Sedation for Less Invasive Surfactant Administration in preterm infants: A Systematic Review and Meta-analysis

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Impact

- The effect of sedative drugs (analgesics, sedatives, anesthetics) compared to the effect of no-sedation for LISA in preterm infants with RDS is underexplored.
- This systematic review and meta-analysis assesses the impact of sedative drugs compared to no-sedation for LISA on short-term pulmonary outcomes and potential adverse events.
- Sedative drugs for LISA temporarily affect the newborn's breathing (desaturation, apnea) and increase the need for nasal intermittent positive pressure ventilation,. For most outcomes, Certainty of Evidence is low/very low.

ABSTRACT

Background

Sedation to preterm neonates receiving Less Invasive Surfactant Administration (LISA) for respiratory distress syndrome (RDS) is controversial.

Methods

Systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies (OS) to evaluate the effect of sedative drugs for LISA on respiratory outcomes and adverse effects.

Results

One RCT (78 neonates) and two OS (519 neonates) were analyzed in pair-wise meta-analysis and 30 studies (2164 neonates) in proportion-based meta-analysis. Sedative drugs might not affect the duration of procedure [RCT: MD (95% CI); -11 (-90 - 67) seconds; OS: Mean difference (MD) 95%CI: -60 (-178-58) seconds; Low certainty of evidence (CoE)]. Evidence for success at first attempt and rescue intubation was uncertain (very low CoE). The risk of nasal intermittent positive pressure ventilation [RCT: 1.97 (1.38-2.81); OS: RR, 95% CI: 2.96 (1.46-6.00), low CoE], desaturation [RCT: RR, 95% CI: 1.30 (1.03-1.65), low CoE], and apnea [OS: RR, 95% CI: 3.13 (1.35-7.24), very low CoE] might be increased with sedation. Bradycardia, hypotension and mechanical ventilation were comparable between groups (low CoE).

Conclusions

Use of sedative drugs for LISA temporarily affects the newborn’s breathing. Further trials are warranted to explore the use of sedation for LISA.

INTRODUCTION

One of the most pressing calls in the care of preterm neonates is that for an effective yet minimally invasive approach to surfactant administration. Exogenous surfactant replacement and non-invasive respiratory support (NRS) have become the most successful treatments for preterm infants with respiratory distress syndrome (RDS)[1]. The combination of NRS and surfactant replacement was first described in 1992[2]. Today, less invasive surfactant administration (LISA) encompasses the delivery of surfactant to spontaneously breathing infants with RDS for whom the application of continuous positive airway pressure (CPAP) alone does not suffice[3]. Acknowledging the increasing evidence of its effectiveness, the current European Consensus Guidelines on RDS management recommend LISA as the preferred mode for targeted surfactant delivery in spontaneously breathing babies with RDS[4]. LISA has proven to be safe in extremely preterm infants of less than 28 gestational age (GA)[5,6]. The recent Cochrane Review[7], together with other systematic reviews and meta-analyses[3,8-12], concludes that LISA effectively reduces the risk of death or bronchopulmonary dysplasia (BPD), the need for invasive mechanical ventilation (IMV) in the first 72 hours and the incidence of major complications compared to surfactant administration through an endotracheal tube (ETT), or continuation of NRS without surfactant administration or surfactant administration followed by continuing IMV. The recently concluded OPTIMIST trial has confirmed the benefit of the procedure in reducing the incidence of BPD at 36 weeks postmenstrual age in extremely preterm infants[13].

However, despite gaining increasing popularity in the last years[14-16], several aspects of the LISA procedure remain unresolved, like the choice of device to deliver surfactant[17,18], the target population[19-21], and most importantly, the insufficient knowledge around the routine use of sedative drugs[22,23].

The objective of this systematic review and meta-analysis is to evaluate the effect of sedation during LISA when compared to non-pharmacological standard measures in preterm neonates of less than 37 weeks gestational age (GA) with RDS.

METHODOLOGY

This systematic review and meta-analysis was conducted in accordance with PRISMA guidance[24] and MOOSE Checklist[25]. The protocol for this systematic review was registered with PROSPERO (CRD42021278954).

