upon
available evidence, consensus view, and a survey of parental opinion/values.

Materials and Methods

Literature Search

A systematic literature search to identify studies that investigated the use of minimally invasive techniques to deliver surfactant via a catheter that were published up to 28 April 2021 was performed on PubMed and Google Scholar databases. Combinations of Medical Subject Headings (MeSH) and non-MeSH keywords used in the search are listed in Table 1. A PRISMA flow diagram detailing how relevant articles were selected is provided in online suppl. File 1. Only human studies in English language were included, but study type was unrestricted. Duplicates were removed based on the title and abstract. One investigator screened abstracts for eligibility before dissemination to the panel. References were manually cross-referenced for duplicates or initially unidentified records and potentially eligible publications reviewed.

Panel Selection

Nine UK specialists in neonatal care were selected based on their previous clinical and scientific experience on the use of minimally invasive surfactant administration techniques in the management of RDS.

Development of Consensus

A modified, iterative Delphi approach was used to develop this consensus [23]. In the first round, the group discussed the identified published evidence on LISA (online suppl. File 1) and agreed the following key areas for a guideline: background and evidence, patient selection, equipment, developing local practice (training and audit and personnel), performing LISA (preparing the baby and performing the procedure), and parental experience. In the second round, a 113-question questionnaire was developed based on the key areas (online suppl. File 2). Preference hierarchy was established by a 9-point Likert scale, and an a priori level of agreement/disagreement was applied (online suppl. File 3). In the final third round, statements and key areas were clarified (online suppl. File 4).

Parental experience and opinion were sought using an online questionnaire posted to all followers on the Facebook site of Bliss (UK Registered Charity 1002973 Fourth Floor, Maya House, 134–138 Borough High Street, London SE1 1LB; www.bliss.org.uk) from 26 to 27 June 2019 (online suppl. File 5). All responses from parents whose premature babies required ventilation support formed the target sample and were assessed. The questionnaire was developed by the Chiesi Medical Team with the aim to understand parents’ views on the decision-making process in neonatal units and their involvement in medical care and choice of medication. While the questionnaire was not developed specifically for RDS and LISA use, it allowed compiling information about parents’ opinions on the decision-making process. This process was supported by an unconditional grant from Chiesi UK Limited. The authors maintained full control over all content.

Results

In the literature search, 168 records were screened based on the title and/or abstract, of which 66 were excluded as they did not meet the inclusion criteria. Full texts of the remaining 102 records were evaluated, of which 53 were included in the evidence base for consideration by the group. Consensus was reached for all 113 questions at the conclusion of the modified Delphi process.

Table 1. Search terms used for searches

<table>
<thead>
<tr>
<th>Keyword 1</th>
<th>Keyword 2</th>
<th>Keyword 3</th>
<th>PubMed results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive surfactant</td>
<td>Preterm infants</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>Less invasive surfactant</td>
<td>Preterm infants</td>
<td>–</td>
<td>79</td>
</tr>
<tr>
<td>Pulmonary surfactant</td>
<td>Preterm infants</td>
<td>Catheter</td>
<td>56</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>Spontaneous breathing</td>
<td>Pulmonary surfactant</td>
<td>55</td>
</tr>
</tbody>
</table>

MeSH keywords: catheter; preterm infants; pulmonary surfactant; respiratory distress syndrome.
**Recommendations**

This manuscript describes our recommendations for implementing LISA in the management of RDS based on evidence, consensus, and parental survey. Training and an agreed local guideline are key elements for successful introduction.

**Patient Selection**

If a baby is stable on non-invasive respiratory support but requires surfactant in line with published guidelines [4, 22], the success of the LISA procedure will depend on the experience of the team and the baby’s tolerance of handling. While non-invasive ventilation may fail in infants of <1 kg weight or <26 weeks gestational age, the outcomes vary individually. There is therefore no lower/upper gestational limit for consideration of LISA, and clinician expertise will improve over time.

It is not always necessary to obtain a chest X-ray or chest ultrasound scan to confirm eligibility for LISA; however, clinicians should consider the risk of other pathology (e.g., pneumothorax). For babies >32 weeks, we recommend that imaging should be performed to confirm RDS, as surfactant deficiency is less common in infants older than 32 weeks. Whilst LISA would most often occur in the neonatal unit, it can be performed in the delivery room. The dose of surfactant by LISA is the same as that given by INSURE or in ventilated patients, and repeat doses may be given by LISA. A failed LISA attempt can be followed by another; a maximum of 2 attempts at LISA are recommended for giving a dose of surfactant. The consensus view was that there should not be an absolute upper threshold of the fraction of inspired oxygen (FiO2) for LISA, although clinical instability, frequent apnoea, or other clinical indicators of imminent requirement for intubation and ventilation would be relative contraindications to LISA.

