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LISA/MIST: complex clinical problems almost never have easy solutions

Daniele De Luca (MD, PhD),^{1,2} Shivani Shankar-Aguilera (MD)¹

and Eduardo Bancalari (MD)³

*1 Division of Paediatrics and Neonatal Critical Care,
“A.Béclère” Medical Centre,*

Paris Saclay University Hospitals, APHP (Paris - France)

*2 Physiopathology and Therapeutic Innovation Unit-INSERM U999,
Paris Saclay University (Paris - France)*

*3 Division of Neonatology, University of Miami Miller School of Medicine
(Miami – FL, USA)*

Daniele De Luca: dm.deluca@icloud.com (ORCID: 0000-0002-3846-4834)

Shivani Shankar-Aguilera: shankaraguilera.shivani@gmail.com

Eduardo Bancalari: ebancalari@med.miami.edu

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Corresponding Author : Daniele DE LUCA (MD, PhD)

Service de Pédiatrie et Réanimation Néonatale,

Hôpital “A. Béclère”- GHU Paris Saclay, APHP

157 rue de la Porte de Trivaux, 92140 Clamart (Paris-IDF), France

Tel: +33 (0)145374837 - Fax: +33 (0)145374546 - Email:

dm.deluca@icloud.com

ABSTRACT

Over the last 10 years, new techniques to administer surfactant have been promoted, based on their presumed lesser invasiveness and they have been generally called LISA (less invasive surfactant administration). We believe that the clinical potential of LISA techniques is currently overestimated. LISA lacks biological and physiopathological background justifying its potential benefits. Moreover, LISA has been investigated in clinical trials without previous translational data and these trials are affected by significant flaws. The available data from these trials only allow to conclude that LISA is better than prolonged, unrestricted invasive ventilation with loosely described parameters, a mode of respiratory support that should be anyway avoided in preterm infants. We urge the conduction of high-quality studies to understand how to choose and titrate analgesia/sedation and optimize surfactant administration in preterm neonates. We offer a comprehensive, evidence-based review of the clinical data on LISA, their biases and the lack of physiopathology background.

KEY WORDS: surfactant, preterm neonates, respiratory distress, INSURE

A. INTRODUCTION

During the last decade, new techniques to administer surfactant have been promoted, based on their presumed lesser invasiveness. They consist of the administration of surfactant through a narrow non-ventilable tube (usually a feeding or vascular catheter or a dedicated one of similar diameter) instead of a regular endotracheal tube (ETT). All these tubes are placed under laryngoscopy, irrespective of their diameter, with or without a Magill or an ophthalmic forceps, depending on the anatomy, the operator's experience, the shape and stiffness of the catheter.[1]

These techniques have been variably called less invasive surfactant administration (LISA), minimally invasive surfactant therapy (MIST) or minimally invasive surfactant administration (MISA), but we will broadly refer to them as LISA in this chapter. Their first description dates back to 1992;[2] however they started to receive attention around the time when international guidelines recommended surfactant replacement for respiratory distress syndrome (RDS) only in case of CPAP failure, instead of the general surfactant prophylaxis.[3,4]

While the general drive towards a reduced invasiveness is certainly pivotal for the care of preterm infants with RDS, we believe that, based on current available data, LISA techniques do not provide any real and generalizable

advantage over the use of an ETT for surfactant administration. We also point out to a lack of solid pathobiological and physiological background supporting LISA. We aim here to discuss these limitations, both from a clinical and translational point of view. We will first define what is LISA, then we will examine clinical studies and provide a meta-analysis of the main results and a synthesis of their potential biases; finally, we will discuss the lack of physiopathological background behind LISA techniques.

B. WHAT IS LISA AND WHAT WE REALLY NEED TO UNDERSTAND?

As the acronym states, LISA is supposed to be a less invasive technique than the traditional methods for surfactant administration through an endotracheal tube (ETT). Interestingly, in his first description, Verder et al administered surfactant using both an ETT and a narrow catheter but they did not consider this latter as “less invasive at all.”[2] In fact, as stated above, the placement of a LISA catheter is as invasive as inserting an ETT, but, because of its smaller diameter and higher resistance, the catheter cannot be used to ventilate the patient. When surfactant is given through an ETT this can be used to ventilate the patient. Ventilation can be gentle (with accurate control of volume and pressure delivery) and short (usually for 10-15 minutes), aiming to facilitate surfactant spreading, or it can be longer in order to support ventilation and gas exchange in sicker infants.

The first option is called INSURE (INtubation - SURfactant – Extubation) technique, and was described for the first time in 1992 in the same manuscript describing the use of narrow catheters.[2] INSURE was tested in a randomized clinical trial in 1994,[5] while the first trial to test LISA was published in 2011.[6] Surfactant is very effective in restoring normal lung mechanics and function and improving clinical outcome in RDS patients.[7,8] Thus, the second possibility (i.e.: the classical use of long invasive ventilation to overcome respiratory failure) is rarely needed if preterm neonates receive optimal perinatal care and are only affected by RDS without other coexisting disorders (such as, perinatal asphyxia, pulmonary hypoplasia, early-onset sepsis or congenital pneumonia, eventually evolving towards neonatal acute respiratory distress syndrome (NARDS) [9]).

Since INSURE prevents the deleterious effects of prolonged ventilation, it has been recommended by international guidelines,[3,4,10] supported by a Cochrane review [11] and further randomized clinical trials.[12] The earlier (ideally within the first 2-3 hours of life) INSURE is performed, the higher is the surfactant efficiency and the chance to improve clinical outcomes.[13] Therefore, any new surfactant administration technique must be evaluated for superiority comparing it with an actual, well-performed INSURE. Thus, in order to understand the clinical value of LISA, we have to formally answer the following PICO question:

P (patients): In preterm neonates with RDS (without other co-existing disorders),

I (intervention): is LISA superior to

C (comparator): early INSURE as surfactant replacement technique

O (outcomes): in terms of **X** clinical outcomes?