Literature search

A systematic database search (PubMed, Embase, Medline Ovid and Cochrane Central) from inception through October 2021 was performed. The search terms used included: “surfactant” OR “poractant” OR “curosurf” OR “lung surfactant”, AND “minimally invasive procedure” OR “catheter” OR “feeding tube” OR “less invasive surfactant administration” OR “noninvasive” OR “non-invasive” OR “lisa” OR “mist”, AND “low-birth-weight” OR “low-birth weight” OR “preterm” OR “premature” OR “infant” OR “newborn”. Additional articles were identified by a manual search of the cited references. The Literature search strategy is provided in the online Supplementary Material.

Inclusion criteria

Titles were screened for relevance and duplications. Studies were selected if they focused on human preterm neonates (<28 days of life, born <37 GA) with RDS and need for surfactant according to the criteria of the study. Randomized controlled trials (RCTs) and quasi-randomized controlled trials (qRCT) evaluating surfactant administration via tracheal catheter with or without the use of sedative drugs (including analgesics, sedatives, anesthetics, and any type of drug to improve comfort) were selected for comparison of outcomes. LISA/Minimally Invasive Surfactant Therapy (MIST) procedure could be performed with flexible or semi-rigid catheter, with or without Magill’s forceps, with or without the use of videolaryngoscopy. Studies whose original aim was to compare LISA/MIST versus surfactant administration via INSURE/endotracheal intubation or versus

conventional treatment (intubation and surfactant with delayed extubation or only non-invasive ventilation) were included as well. Observational studies with a prospective or retrospective designs were also eligible for inclusion. Letters to Editors/Commentaries, case series, unpublished studies (e.g., conference abstracts) and animal studies were excluded. In addition, studies including populations of mixed age groups were excluded unless they provided sub-group data for neonates under 28 days of age and born less than 37 weeks GA, or those resident within the neonatal unit. Abstracts for which full texts were unavailable and those published in non-English literature were excluded. In the case of included abstract but full text unavailable authors' were contacted directly by the reviewers.

Outcomes

The primary outcomes were success at first attempt of trachea catheterization, the need for early intubation (rescue intubation during the procedure or within 2 hours from LISA), and the duration of LISA procedure (in seconds). Secondary outcomes included the need for nasal intermittent positive pressure ventilation (nIPPV) during the procedure, rate of IMV in the first 24 and 72 hours, and the incidence of side effects (oxygen desaturation, bradycardia, apnea, hypotension).

Data extraction and synthesis

Two authors independently extracted data in pairs. In case of any conflicts, a third reviewer was consulted. RCTs and observational studies with an intervention and comparator arm were synthesized in a pairwise meta-analysis. A random effects model was used to pool the data. Mantel Haenszel method was used for the synthesis of dichotomous outcomes and an inverse variance method was utilized for pooling of continuous outcomes. Heterogeneity was evaluated with Cochran Q, I^2 and τ^2 values. The effect estimates were depicted in forest plots as risk ratio (RR) with 95% confidence interval (95% CI). For the proportion-based meta-analysis of observational studies and single arms of RCTs, raw data, logit transformed data or Freeman-Tukey double arcsine

transformation was used as appropriate. Inverse variance method was utilized to pool the data in proportion-based meta-analysis. R-software (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis.

Risk of bias (RoB) and Certainty of evidence (CoE)

Risk of bias (RoB) was performed using RoB version 2.0 for the RCT[26] and Risk Of Bias In Non-randomized Studies-of Intervention (ROBINS-I)[27] for non-randomized studies with an intervention and comparator arm. RoB was not ascertained for studies included in the proportion based meta-analysis. Certainty of evidence (CoE) was evaluated based on the GRADE working group recommendation[28]. CoE assessment was not feasible for the effect estimates of proportion-based meta-analysis.

RESULTS

A total of 670 studies were assessed for full text extraction after the removal of 294 duplicates. Of the full texts evaluated, 637 were excluded due to valid reasons and 33 studies were included in the final synthesis (**Table 1**). **Figure 1** shows the PRISMA flow diagram. One RCT[29] and two observational studies[30,31] with an intervention and comparator arm were analyzed in a pairwise meta-analysis. Nineteen single arms of RCTs[5,6,32-34,37,40-42,44,45,47-53,56] and 11 observational studies[16,17,20,35,36,38,39,43,46,54,55] were analyzed in a proportion-based meta-analysis for the various outcomes. One study was available only as protocol and abstract at the time of the analysis, therefore it was not included[13]. The characteristics of the included studies are given in **Table 1.**

Pair-wise meta-analysis

Primary outcomes

Meta-analysis of observational studies[30,31] indicated that the chance of successful endotracheal catheterization at the first attempt was similar in LISA with sedatives compared to LISA without sedatives [RR 95% CI: 0.94 (0.87; 1.02); CoE: Very low] (**Figure 2**).