**Equipment**

Use of different catheters are described for LISA, such as a nasogastric tube with the use of Magill forceps or use of a vascular catheter such as AngiocathTM (Becton Dickinson, Sandy, UT, USA). However, we recommend that catheters designed for the purpose of LISA should be used.

A laryngoscope should be used to visualize the vocal cords, and a video-laryngoscope was felt to be particularly useful. Whilst LISA may be perceived as being less technically difficult than intubation, confirming correct catheter placement requires confidence in the operator’s capability to recognize appropriate placement, and video-laryngoscopy enhances that.

**Developing Local Practice**

**Training and Audit**

We recommend neonatal team members should receive training and meet agreed competencies to facilitate safe and successful execution of LISA. Endotracheal intubation and LISA are different procedures both in terms of required training and purpose. Neonatal team members competent in endotracheal intubation can learn LISA and agreed competencies through specific training, for example, through simulation followed by supervised practice; the use of video-laryngoscopy is helpful. It may be useful to ask experienced clinical teams in other neonatal units to provide local training and development or to visit units where LISA is an established procedure.

We recommend that audit of local guidelines (such as time from decision to administer surfactant to completion of the procedure) should be performed to evaluate compliance, competence, effectiveness, and complications, and that tools such as the Learn-See-Practice-Prove-Do-Maintain training approach should be used for developing competency in LISA [24]. Mannequin training for LISA has been shown to be useful in evaluation of the preferred technique [25].

**Personnel**

The active assistance of a member of the neonatal team, ideally a nurse, is essential for successful LISA. Nursing staff may require specific training for assisting with the LISA procedure and should be involved in the development and agreement of local clinical guidelines. There should be a checklist for babies undergoing LISA, an example of which is presented in online suppl. File 6. We also recommend following the
Performing LISA
Preparing the Baby
All babies should be assessed for comfort, and although LISA is normally a brief procedure, good thermal management during LISA is important; hypothermia may affect the outcome of the procedure [4]. A naso/orogastric tube should be placed prior to commencing the LISA procedure. Given that LISA is not an emergency procedure, the requirement for additional medications can be reconsidered as part of the overall procedure. While babies undergoing LISA in a neonatal intensive care unit (NICU) would normally have intravenous (IV) access secured, it is not necessary to routinely use IV medications for this procedure. Rather, babies should be assessed individually, as their age, maturity, and responsiveness will determine the need for medications and route of administration. The experience of the practitioner is also an important factor [26].

Non-Pharmacological Comfort
We recommend that babies should be swaddled to alleviate pain and improve comfort [27], and oral/buccal sucrose and/or breast milk should be considered for analgesia [28–30]. Our experience is that most babies can be satisfactorily managed with these non-pharmacological options.

Caffeine
Most preterm babies <30 weeks gestation undergoing LISA will have received IV caffeine citrate, which is recommended to maintain non-invasive respiratory support [4]. The decision for LISA should not be delayed by the need to administer caffeine.

Atropine
The use of atropine to prevent vagally induced bradycardia is not routinely recommended. Whilst lower incidence of bradycardia has been reported [31], a single IV dose of 10 µg/kg atropine can be administered if a baby has a bradycardia, which is deemed by the team to be clinically significant.

Sedation/Analgesia
There is no single medication that can be recommended as being preferred if sedation/analgesia is required, but fentanyl and propofol are often used. Sedation should particularly be considered in babies >32 weeks, but the need for sedation should be considered in all babies. Fentanyl, an analgesic, was used (at a dose of 1 µg/kg) in 1 small RCT of LISA and was generally well tolerated [32]. Propofol (1 mg/kg) has been shown to improve comfort compared with no premedication in 2 small studies (1 observational and 1 RCT) [33, 34], but concerns regarding associated transient arterial hypotension and need for non-invasive positive-pressure ventilation, together with potential for neurotoxicity following extend- ed exposure to high doses, exist [35, 36]. For these reasons, we preferred fentanyl (0.7 µg/kg) if pharmacological sedation/analgesia is required. In our experience, this fentanyl dose can achieve light sedation while preserving respiratory drive. Fentanyl should be instilled slowly to avoid interference with breathing. No dosing for propofol was recommended. Ketamine and midazolam were not recommended. If sedation/analgesia is being administered, the recommendation is to refrain from drawing up additional intubation drugs.