C. CLINICAL ISSUES

C1. Meta-analysis for pre-specified or important clinical outcomes

Ideally, a technique to administer a life-saving drug, such as surfactant, should aim to improve mortality, which is, however, the most difficult outcome to change. Alternatively, an improvement of a main short-term respiratory outcome (such as the incidence of bronchopulmonary dysplasia (BPD)) may also represent an important outcome. As recently acknowledged by the International Neonatal Consortium, long-term respiratory outcomes, such as respiratory status at 1 year are even more valuable.[14] “Softer” outcomes such as the need, or the duration of invasive mechanical ventilation (IMV) are much less interesting for several reasons. In fact, invasive ventilation is only one of the many factors contributing to the development of BPD and other long-term outcomes: many others (extra-pulmonary inflammation, genetic predisposition, extra-uterine growth retardation - just to name a few), independent from ventilation and occurring at different developmental stages and postnatal age, play a crucial role.[15] Consistently, BPD may even occur

in babies that have never been invasively ventilated.[16] Conversely, a preterm infant may need IMV for different reasons (such as, hemodynamic impairment, neurological abnormalities, refractory apneas) independent from RDS, even several weeks after surfactant administration.[17] Therefore, it is difficult to claim a direct effect of LISA on the need or duration of IMV. The use of a short time window (for instance, the need of IMV in the first 72h of life) is compelling, since it is more likely that a surfactant administration technique would influence (if any) the need for IMV shortly after surfactant treatment rather than later during the NICU course.

Tab.1 shows that, strikingly, LISA trials [6,18–28] have been almost invariably designed and powered only for the need for IMV as primary outcome and some do not even have a clear power analysis: thus, quality of data is not high and it is difficult to give evidence-based guidance regarding other outcomes.

{insert Tab.1 here}

Fig.1 provides the meta-analysis of LISA trials for each of these outcomes (mortality, incidence of BPD, need of IMV in the first 72h of life). Since mortality is a rare outcome, we considered all studies for this analysis. Conversely, for BPD incidence and need of IMV, only trials having these as pre-specified outcomes were included. Methodological details are described in figure legends; analyses were performed with Meta-Analyst 10.1,[29]

following best practices recommended for meta-analyses.[30] Two authors evaluated the bias assessment, data extraction and synthesis; discrepancies were resolved through discussion until a consensus was reached. The results show that LISA does not provide significant improvements in mortality or BPD incidence, whereas it significantly reduces need for IMV in the first 72h of life.

{insert Fig.1 here}

C2. Biases of LISA trials

The above-described meta-analytical results must be seen in light of potential biases affecting the trials. **Fig.2** reports the classical bias evaluation according to Cochrane risk of bias assessment tool.[31]

{insert Fig.2 here}

LISA trials may have biases like any other studies and they particularly suffer of lacking allocation concealment and treatment blinding. We admit that these are difficult, but not impossible to achieve in NICU care and at least the outcome assessors can be quite easily blinded to the intervention.[32]

However, while these biases may be common for trials in various fields, some others are peculiar to LISA and have been considered under the “others” group. They are analyzed below:

- **Lack of comparison between LISA and the real INSURE**

The biggest problem with the data is that none of these trials compares LISA with correctly done INSURE, since patients were subjected to unrestricted

ventilation or presumed to be treated with INSURE, but without clear description of duration of ventilation and ventilatory parameters.[33] The only trial accurately reporting a very short ventilation was the latest published by Gupta et al who did not report a significant reduction in the need for IMV during the first 72 of life.[28] Moreover, some trials were originally not designed to compare LISA with INSURE, but rather with unrestricted ventilation, applied with unclear modes, parameters and duration.[6,20] For example, the first multi-center trial reported that only 33% of neonates in the control arm were extubated within the first 24 hours (that is, 77% were continuously ventilated beyond the first day of life).[6] Thus, these data are not generalizable and, for those NICUs that routinely apply INSURE and have strong policies to reduce IMV, Gupta's study is more informative than the former larger multicenter trial.[6,28] However, in other studies, LISA was supposed to be compared with INSURE, but this was not clearly described. Proper INSURE should be based on the following characteristics: [1]

- short duration (of about 10-15 minutes);
- gentle ventilation (avoiding bagging and using electronic control of pressure) with adjustment of the delivered volume (between 4 and 6 mL/Kg), as compliance changes rapidly following surfactant administration, thus volume guarantee techniques are preferred;[34,35]
- extubation followed by adequate CPAP (6-8 cmH₂O is better than lower levels) or non-invasive positive pressure ventilation.[34,36,37]

Preliminarily, a light sedation/analgesia should be provided as laryngoscopy causes discomfort and dangerous physiological responses, but this should not be deep enough to prevent a quick extubation. Oral intubation might be considered preferable as it is usually quicker, requires less manipulations and reduces leaks and post-extubation atelectases.[38] *Therefore, a trial comparing LISA to a group receiving early and optimal INSURE as described above is yet to be conducted. To date, we can only say that LISA is better than intubation followed by invasive ventilation of an undefined duration, modality, and ventilatory parameters. Nonetheless, it is well established that INSURE is better than this unrestricted ventilation policy. Therefore, with the available evidence, it is impossible to decide whether LISA offers any advantage when compared to INSURE.*

- **Unequal co-interventions between the study arms**

This is another major bias of LISA trials. In some larger studies sedation was used at the clinicians' discretion [6,20] and, since the frequent message is that LISA is "less painful" than an ETT placement, there is a high risk of having an uneven exposure to analgesic and sedative drugs between the study groups. When the primary outcome is the need for IMV, this represents a serious flaw, since more sedated babies are likely to have an increased need for respiratory support. Other studies did not use sedation or analgesia in any arm: as laryngoscopy is needed exactly in the same way for both LISA

and ETT placement, patients are likely to experience similar discomfort, raising some ethical questions.[1]

As described above, since laryngoscopy is used in the same way for LISA and ETT placement, and, according to classical physiology and anesthesiology literature, [1] there is no reason to believe that inserting a LISA catheter would be less painful or stressful than an ETT. The STRASS (STRess ASSEssment with and without analgesia during surfactant administration - NCT04073173) trial is currently ongoing and hopefully will clarify the level of stress and pain associated with the different procedures.