The analysis of the RCT[29] and the pooled estimate from the observational studies[30,31] did not reveal any statistically significant difference in early intubation when LISA was performed with or without sedatives [RCT: RR 95% CI: 0.21 (0.03; 1.83); CoE: Very low; OS: RR 95% CI: 2.52 (0.50; 12.79); CoE: Very low] (**Figure 3A and 3B**).

Time to completion of the procedure did not show any statistically significant difference between the sedation and the no-sedation groups, as evaluated in the RCT[29] [Mean difference (MD) (95% CI): -11 (-90 to 67) seconds; CoE: Low] and in the observational study[30] [MD 95% CI: -60 (-178; 58) seconds; CoE: Very low] (**Figure 4A and 4B**).

Secondary outcomes

Pooled estimates from two observational studies[30,31] indicated that the risk of apnea might be statistically higher in the LISA sedation group when compared to the no-sedation group [RR 95% CI: 3.13 (1.35; 7.24); CoE: Very low] **(Figure 5A).**

The requirement of nIPPV during LISA procedure was higher in LISA with sedatives when compared to LISA without sedatives [RCT[29]: RR 95% CI: 1.97 (1.38; 2.81); CoE: Low; OS[31]: RR 95% CI: 2.96 (1.46; 6.00); CoE: Very low] **(Figure 5B and 5C).**

The RCT[29] and the pooled results from observational studies[30,31] did not shown an increased risk of bradycardia [RCT: RR 95% CI: 1.50 (0.55; 4.06); CoE: Low; OS: RR 95% CI: 0.57 (0.24; 1.36); CoE: Very low] when sedation was used with LISA when compared to no sedation.

For the outcome desaturation, whilst there was increased risk in the LISA sedation group when compared to the no-sedation group in the RCT[29] [RR 95% CI: 1.30 (1.03; 1.65); CoE: Low], similar findings were not evident from the observational study[31] [RR 95% CI: 1.35 (0.92; 1.97); CoE: Very low].

The risk of hypotension was similar during LISA with and without sedatives [RCT[29]: RR 95% CI: 2.55 (0.62; 10.46); CoE: Low; OS[30]: RR 95% CI: 1.18 (0.24; 5.87); CoE: Very low] These outcomes are summarized in **Figure 6.**

There was no difference in the risk of IMV within 24 hours in the LISA sedation group when compared to the no-sedation group [RCT[29]: RR 95% CI: 1.43 (0.58; 3.55); CoE: Low; OS[30,31]: RR 95% CI: 1.48 (0.94; 2.33); CoE: Very low] (**Supplemental Figure S1).**

For the outcome need for IMV within 72 hours only proportion-based meta-analysis could be performed.

Proportion-based meta-analysis

Proportion-based meta-analysis of single arms of RCTs[5,6,33,37,40-42,45,46,48,49,53,56] and observational studies[17,20,30,31,38,55] showed no statistically significant differences between LISA conducted with sedation and without sedation for the primary outcome successful endotracheal catheterization at first attempt. Pooled estimate indicated that 86% (80%-90%) of the neonates who were instituted LISA had successful tracheal catheterization at first attempt (**Supplemental Figure S2).**

The need for early intubation did not differ between LISA with sedatives and LISA without sedatives from the proportion-based meta-analysis of studies[29-31,35,36,39,41,46,47,51]. Seven percent (3%-11%) of the neonates instituted LISA with or without sedation required early intubation (**Supplemental Figure S3).**

Time to completion of the procedure did not show any statistically significant difference between the sedation and the no-sedation groups[20,29,30,35,36,42] (**Supplemental Figure S4).**

There were no sub-group differences between LISA with sedation (ketamine, propofol, fentanyl, multiple drugs analyzed together, and rescue sedation) and LISA without sedation for the outcome IMV within 72 hours. The overall rate of IMV requirement within 72 hours in the whole LISA group was 25% (19%-31%)[5,6,16,17,20,31-37,39-41,43-49,51-55] **(Supplemental Figure S5).**