Naloxone
Some units may routinely prepare naloxone if bolus IV opiates are being used for premedication. However, naloxone should not be routinely given after LISA in an attempt to ensure adequate respiration. It is unlikely that any short-term discomfort encountered during LISA will result in long-term developmental harm, but the side effects of sedative/analgesic drugs, particularly respiratory depression [37], should always be considered.

Performing the Procedure
The time from the decision to administer surfactant to performing LISA should ideally be <30 min, with timely intervention requiring effective communication between the medical and nursing teams. The plan to administer surfactant should be discussed with the parents soon after NICU admission, to give them enough
time to make an informed decision. Prior to instillation, surfactant should be removed from the refrigerator and allowed to warm in ambient room temperature. As a minimum, all babies should be monitored continuously for pulse rate and oxygen saturations (SpO2). It is good practice to introduce a “time out” prior to the commencement of the LISA procedure, which should form a part of the LISA procedure checklist (online suppl. File 6).

Non-invasive respiratory support should continue throughout the procedure. The catheter should be passed 1.5–2 cm below the vocal cords under direct laryngoscopy, after which the laryngoscope is removed. Connecting an IV cannula extension to the catheter before placing it may be useful to reduce risk of subsequent dislodgement. Some users find a neck roll useful. Surfactant should be very slowly administered over 2–5 min (our recommended rate: 0.5–1.0 mL/min) to minimize reflux and episodes of hypoxia-bradycardia. Oxygen requirements usually fall quickly after LISA and may continue to fall for a few hours afterwards.

**Parental Experience**

Parent opinions were collected via random sampling using an online questionnaire posted on the Bliss Charity Facebook page. Overall, 54 parents provided answers to questions about their experiences of the care their babies received while staying in an NICU; most babies (38%) were born with <28 gestational weeks and 51% were diagnosed with RDS.

When considering a short but potentially uncomfortable medical procedure, where there is an option to use pain-relieving medications that have potential side effects, 43% of parents felt the success of the procedure was the most important, while for 35% making their baby comfortable while accepting a risk of side effects was most important. Interestingly, 35% agreed (and 4% strongly agreed) that they would rather not use any medication that made their babies more comfortable even if that meant that a short and potentially uncomfortable procedure might be less likely to be successful. Overall, 86% of parents trusted the doctors with decision-making regarding best medication choices for their babies. These results suggest that appropriate information needs to be provided for the parents, alongside a sufficient explanation of risk, to ensure that parents are making informed decisions, following the British Association of Perinatal Medicine shared decision-making framework [38].

**Implications for Research**

Several of the recommendations in this guideline are based on the authors’ experience, and further research would be valuable. The choice of a thin/small bore catheter, the speed at which the surfactant is administered, the timings of the doses, and the use of sedation/analgesia are all areas where further evidence would strengthen the recommendations.

**Conclusion**

LISA is an evidence-based strategy that augments non-invasive respiratory support for RDS in preterm infants. Clinicians aiming to introduce LISA to a neonatal unit are advised to have a bespoke guideline for when and how to perform LISA. There needs to be a focus on staff training with clear demonstration of LISA competency; the recommendations in this manuscript may be used for staff training and skill retention. Parents are often concerned about the potential side effects of medications and should be involved in treatment discussions. It is our view that LISA can be implemented safely and effectively and that, with increasing experience, any eligible baby can be treated for RDS by LISA.

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**Statement of Ethics**
The study is exempt from ethics committee approval. This study is a consensus guideline prepared by the authors based on their experience and interpretation of published literature and did not involve research of human subjects.

Conflict of Interest Statement

P.R. has previously received honoraria and travel support from Chiesi, Vapotherm, Inspiration Healthcare, and Fisher and Paykel.
P.B. has received honoraria from Chiesi for lectures and meetings.
C.D. has received honoraria from Chiesi for educational session.
J.R.F.A. has received honoraria and travel support from Chiesi.
G.F. has received honoraria from Chiesi for educational sessions.
S.J. has nothing to disclose. S.J.R. has received honoraria and travel support from Chiesi. V.V. has received honoraria and travel support from Chiesi. C.C.R. has received honoraria from Chiesi, Abbott Pharmaceuticals, Fisher & Paykel Healthcare, and Inspiration Healthcare for lectures and educational session.

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Author Contributions

All authors made equal contributions to the development of the statements, preparation and critical revision of the manuscript, and provided final approval of the version published. All authors agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online suppl. files. Further enquiries can be directed to the corresponding author.

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