Choosing and titrating the level of sedation may not be easy in neonates: however, particular effort and research should be directed to these questions, as sedation for laryngoscopy is recommended by both American and European guidelines.[39,40]

Caffeine is another co-intervention that may affect outcomes and that has not been clearly standardized in most LISA trials. Some advocate the early administration of caffeine coupled with LISA to reduce ventilatory needs. However, there is no physiopathological reason preventing early caffeine administration right before INSURE and early caffeine administration is usually indicated for all very preterm neonates,[41,42] especially those under non-invasive respiratory support.[34]

- **Unclear indications for surfactant treatment or different surfactants and doses**

Some LISA trials do not have clear indications for surfactant administration and/or these are not equal between the study arms.[6,18,20,24,26] Moreover, patients received undefined surfactant doses or even different surfactant preparations according to availability and clinicians preference.[6,20] These are serious flaws, as it is pivotal that the randomized intervention (i.e.: the surfactant administration technique) must be used to give exactly the same drug, with an equal dose, at the same timepoint of the disease course, in all patients. In fact, the timeliness of surfactant replacement, its dose or formulation significantly affect clinical outcomes.[13,43,44] Interestingly, we previously reported that 42% of surfactant trials published in the last decade have at least some dosing errors [45] and that sub-optimal porcine surfactant doses are often given, with increasing risk of re-treatment.[46]

- **Questionable outcomes**

Many LISA trials focused on outcomes with unclear relevance or very low likelihood to be affected by the treatment. For instance, the NINSAPP trial chose a composite endpoint consisting of survival without prematurity-related complications.[20] From a statistical point of view, this choice may increase the chance to detect a significant difference, but it is unclear if extra-pulmonary complications (for instance, intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis) are actually affected by

surfactant therapy and a clear physiopathological link is lacking.[47,48] Anyway, in the NINSAPP trial, LISA failed to improve such composite primary outcome.[20] Other trials also focused on these extra-pulmonary outcomes and found no differences.[18,26] Interestingly, a recent meta-analysis showed no difference in extra-pulmonary outcomes between different surfactant preparations,[44] thus it seems even more unlikely that the administration technique would have any effect. Not surprisingly, the 2-years follow-up of the first multi-center LISA trial failed to show any difference in growth or neuro-development.[49] Yang's trial [27] examined these outcomes in more mature neonates (between 32- and 36-weeks' gestation), but these complications are extremely rare in these patients. The NINSAPP trial also seems to have an overlap between the studied interventions (LISA or IMV) and one of the outcomes (need of IMV in the first 72h of life).[20] As surfactant was given during ventilation in the control arm, $\approx 100\%$ of patients enrolled in that arm were ventilated, leading to a meaningless outcome measure.

- **Maturity of the enrolled populations**

Most of LISA trials enrolled relatively mature preterm neonates, that is, those less at risk of negative outcomes and long-term consequences. Only two trials [6,20] enrolled neonates with a gestational age less than 28 weeks: one of them was targeted to detect differences in the need of IMV and the other in BPD-free survival. Both of them did not report any improvement in BPD or mortality, besides being affected by relevant flaws (see above). As the other

trials studied newborn population less at risk of negative outcomes, they are less likely to provide any practically significant improvement in neonatal care and their results are less interesting.

C3. Potential confounders

It is unknown if LISA may be beneficial in patients within a specific gestational age range or under certain particular conditions. Moreover, LISA trials were not homogeneous for the surfactant type and dose, the type of catheter or other factors. As the only significant effect of LISA so far is the reduction in need of IMV in the first 72 hours of life, we performed meta-regressions adjusting this outcome for some confounders; meta-regressions were conducted with only one covariate in each model to reduce false positives.[50] We found that:

- GA is not associated with the effect size (coefficient 0.082: (95%CI: -0.076; 0.241), $p=0.307$, seven studies [6,18,21,22,24,25,28]). It is likely that GA might be an effect modifier, but further studies are needed to make this evident.
- use of poractant-alpha (Curosurf®, Chiesi Farmaceutici, Parma, Italy) (the more concentrated porcine surfactant administrable in a higher dose) was significantly associated with the effect size (coefficient: 0.708 (95%CI: 0.131; 1.284), $p=0.016$, four studies [18,21,22,28]).

This information is consistent with the better clinical outcomes associated with poractant-alpha in recent meta-analyses comparing porcine and bovine surfactant.[43,44,51] However, this was only a secondary analysis and it is not sufficient to conclude that LISA is more beneficial with any particular surfactant preparation.

C4. Unverified or unlikely benefits of LISA

There are some potential LISA effects that are worthy of a deeper investigation, as they have not been studied in randomized clinical trials but only in observational studies. Other effects have been hypothesized, but are quite unlikely to happen.

- The psychological effect of LISA

LISA has been claimed to be useful to reduce the duration of IMV because the use of small catheters avoids any ventilation before, during and right after surfactant administration and this would force clinicians to quickly pull the catheter out. Thus, clinicians would resist the temptation to keep ventilating patients, although it is known that keeping stable babies on IMV does not improve the chance of a successful extubation [52] and worsens clinical outcomes.[53,54] This may be “the psychological effect of LISA” and can certainly exist, at least in some situations. However, this has not been formally studied so far and the potential advantage should be balanced

against risks and possible detrimental effects. Interestingly, a recent study found that the placement of LISA catheter and surfactant injection lasted twice as long (122 seconds), than the placement of an ETT and the surfactant injection through it (65 seconds).[26]

- **Effect of LISA on infections**

LISA is claimed to reduce infections because of its presumed minor invasiveness, however the incidence of pulmonary or airway infections has not been studied. The definition of ventilation-associated pneumonia would not qualify, as this requires the presence of an airway device for at least 48h [55] and both LISA and INSURE are much shorter procedures. Sepsis rate has been studied in some LISA trials and was not different between arms.[19,25–27] Moreover, as long as both ETT and LISA catheters are sterile and placed under optimal condition, there is no obvious reason to consider LISA a procedure with lower infection risk.

