

# Implementing and improving less invasive surfactant administration (LISA)

LISA (less invasive surfactant administration) describes the administration of surfactant directly into the trachea via a fine tube or catheter. Evidence suggests that this procedure leads to better outcomes than the more widely practised INSURE technique. To enable widespread adoption, LISA needs to be straightforward and effective for the clinician and infant. This article describes how practice has evolved at St Peter's Hospital over the last three years. Using audit and continuous improvement, four key determinants have been identified that have improved the training, acceptability and success of LISA.

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Respiratory distress syndrome (RDS) is common in preterm infants, with up to two-thirds born before 33 weeks' gestation requiring surfactant therapy.<sup>1</sup> Exogenous surfactant administration reduces work of breathing and improves oxygenation in the short-term while in the long-term it reduces the risk of death and bronchopulmonary dysplasia (BPD).<sup>2</sup> The most common mode of rescue surfactant delivery is still via endotracheal intubation using the INSURE (also known as 'in and out') technique.<sup>3</sup> After surfactant is delivered the infant is extubated and recommenced on their non-invasive respiratory support. However intubation/ventilation carries potential risks, including airway trauma from direct instrumentation and ventilation-induced lung injury from over-distension of the fragile preterm infant's lungs with intermittent positive pressure ventilation (IPPV). The use of pre-intubation anaesthetic drugs may also lead to prolongation of ventilation until the baby starts breathing again.

To minimise these risks, increasing numbers of neonatologists will consider performing the less invasive surfactant administration (LISA) technique to administer rescue surfactant, using a fine flexible catheter or a semi-rigid catheter passed under direct vision into the upper trachea (MIST; minimally invasive surfactant therapy). There is no evidence yet that one technique is superior to the other, so minimisation of discomfort to the baby and procedural success are the key determinants at present.

## Evidence of effectiveness of LISA

Two recent meta-analyses<sup>4,5</sup> involving six randomised controlled trials comparing LISA (n=447) against standard INSURE surfactant delivery controls (n=405) have shown LISA to reduce the risk of death or BPD at 36 weeks by 25% (relative risk 0.75; 95% CI 0.59-0.94; p=0.01), and reduce the risk for needing mechanical ventilation within 72 hours of birth by 29% (relative risk 0.71; 95% CI 0.53-0.96; p=0.02). In addition, the duration of non-invasive ventilation in the form of continuous positive airway pressure therapy (CPAP) was less in the LISA group (mean difference -28 hours; p=0.01). 'Trends' towards fewer pneumothoraces and pulmonary haemorrhages were noted but did not reach statistical significance. No significant reductions were noted in other morbidities such as patent ductus arteriosus requiring medical or surgical therapy, necrotising enterocolitis ≥stage 2, retinopathy of prematurity >stage 2, intraventricular haemorrhage >stage 2 or periventricular leukomalacia. The National Institute for Health and Care Excellence (NICE) is currently developing the guideline *Specialist Neonatal Respiratory Care for Babies Born Preterm* due for publication in April 2019, which will include LISA.

## How easy is it?

The outcome of procedural failure was not different between the LISA and INSURE groups (relative risk 0.97, p=0.91).<sup>4</sup> Since introducing LISA to the neonatal intensive

## Keywords

LISA; surfactant; respiratory distress syndrome; INSURE; non-invasive

## Key points

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1. In spontaneously breathing babies, LISA offers improved outcomes compared to INSURE.
2. Recent evidence suggests that, in the smallest babies, surfactant should be given at lower thresholds of oxygen.
3. The implementation of LISA requires guidance, supervision and training.
4. The use of 'awake' sedation has improved the success and acceptability of the procedure.

care unit at St Peter's Hospital in 2013, we have aimed to improve the quality of the procedure with a survey and ongoing audit focussed on:

- effectiveness – was the procedure successful and did the RDS improve?
- experience – was the baby comfortable? What are staff views?
- safety – were there adverse events such as hypothermia, cardiovascular instability, equipment issues etc?

## Practical insights

At St Peter's Hospital we have a long-standing and successful culture of using nasal high flow (nHF) (Vapotherm) for the non-invasive management of respiratory distress in all gestations, and we pioneered the use of high flow for stabilisation of the preterm infant in the delivery room. LISA is a natural extension to our ethos of allowing babies to keep breathing spontaneously. We have performed the LISA procedure since 2013 and have collected routine audit data to look at the factors that determine a successful procedure and/or outcome for the baby. We have used the audit findings to improve the quality of the procedure. Our staff survey in 2014 showed that 80% of staff believed LISA should be the 'norm', but also showed that the majority believed the procedure needed improvement.

The audit data (TABLE 1) shows that over 85% of LISA procedures were successfully carried out. The majority were performed by registrar grade doctors. Episodes of bradycardia occurred in about 35% of cases but were brief. The FiO<sub>2</sub> fell quickly in over 90% of successful procedures.