RoB and CoE assessment

The only RCT[29] included in this systematic review and for the pair-wise meta-analysis had 'some concerns' for the domain 'deviation from intended intervention' as some randomized neonates were subsequently excluded from the analysis. Further, the domain of 'missing outcome data' was assessed as having a high risk as unequal number of participants' data were missing from the final analysis and the reasons for this were not the same between the groups. It is likely that missingness depended on the true value. Hence, an overall high risk of bias was adjudged for this RCT. The observational studies[30,31] were scored as having serious risks of bias as there was serious risk of confounding for one study and serious risk of confounding, selection and selective reporting for the other study. The RoB table is given in **Supplementary Table S1.**

CoE for most of the outcomes from the RCT and observational studies was very low to low. The summary of findings table and the reasons for downgrading the level of evidence are given in **Tables 2 and 3.**

DISCUSSION

The use of sedative drugs to improve the quality of the procedure and to decrease the distress of the newborn during LISA is an important topic of debate where currently no consensus has been achieved. The American Academy of Pediatrics[57] and groups of European neonatologists[58] recommend that for non-emergency intubations, premedication including analgesia and sedatives should be used. Similarly, the 2019 RDS European Consensus Guidelines consider "good practice to avoid discomfort during elective intubation by using a sedative or analgesic"[4]. A summary of the most used sedative and analgesic drugs in neonatology with their properties and potential side effects is given in **Supplementary Table S2.**

LISA implies the insertion of a laryngoscope and possibly the use of a Magill forceps. Both these actions are considered painful and distressing[59], and can be complicated by adverse events like apnoea, bradycardia[60], chest-wall rigidity and crying. Consequences may also include failed

attempts at tracheal catheterization and a potential increase of the intracranial pressure with impaired cerebral venous return and risk for intraventricular haemorrhage[61,62]. Nevertheless, the thin catheter delivery of surfactant relies on the baby's spontaneous breathing on CPAP to enhance surfactant distribution, which might be easily depressed by the use of sedative drugs[63], increasing the risk of apnoea and the need for rescue intubation during the procedure. For this latter reason, infants treated with LISA receive about 30% less analgesics and/or sedatives than infants receiving surfactant via ETT[64], and most surveys conducted so far show that around 50% of neonatologists perform the first LISA attempt without sedation[14,64-71] (**Supplementary Table S3**). However, the opinion of many authors is that sedation performed by expert neonatologists with pharmacological knowledge should be used to ensure patients' comfort and reduce the risk of acute responses induced by awake laryngoscopy[63,72].

Proper use of sedative drugs for LISA should reduce discomfort while maintaining good balance between sedation and self-ventilation. Drug properties should ideally include a rapid onset, a very short duration of action, and no suppression of spontaneous breathing with an overall short- and long-term safety profile. From a developmental pharmacological perspective, it seems almost impossible to find the suitable drug to sedate preterm neonates adequately for a short period of time. The premature infant's body composition, that contains about 90% of water, warrants relatively higher doses to reach an adequate plasma level for most water-soluble drugs, whereas drug clearance is known to be extremely low over the first day of life, because of low urinary excretion and low activity of drug metabolizing enzymes. Consequently, safe short-acting drugs may act as long-lasting medicines with side effects.

In most studies using sedative drugs for LISA, either low dose propofol[29,30,39] or a combination of atropine and ketamine was administered[35]. Interestingly, promising sedative drugs capable of maintaining spontaneous breathing with less risk of respiratory depression, like dexmedetomidine, are still underexplored for this purpose.

The results of our meta-analysis indicate with low CoE that sedation for LISA might not affect the duration of the procedure, when compared to LISA without sedation. However, this outcome may be influenced by the experience of the proceduralists, who were highly variable among the included studies ranging from expert neonatologists to pediatric residents. In the study by de Kort et al.[38], in fact, the success rate was significantly correlated with quality of technical conditions and experience of the performer. In our review, the CoE was very low for the other primary outcomes of success at first attempt of catheterization of the trachea and requirement of early intubation, thus precluding any reasonable conclusions.

The results of our meta-analysis also show that LISA performed with sedative drugs may provoke an increased risk for desaturation and requirement for nIPPV during the procedure, with the CoE being low. The risk of apnea was also higher in the LISA sedation group, but the CoE was very low. Hence, the evidence for this outcome is also uncertain. Whether the use of caffeine as a pre-medication along with the routinely utilized drug atropine[35,38,47,48,51] prior to LISA procedure would reduce many of these short-term adverse events needs to be evaluated in future trials.