- **The ease to perform LISA**

LISA is generally considered to require less expertise, but this has not been clearly defined. Videos and illustrative tools are available, but the training curve for a LISA procedure has never been formally studied. A standardized training program in Poland demonstrated that LISA is quite easy to learn but this has not been compared to the ETT placement.[56] This deserves to be

studied, especially because pediatricians risk to lose competency for laryngoscopy.[57] Han et al found that clinicians performing LISA or ETT placement had comparable levels of experience.[26]

- **Reduction of airway injury**

Some authors hypothesized that using narrow catheters instead of larger ETT may reduce airway injury and the incidence of granulomas. However, these injuries are likely to occur only after several days of intubation and even after long periods their incidence is extremely low.[58–60] Moreover, in adults, the insertion of a catheter of limited diameter relative to the tracheal size can still increase laryngeal resistance: therefore, even the use of narrow catheter can induce a laryngeal irritation with a functional response.[61,62] Consistently, vocal cord adduction has been observed in LISA trials and is shown in training videos.[6] Thus, there is no reason to postulate that LISA would be less injurious on the airways than the use of a standard ETT for short periods of time.

C5. Potential detrimental effects of LISA

LISA may be associated with detrimental effects that need to be better investigated. For instance, in many large LISA trials there is a high proportion of patients needing subsequent IMV.[6,18,20] This is worrisome, and the

reasons for this are unclear, as it may be related to the intervention, to sub-optimal non-invasive ventilation policies or even to extra-pulmonary reasons.

We have previously shown that using narrow catheters leads to inadvertent surfactant loss, because the drug may partially adhere (despite an air flush) to the inner tube surface.[63] If surfactant injection is not done through classical ETT and followed by a brief ventilation, approximately 10–15% higher doses should be used to compensate this inadvertent loss.[63]

Nonetheless, we do not know if this loss is clinically relevant or not. It is also unknown whether the same effect is present when using catheters made of different materials.

A crucial point is the surfactant distribution when the drug is administered through LISA. It is unknown if the diffusion of surfactant is sufficient when given by LISA, as it is conceivable that a brief ventilation is needed to facilitate surfactant spreading through the periphery of the lungs. Conflicting data exist on this matter since dedicated and controlled animal data show an imbalanced surfactant distribution,[64] while electrical impedance tomography showed opposite findings but in a small and uncontrolled series of neonates.[65] However, more recently, semi-quantitative lung ultrasound has been used before and after surfactant administration to evaluate lung aeration and the lung ultrasound score did not change in LISA-treated

babies,[66] whereas it significantly decreased in neonates treated with INSURE:[67] this means that surfactant distribution and lung aeration are better after INSURE than after LISA. More and above this, there are not definite data about the number of neonates requiring surfactant re-treatment, which is an important outcome, both from a clinical and financial point of view. The unclear indications for surfactant treatment and the use of different surfactants or doses in LISA trials (see above) makes impossible to conclude on this point. We need more data to conclude on this important matter but caution is advised because uneven surfactant distribution and small airway obstruction can occur, given the absence of ventilation and the lack of CPAP transmission during LISA (see below).[1]

Whether or not LISA can influence vital parameters and cause relevant side effects is still to be determined but, as we explain below, there is a solid pathophysiological background to hypothesize that detrimental effects can occur, at least in some cases.[1] The majority (7 out of 12) of LISA trials reported significantly lower peripheral oxygen saturation and heart rate during surfactant replacement in the LISA arm (**Tab.2**).[6,18,20,21,25–27]

{insert Tab.2 here}

The magnitude of the desaturations and bradycardias seems clinically important in at least two trials.[20,25] Of note oxygenation has not been studied in a comprehensive way, as only FiO_2 is reported. Thus, we lack

definite data about the oxygenation in babies undergoing INSURE or LISA during and immediately after the procedures and it is possible that oxygenation status would be worse in LISA-treated neonates. Apneas requiring some intervention, and surfactant reflux through the LISA catheter, have also been noticed,[18,21] and this may add to the already described surfactant inadvertent loss.[63] These side effects are related to the impossibility to ventilate through LISA catheters, the airflow limitation and the poor CPAP transmission during the procedure (see below). These side effects have, surprisingly, not been investigated in every trial and many of the studies have not provided rates of failure when LISA had to be aborted and infants had to be intubated because of apnea and hypoxia. Furthermore, there is absolutely no information on carbon dioxide levels during and after LISA: hypercarbia might occur as during flexible bronchoscopy in adults and children, due to the airflow limitation.[68] These issues are relevant since they may lead to emergency intubation with the associated negative consequences (i.e.: risk of airway trauma, lack of sedation/analgesia).

On the same line, the effect of LISA techniques on cerebral hemodynamics is unclear. Two studies describe similar cerebral oxygenation in babies undergoing INSURE or LISA,[23,69] whereas another reports worse cerebral oxygenation during LISA and a consistently higher fractional oxygen extraction.[70] An animal study suggests that the reduction in cerebral

oxygenation depends on the type of LISA catheter. These results are however difficult to explain since catheters of equal diameters have been used.[71] Cerebral hemodynamics and electrical activity can also be influenced by surfactant instillation itself, irrespective of the type of tube used:[72,73] *therefore, this further refutes the minor invasiveness of LISA and highlights the importance of sedation/analgesia during surfactant replacement.* With the recent diffusion of LISA, a trend not to use analgesia or sedation has been described in surveys and observational studies:[74,75] this is worrisome and ethically questionable because the acute physiological responses associated with laryngoscopy and surfactant instillation are undesirable and in some cases very dangerous.