In our experience, the main technical determinants of success are:

1. correct timing of LISA
2. pre-procedure preparation
3. use of 'awake' sedation
4. training and supervision.

## Timing of LISA

The latest European consensus guidelines suggest that babies with RDS should be treated with rescue surfactant if their FiO<sub>2</sub> is more than 30% in babies <26 weeks' gestation, or more than 40% if >26 weeks' gestation.<sup>6</sup> However, we increasingly consider the 30% FiO<sub>2</sub> threshold for babies <28 weeks' gestation, based on further work showing increasing complications in babies with untreated RDS.<sup>7</sup> Once the FiO<sub>2</sub> is above 30%, especially if there is evidence of increased work of breathing or a

Completed audit forms	32
Mean gestational age	29 <sup>+6</sup> (range 25 <sup>+1</sup> -37 <sup>+0</sup> )
Ventilation mode	100% on nasal high flow
Mean FiO <sub>2</sub> prior to LISA	0.45 (range 0.32-1.0)
Mean FiO <sub>2</sub> 60 mins post-LISA	0.28 (range 0.21-0.5)
Operator	25 junior doctors, 9 senior doctors (ST2-consultant)
Slow FiO <sub>2</sub> fall post-LISA	No = 9 %, yes = 91%
Bradycardia <80 beats/min	No = 66%, yes = 34%
LISA 'successful'	No = 13%, yes = 87%

TABLE 1 The LISA audit data.



FIGURE 1 Preparation for LISA: Magill forceps, a surfactant administration kit and sterile, appropriately sized, laryngoscope blade on a sterile paper towel surface.

sustained or rapid rise in FiO<sub>2</sub> requirements, LISA should be initiated, particularly in the smallest babies. We aim to administer approximately 200mg/kg of Curosurf surfactant, prescribed to the nearest vial, which is our standard practice.

## Pre-procedure preparation

Pre-procedure preparation is similar to steps taken for elective intubation, ie we ensure a naso- or orogastric tube is in place (we use the latter for small babies on nHF) and the stomach has been aspirated. Safety checks include intra-venous access, cardiorespiratory monitoring and available IPPV equipment attached to supplemental oxygen. All drugs are clearly labelled and drawn up before the procedure. We take adequate proactive measures to keep the infant warm, such as the use of heating pads and/or warm towels. Equipment and drugs for intubation should be ready in case they are needed in the event of an unsuccessful procedure or cardiorespiratory deterioration. Non-invasive respiratory support (nHF or CPAP) is not interrupted during the procedure. The surfactant vial is warmed

by hand. Required equipment includes Magill forceps, a surfactant administration kit and a sterile, appropriately sized, laryngoscope blade (FIGURE 1).

## Use of sedation

When we started performing LISA we did not use sedation but we found that, especially for less experienced intubators, the procedure was more difficult for all involved and sometimes distinctly 'invasive'. It is known that successful intubation is facilitated by sedation<sup>8</sup> and a recent study showed falls in cerebral regional oxygenation – greater during LISA compared to INSURE – without sedation or analgesia in either.<sup>9</sup> Only 20% of staff in our survey felt the procedure was 'very comfortable' without sedation and a third thought it was either 'fairly' or 'very uncomfortable' for the baby. Therefore our practice for LISA has adapted to give 'awake' sedation.

We give a small dose of intravenous fentanyl (0.67µg/kg) and wait for five minutes for it to take full effect. A further dose is drawn up in case further sedation is required, which seems to be more common in larger babies. Standard intubation dose atropine (15µg/kg) is given intravenously immediately pre-procedure and suxamethonium is prepared in case fentanyl-induced chest wall rigidity ensues (in this event intubation would be the next step rather than LISA). We also routinely prepare a dose of naloxone in the event that there is opiate-induced apnoea/shallow breathing post-procedure, which in our experience seems to occur more commonly in the extremely preterm infants, but can be unpredictable. Naloxone appears to be safe.<sup>10</sup> We find that this sedation regime strikes the balance

between the invasive nature of the procedure and the need to maintain spontaneous, non-ventilated breathing. We also think that shallow breathing, if caused by the opiate, may hamper the distribution of surfactant.

## Training and supervision of procedure

Our trainees are doing less and less intubation and while this is proven to be good for babies, their concerns about their technical abilities are important ones. We have taught the LISA procedure using simulation, we have created a video of the procedure and we have a clear guideline. In addition the use of videolaryngoscopy for training and also for providing clinical assurance of successful catheter placement is an important advance. In the smallest babies, blade size can still be problematic.