Other adverse short-term and medium-term outcomes which might be considered severe, such as bradycardia, hypotension and need for mechanical ventilation, were similar in the LISA sedation group when compared to the no-sedation group, as evaluated in our meta-analysis.

The RCT[29] and one of the two observational studies[30] with the intervention and comparator arms included in our review indicate that low dose propofol (1 mg/kg) may reduce the COMFORTneo score compared to “awake” administration of surfactant during LISA. However, this benefit was obtained at expenses of major risks of desaturation and need for nIPPV in both studies.

It should be considered that the highly variable pharmacokinetics and -dynamics among preterm neonates, especially in the first days of life, may affect the response to sedatives and explain why in some cases, despite their use, the infants may not receive sufficient comfort[35]. It is probable that procedural sedation and analgesia for these infants should be based on an individualized, tailored approach rather than a standardized one[23].

Our review and meta-analysis highlight the uncertainty of evidence for many of the outcomes due to paucity of studies on the use of sedation for LISA. Further dose finding trials and adequately powered multi-center RCTs comparing LISA with and without sedative drugs with robust study designs are warranted. These trials should explore the effect of no sedation versus the use of sedatives, anesthetics or analgesics and evaluate possible effect modifiers of these drugs, such as gestational age, different dosages, timing of caffeine administration and use of atropine. Minimization might be an appropriate strategy to evaluate these in large multi-center trials. Further, the personnel involved in the trials needs to have comparable expertise in the LISA procedure. Finally, the trials should be adequately powered to assess long-term neurodevelopmental outcomes including motor and cognitive functions.

At the time of writing, one systematic review on the topic was published with similar findings on most of the included outcomes (eight studies, 945 infants)[73], and there were four ongoing trials on use of sedation for LISA, of which one compares propofol versus placebo[74,75], one the use of ketamine vs fentanyl[76], one ketamine vs placebo[77], and one fentanyl along with atropine versus placebo[78]. Two currently recruiting Italian studies aim to assess stress during surfactant administration by cortisol concentration in preterm infants receiving or not remifentanil for LISA or INSURE[79], or fentanyl for LISA[80]. These studies will provide further precious information on the best sedation strategy for non-invasive surfactant administration.

Our review has its limitations. Due to paucity of studies evaluating this PICOST, we performed proportion-based meta-analyses for some of the outcomes with an aim to study indirect comparisons. However, there are no clear recommendations for CoE assessment of results derived from such analysis, which lacks control groups and can only provide the estimate of the proportion of events with the intervention. Further, this review predisposes for selective reporting bias. Finally, there was significant heterogeneity between studies on the type of non-pharmacological measures instituted in the control arm.

CONCLUSION

The use of sedative drugs for LISA in preterm neonates with RDS might be associated with an increased risk of desaturation and requirement of nIPPV, without an effect on duration of the procedure, risk of bradycardia, hypotension and requirement of mechanical ventilation. The evidence is very uncertain for most of the other outcomes due to very low CoE. Multi-center RCTs with robust study designs are warranted to compare short and long-term outcomes of LISA when performed with or without sedative drugs. It is probable, however, that procedural sedation and analgesia for preterm infants should be individualized.

Data availability statement

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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FIGURE LEGEND

Figure 1. PRISMA flow diagram.

Figure 2. Pair-wise meta-analysis for the outcome 'Successful catheterization of trachea at first attempt'.

Figure 3. Figure 3A and 3B: Pair-wise meta-analysis of RCT and of observational studies for the outcome ‘Early intubation during or within 2 hours of LISA’.

Figure 4A and 4B. Forest plots for the outcome ‘Time to completion of the procedure’ from the RCTs and observational studies.

Figure 5. Figure 5A: Pair-wise meta-analysis of observational studies for the outcome ‘Apnea during LISA’; **Figure 5B and 5C:** Pair-wise meta-analysis of RCT and observational studies for the outcome ‘Requirement of nasal intermittent positive pressure ventilation during LISA’.

Figure 6. Pair-wise meta-analysis of RCT and observational studies for the outcomes ‘Bradycardia’, ‘Desaturation’, and ‘Hypotension’.