D. PHYSIOPATHOLOGICAL ISSUES

Besides the aforementioned clinical data, there is no clear physiopathological and biological base for the proposed benefits of LISA. This is important because clinical choices should be based not only on trials results, but also on a solid plausibility. Moreover, The US Food and Drug Administration recommends that the development of any medical device should follow a pathway similar to that of drugs.[76] LISA techniques started to spread without sufficient preliminary bench and/or animal studies demonstrating a clear pathobiological plausibility, allowing researchers to hypothesize benefits to be subsequently tested in complex clinical trials. With LISA, the

mechanisms to explain its possible benefits have been hypothesized *a posteriori*. These presumed LISA “mechanisms of action” are:

- improved CPAP transmission;
- reduced pain and stress;
- avoidance of any exposure to IMV even of short duration;

These points have been discussed elsewhere, [1] and we will only offer a short summary here.

D1. LISA does not provide better CPAP transmission

Experimental data demonstrated that CPAP is not transmitted during LISA due to the leaks (up to 50%) through nostrils and mouth, which are independent on the type of non-invasive respiratory support.[77,78] These pressure leaks have been associated with clinically relevant derecruitment *in vivo*. [79] Even if leaks could be completely avoided, pressure would be hardly transmitted, because LISA catheters significantly reduce the cross-sectional area of the trachea and increase resistance to airflow.[1] This phenomenon, coupled with the frequent turbulent flow and the active crying due to the common absence of sedation during LISA [74,75] may increase airway resistance from 40 to 1000 cm H₂O/L/s, when using a 5Fr catheter.[1] This same mechanism causes hypoxia, hypercarbia and arrhythmias in children and adults under bronchoscopy and is even more important in preterm neonates due to the relative size of trachea and LISA catheter (**Fig.3**).[1]

{insert Fig.3 here}

Similarly, the claim that LISA would be more efficacious because the patient maintains the spontaneous breathing during the procedure is questionable. A light analgesia/sedation should be provided for laryngoscopy and spontaneous breathing should not be totally suppressed. There are no data showing that the spontaneous breathing effort would improve surfactant spreading compared to the brief application of accurately controlled positive pressure breaths through an ETT. This hypothesis is not supported by the conflicting data on surfactant distribution during LISA (see above).[64–67] Some animal data have been cited to support this theory, but these were obtained in a model quite distant from the clinical situation (small animals, pharyngeal surfactant deposition, spontaneous breathing during the deposition and then 4 hours of IMV).[80] Finally, the negative pressure generated by the spontaneous breathing efforts would be difficult to transmit through the trachea due to the airflow limitation and increased resistance caused by the intratracheal LISA catheter.

D2. LISA is not likely to be less painful or stressful

No study has investigated the level of pain or stress in patients undergoing LISA or ETT placement, thus it is not possible to claim this technique is actually less painful. The STRASS trial (NCT04073173) is investigating this

issue but meanwhile we have to remember that data coming from classical physiology and anesthesiology demonstrates that discomfort is caused by the laryngoscopy itself and particularly by the traction applied on its blade, rather than by the tube diameter.[1] Cerebral hemodynamics and electrical activity measurements have shown that surfactant injection can be stressful, irrespective of the size of the tube used.[72,73]

Classical data shows that in as short as 5 seconds, laryngoscopy increases catecholamine release, causes systemic and pulmonary hypertension, tachycardia, arrhythmias, and, even increased intracranial and intraocular pressures, irrespective of subsequent intubation.[1] These responses are totally independent from the catheter or ETT placement, as they are due to the blade-induced stimulation of the supraglottic region, which is a highly reflexogenic area,[81] and could be enhanced by the subsequent surfactant instillation. None of these phenomena can be reduced or modified by inserting a tube of smaller diameter, thus LISA cannot be considered less invasive as long as laryngoscopy blade is used.

Given the risk of intracranial hemorrhage, blunting these responses is even more important in preterm neonates and analgesia/sedation is recommended both by American and European guidelines in this regard.[39,40]

Interestingly, these echo the guidelines for adults undergoing laryngoscopy or fibro-bronchoscopy,[68,82] a procedure technically similar to LISA.

D3. The avoidance of few minutes of gently controlled ventilation is not likely to be beneficial

Many experimental data have shown that a short period of ventilation may be injurious to the immature lung and trigger the inflammatory cascade.

However, all these studies have applied quite aggressive ventilation patterns, without adequate PEEP level and control of the delivered volume.[1] In short,

the ventilation provided in experimental models is far from the state-of-the art neonatal ventilation provided in modern NICUs. Moreover, for ventilation-

induced lung injury to be triggered the duration is also important: many experimental data show that the duration of exposure to aggressive

ventilation is important for the development and progression of lung injury.[1]

Prolonged ventilation times (1–54 h) are often needed before damage occurs in lungs in newborn animals (**Tab.4**). This is consistent with the pivotal

Ranieri's data in adult patients [83] and with our findings showing that neutrophil influx significantly increases only after 48 hours of gentle

ventilation.[84] Experimental data also suggest that the newborn lung is more resistant than the adult to the mechanisms of ventilation-induced lung

injury.[85]

In conclusion, it is unlikely that a short period of gentle, volume-targeted ventilation (such as the ventilation that should be provided during proper INSURE) might trigger clinically significant injury and therefore, it is unlikely that LISA provides benefits over INSURE by tempering these lung injury mechanisms.

E. CONCLUSION

We believe that the clinical potential of LISA techniques is currently overestimated. LISA should still be subjected to rigorous basic studies to understand its possible beneficial mechanism and, then, to well-conducted randomized trials comparing LISA with well-performed INSURE. It is possible that LISA might be a good choice exclusively for settings where INSURE is not feasible and the only remaining option would be inappropriate and/or long ventilation. However, clinicians should understand why INSURE is not an option and adequate efforts should be made to improve its feasibility and performance.

More importantly, we urge further research to better understand how to choose and titrate analgesia/sedation in preterm neonates with respiratory failure, in order to improve safety of laryngoscopy and surfactant instillation. This will not only improve the care of preterm infants but also improve our understanding of basic physiology and pathophysiology. Cross-disciplinary

knowledge should not be forgotten and should be part of the core curriculum of NICU practitioners.[86] Complex problems almost never have easy solutions and what seems new is not always the best for the patient.