## The LISA procedure

A fine bore tube (we currently use a surfactant administration kit), or infant feeding tube (4-5Fr), or a semi-rigid catheter, is inserted 1.5-2cm through the vocal cords under direct laryngoscopy (FIGURE 2). A Magill forceps may be helpful in directing the tube in the right direction, but is often not needed in extremely preterm infants as the distance from mouth to larynx is relatively short. Once the tube is seen to pass through the cords, the forceps is removed first under direct vision (to ensure the catheter is not accidentally displaced), followed by the laryngoscope while holding the catheter in place at the mouth with the operator's fingers. Still holding onto the catheter, surfactant is then instilled slowly over five minutes in order to reduce the risk of bradycardia, apnoea and surfactant reflux. After the surfactant has been given, the infant is placed back into the incubator and, if successful, a marked reduction in supplemental oxygenation and work of breathing should be seen. A quick guide to performing LISA can be seen in TABLE 2.

## Overcoming challenges

Staff completing our audit forms consistently commented on three challenges. These are:

1. Visualising the cords – improved with better equipment (small 00 laryngoscope blade, small Magill forceps, using straight artery forceps). One advantage of LISA over intubation is that the view



**FIGURE 2** The LISA procedure. Note the surfactant tube is being held to reduce any 'drag'. (Photograph taken from a training video made with parental permission.)

- **Equipment:** surfactant administration tube/kit, laryngoscope and appropriate sized blade, Magill forceps, warm towels/warming mat, hat, intravenous access. Have available: straight forceps, endotracheal tube, suction, IPPV.
- **Medication:** fentanyl, atropine, surfactant (Curosurf). Have available: additional fentanyl, suxamethonium, naloxone.
- **Timing:** consider if  $\text{FiO}_2 \geq 0.3$  if <28 weeks' gestation,  $\text{FiO}_2 \geq 0.4$  if >28 weeks' gestation, and increased work of breathing
- **Training:** direct supervision, simulation, guideline.
- **Audit:** data collection to improve learning.

**TABLE 2** How to perform a LISA procedure: a quick guide.

1. Handling the laryngoscope to pass the tube – is not obscured when the flexible catheter is placed in the oropharynx (a problem that is often encountered during preterm infant intubation).
2. Handling the forceps to pass the tube – improved with simulation training and familiarity with equipment, having additional hands to support the fine tube externally to avoid 'drag'.
3. Spillage of surfactant from trachea – improved by ensuring tube is 1.5-2cm below cords and slower administration of surfactant.

## Summary

There is evidence that minimally invasive surfactant delivery using the LISA technique should be the preferred method of rescue surfactant therapy for the preterm infant with RDS. It reduces the risk of death or BPD, need for mechanical ventilation and duration of non-invasive respiratory support. Its safety profile appears good and with adequate staff training and equipment availability, it is a relatively easy skill to acquire. Our staff survey and audit of procedure has shown

that staff are generally enthusiastic and that ensuring the comfort of the baby during the procedure is important. We anticipate that further improvements in sedation protocols, advances in equipment including new types of tracheal catheters, and consistent training will enable staff with limited intubation experience to perform LISA quickly and effectively.

## References

1. Isayama T., Chai-Adisaksopha C., McDonald S.D. Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: a systematic review and meta-analysis. *JAMA Pediatrics* 2015;169:731-39.
2. Seger N., Soll R. Animal derived surfactant extract for treatment of respiratory distress syndrome. *Cochrane Database Syst Rev* 2009:CD007836.
3. Stevens T.P., Harrington E.W., Blennow M. et al. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007:CD003063.
4. Aldana-Aguirre J.C., Pinto M., Featherstone R.M. et al. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Childhood Fetal Neonatal Ed* 2017;102:F17-F23.
5. Lau C.S.M., Chamberlain R.S., Sun S. Less invasive surfactant administration reduces the need for mechanical ventilation in preterm infants: a meta-analysis. *Global Pediatric Health* 2017;4:2333794X17696683.
6. Sweet D.G., Carnielli V., Greisen G. et al. European consensus guidelines on the management of respiratory distress syndrome – 2016 update. *Neonatology* 2017;111:107-25.
7. Dargaville P.A., Aiyappan A., De Paoli A.G. et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. *Neonatology* 2013;104:8-14.
8. Le C.N., Garey D.M., Leone T.A. et al. Impact of premedication on neonatal intubations by pediatric and neonatal trainees. *J Perinatol* 2014;34:458-60.
9. Bertini G., Coviello C., Gozzini E. et al. Change of cerebral oxygenation during surfactant treatment in preterm infants: LISA versus InSurE procedures. *Neuropediatrics* 2017;48:98-103.
10. Elmekawi A., Abdelgadir D., Van Dyk J. et al. Use of naloxone to minimize extubation failure after premedication for INSURE procedure in preterm neonates. *J Neonatal Perinatal Med* 2016;9:363-70.