PRACTICE POINTS

- There is no sound physiopathological or biological base to suggest that LISA should produce better results than properly executed INSURE.
- To date, the only evidence is that LISA reduces the duration of ventilation (within the first 72h of life) when compared to intubation followed by unrestricted invasive ventilation of unspecified modality or ventilatory parameters.
- While it is well known that INSURE produces better results than unrestricted invasive ventilation, there are no data on how to choose between INSURE and LISA.
- LISA might be a good alternative if INSURE is not feasible and the only remaining option is unrestricted invasive ventilation. However, it is not clear why INSURE would not be feasible. In this situation, clinicians should identify the barriers for INSURE and take the necessary steps to make it feasible.

RESEARCH AGENDA

- Understand how to titrate and optimize sedation and analgesia for neonatal laryngoscopy.
- Understand how to optimize surfactant delivery in preterm neonates with RDS.
- Develop tools to predict continuous positive airway pressure failure and give surfactant as early as possible to neonates failing noninvasive support.

CONFLICT OF INTEREST

A/Prof. De Luca has received research and educational grants from Chiesi Pharmaceuticals spa and ABBVIE inc. He served as lecturer for Airway Therapeutics, Chiesi Pharmaceuticals spa and ABBVIE inc. Finally, he has been member of advisory boards for Chiesi Pharmaceuticals spa and ABBVIE inc. Dr. Shankar-Aguilera received a travel grant from Chiesi Pharmaceuticals spa.

These companies produce surfactants or surfactant proteins, but had no role in design, preparation, review, approval of the manuscript or decision to submit it for publication. The declared conflicts are all unrelated to the present manuscript.

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Table 1. Randomized clinical trials about LISA according to PICO framework. Gestational age was considered as the weighted mean of the two trial arms. INSURE was considered unclear when it did not follow the principles of short and gentle ventilation (more details in the text). Surfactant preparations used in trials were as follows: poractant-alpha (Curosurf®, Chiesi Farmaceutici, Parma – Italy); beractant (Survanta®, Abbvie, Chigago-IL, USA), BLES (Neosurf®, Ciplamed, Mumbai, India), Calf surfactant (Kelisu®, Double Crane, Beijing, China). A trial was considered powered when a sample size calculation for the primary outcome was provided and respected. Plus (+) indicated the level of bias in the study as detailed in Fig.2. **Abbreviations:** BPD: bronchopulmonary dysplasia; GA: gestational age; IMV: invasive mechanical ventilation in the first 72h of life; INSURE: INTubation-SURfactant-Extubation; PICO: patient/intervention/comparator/outcome.
 * as this is the first trial on late preterm neonates, it can be considered pilot and not needing a formal sample size calculation.

First author/year (Country) - [Reference]	Patients (mean GA)	Intervention	Comparator	Outcome	Powered	Bias
Gopel/2011 (Germany) - [6]	Extremely preterm neonates (GA 26)	Various surfactants bolus through various catheters	Unrestricted IMV	Need of IMV	Yes	+++
Kanmaz/2013 (Turkey) - [18]	Very preterm neonates (GA 28.1)	Poractant-alpha bolus through 5Fr catheter	Unclear INSURE	Need of IMV	Yes	+++
Mirnia/2013 (Iran) - [19]	Preterm neonates (GA 29.6)	Poractant-alpha bolus through 5Fr catheter	Unclear INSURE	Unspecified	No	+++++
Kribs/2015 (Germany) - [20]	Extremely preterm neonates (GA 25.3)	Poractant-alpha bolus through 4Fr catheter	Unrestricted IMV	BPD-free survival	Yes	+++
Bao/2015 (China) - [21]	Preterm neonates (GA 29.2)	Poractant-alpha bolus through 5Fr catheter	Unclear INSURE	Need of IMV	No	+++++
Mohammadizadeh/2015 (Iran) - [22]	Preterm neonates (GA 30.5)	Poractant-alpha bolus through 4Fr catheter	Unclear INSURE	Need of IMV	No	++++
Li/2016 (China) - [23]	Preterm neonates (GA 29.4)	Poractant-alpha bolus through 4Fr catheter	Unclear INSURE	Unspecified	No	++++

Halim/2019 (Pakistan) - [24]	Preterm neonates (GA 31.3)	Beractant bolus through 6Fr catheter	Unclear INSURE	Need of IMV	No	+++++
Jena/2019 (India) - [25]	Preterm neonates (GA 31)	BLES bolus through 5Fr or 6Fr catheters	Unclear INSURE	Need of IMV	Yes	+++
Han/2020 (China) - [26]	Preterm neonates (GA 30.7)	Calf surfactant bolus through 5Fr catheter	Unclear INSURE	BPD	Yes	+++
Yang/2020 (China) - [27]	Preterm neonates (GA 33.9)	Poractant-alpha bolus through 6Fr catheter	Unclear INSURE	Unspecified	No*	++++
Gupta/2020 (India) - [28]	Preterm neonates (GA 30)	Poractant-alpha bolus through 5Fr catheter	Unclear INSURE	Need of IMV	Yes	+++

Figure 1. Forrest plots for mortality (panel A, 1544 patients), BPD (panel B, 606 patients) and need of invasive ventilation within the first 72h of life (panel C, 1056 patients). Since mortality is a rare and difficult-to-change outcome, all LISA trials have been considered for this meta-analysis. For the meta-analysis on BPD incidence, we only considered trials having BPD as pre-specified outcome and the Yang’s trial,[27] which has no prespecified outcomes. For the meta-analysis on the need of IMV, only trials having this as pre-specified outcomes were included. Consistency across the studies was evaluated using the I^2 statistic (variation in odd ratios attributable to heterogeneity) and performing a χ^2 test for heterogeneity. Given the high heterogeneity, analyses were performed with random-effects using Sidik-Jonkman method. LISA and the comparator are considered as treatment (Trt) and control (Ctrl) arm, respectively; events per arm and odds ratio (95% confidence interval) are reported. Square size is proportional to trial weight. Diamond width indicates the 95% confidence interval.

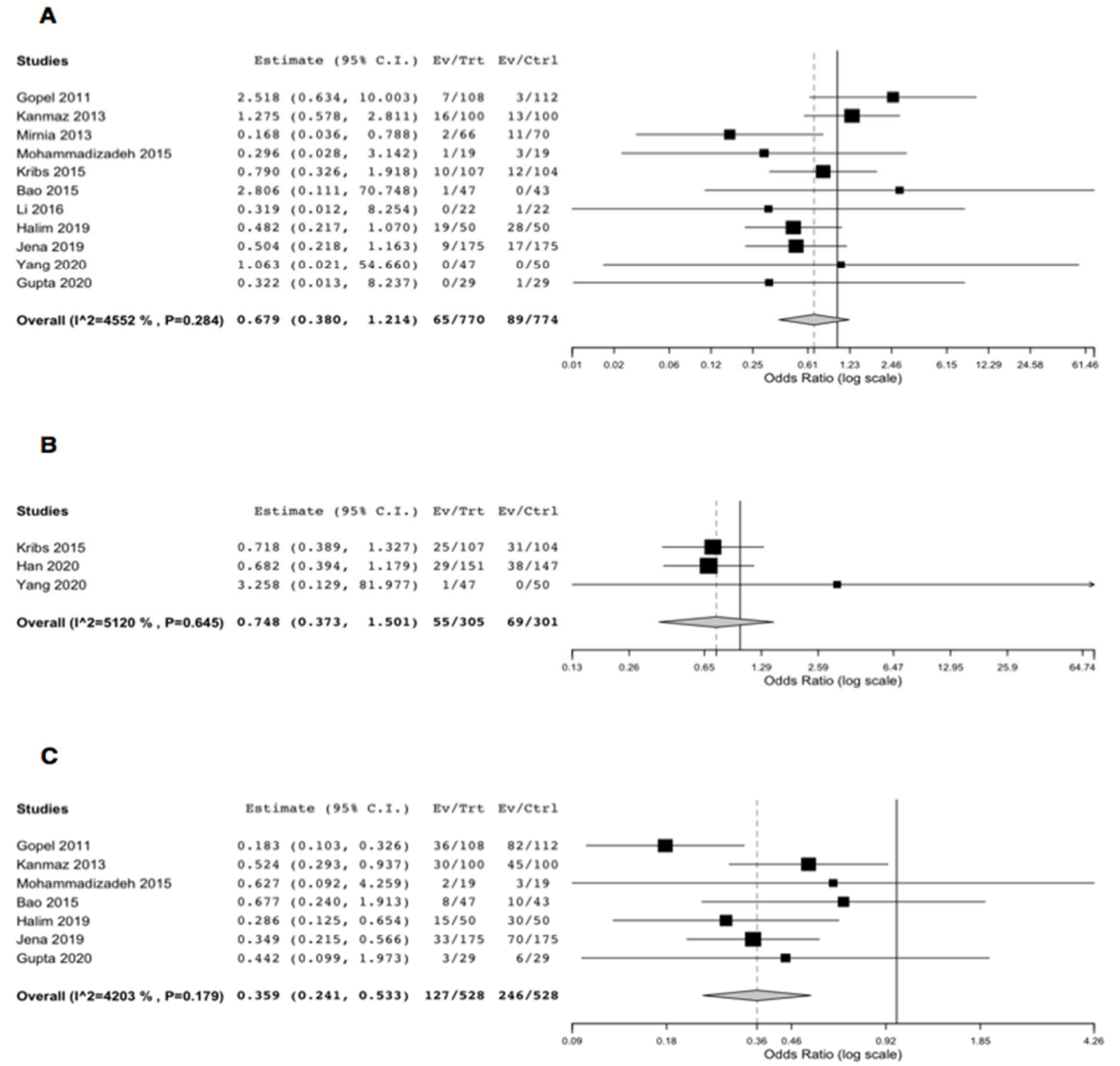


Figure 2. Bias analysis for LISA trials. Risk of bias for each trial as evaluated according to the Cochrane Risk of Bias assessment tool.[31] Each item was assessed as “low”(+, green squares) or “high risk” (-, red squares) of bias, or unclear (? , yellow squares), when it was impossible to determine, on the basis of the available data). ‘Others’ indicates trials specific of surfactant administration policies and are detailed in the text.

Studies	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessment	Outcome analysis and reporting	Others
Gopel (2011)	+	+	-	-	+	-
Kanmaz (2013)	+	?	-	-	+	-
Mirnia (2013)	?	-	-	-	-	-
Kribs (2015)	+	+	-	-	+	-
Bao (2015)	?	-	-	-	-	-
Li (2016)	?	-	-	-	+	-
Mohammadizadeh (2014)	?	-	-	-	+	-
Halim (2019)	+	-	-	-	-	-
Jena (2019)	+	+	-	-	+	-
Han (2020)	+	+	-	-	?	-
Yang (2020)	?	-	-	-	+	-
Gupta (2020)	+	+	-	-	+	-

Table 2. Short-term side effects of LISA. Only findings from trials reporting detrimental side effects are shown. *The magnitude of desaturations and bradycardias seem clinically important in these trials. More details in the text.
Abbreviations: SatO₂: peripheral oxygen saturation.

First author/year – [Reference]	Side effects	
Gopel/2011 - [6]	↓ SatO ₂	↓ Heart rate
Kanmaz/2013 - [18]	↑ Apneas	↑ Surfactant reflux
Kribs/2015 - [20]	↓ SatO ₂ *	↓ Heart rate*
Bao/2015 - [21]	↓ SatO ₂	↑ Surfactant reflux
Jena/2019 - [25]	↓ SatO ₂ *	↓ Heart rate*
Han/2020 - [26]	↓ Heart rate	
Yang/2020 - [27]	↓ SatO ₂	

Figure 3. Cross-sectional area available for ventilation during tracheal catheterization with non-ventilable tubes in adults (A), term (B), and preterm neonates (C). A flexible bronchoscope (≈ 13 Fr; ≈ 4.3 mm; A) and a feeding tube (≈ 4 Fr; ≈ 1.35 mm; B, C) are used as devices in this illustration. *Diameters are fairly estimated from available literature data [58] and proportioned between them. Reproduced with permission from [1]. More details in the text. **Abbreviations:** Fr=French catheter scale units.

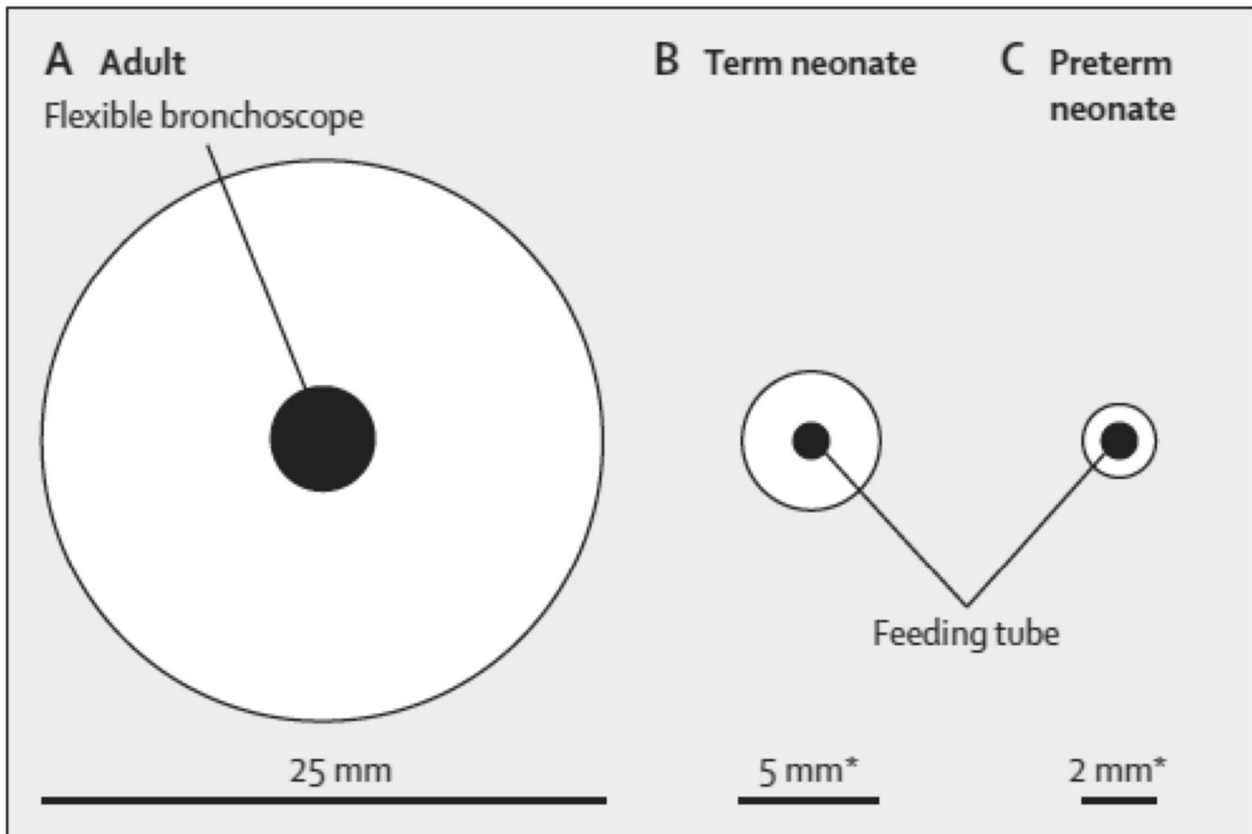


Table 3. Studies on experimental ventilation-induced lung injury in neonatal animal models: lung injury was produced by aggressive and/or long-lasting ventilation. Adapted from [1]. More details in the text. **Abbreviations:** NA: not available data; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure.

Author/year – [Reference]	Model	Volume (mL/kg)	PIP (cmH₂O)	PEEP (cmH₂O)	Exposure time
Naik AS/2001 - [87]	Preterm lambs	9-12	40	0-7	2-7h
Jobe A/2002 - [88]	Preterm lambs	10	NA	4	2h
Hillman NH/2007 - [89]	Preterm lambs	15	NA	0	15min
Allison BJ/2008 - [90]	Preterm lambs	NA	40	4	1h
O'Reilly M/2009 - [91]	Preterm lambs	NA	40	4	6-12h
Wallace MJ/2009 - [92]	Preterm lambs	20	NA	0	15min
Te Pas AB/2009 - [93]	Preterm rabbits	10	35	0-4	7min
Polglase GR/2009 - [94]	Preterm lambs	8	30	5	3h
Polglase GR/2010 - [95]	Preterm lambs	7-15	35	5	15min

Hillman NH/2010 - [96]	Preterm lambs	15	NA	0	15min
Brew N/2011 - [97]	Preterm lambs	NA	40	0	2h
Hillman NH/2011 - [98]	Preterm lambs	15	55	0-8	15min
Hilgendorff A/2011 - [99]	Newborn mice	7-8	NA	NA	8-24h
Hodges RJ/2012 - [100]	Preterm lambs	NA	40	4	12h
Preuß S/2014 - [101]	Newborn pigs	14	NA	0	2h
Deputla N/2016 - [102]	Preterm lambs	7-15	40	0	15min
Huang J/2016 - [103]	Newborn rats	25	NA	NA	3-5h
Yaroshenko A/2016 - [104]	Newborn mice	≈9	NA	NA	2-8h
Inocencio IM/2017 - [105]	Preterm lambs	15	50	0	15min
Kothe Brett T/2019 - [106]	Preterm lambs	8	30	5	2-24h