LISA: does mild sedation increase the risk of intervention due to loss of respiratory drive? A systematic review

Less invasive surfactant administration (LISA) has become the preferred way to administer surfactant to neonates. However, discussion is still ongoing on whether sedation is required, particularly to preterm neonates. This paper is a review of the literature and evidence on sedation versus non-sedation for LISA.

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Keywords

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Key points

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1. There are no current guidelines on the use of sedation for LISA. As a result of sedation, preterm infants could become apnoeic, bradycardic, and may consequently require positive pressure ventilation.
2. Preterm infants administered sedation who become apnoeic, may require intubation and mechanical ventilation.

In the past, infants with respiratory distress syndrome (RDS) were mechanically ventilated (MV) and administered surfactant via endotracheal tube.[1] However, it has been shown that prolonged periods of MV or positive pressure ventilation (PPV) in neonates increases risk of bronchopulmonary dysplasia, pneumothorax and intra-ventricular haemorrhage (IVH), especially in the preterm infant.[2,3] Following Verder et al's[4] introduction of a "less invasive" technique to administer surfactant called INSURE in the 1990s,[5] an even less invasive technique was introduced, known as less invasive or minimally invasive surfactant administration (LISA).[6,7] During LISA, the spontaneously breathing infant on non-invasive respiratory support is delivered surfactant via a thin catheter passed through the vocal cords. It works to reduce the need for intubation and ventilation.[7,8]

LISA involves use of a laryngoscope to place the catheter between the vocal cords. Previous neonatal studies have determined that awake laryngoscopy is distressing and painful. Therefore, sedation is often used to comfort the patient during the procedure. Sedation is also used to reduce adverse events associated with pain, such as raised intercranial pressure, which can lead to IVH.[9,10] However, it is also evidenced that with sedation, apnoea and bradycardia can result and lead to requirement for invasive ventilation, thus defeating the purpose.

Before LISA is carried out, clinical condition, gestation and age in hours will be considered.[10-12]

This systematic review will analyse the literature and evidence surrounding LISA for the preterm infant, with or without sedation.

Methods

Search strategies

The PICO (Population, Intervention, Comparator and Outcomes) tool was used to identify components of clinical evidence for this systematic review. PICO is also recommended by the Cochrane Collaboration of Systematic Reviews.[13]

Nine electronic databases, including the Cochrane Library, Medline, EMBASE, CINAHL, PUBMED, Academic Search Index, Science Citation Index, clinicaltrials.gov and Google Scholar were searched from the year 2012 up until 20th September 2022.

The first search strategy was ("Neonates requiring LISA" OR Neonates OR Respiratory distress OR RDS OR Neonate* OR NICU OR neonatal intensive care unit OR newborn OR intensive care Preterm infants OR Premat* OR newborn OR baby OR babies OR Respiratory distress syndrome OR RDS OR surfactant OR Less invasive surfactant OR LISA) AND (Sedation OR Intravenous fentanyl OR IV fentanyl OR Intravenous propofol OR IV propofol OR intravenous morphine OR IV morphine OR sedation OR analgesia OR pre medication) AND (Non-sedation, comfort care) The papers found from Search A were initially examined. However, there were a large number of records, so the terms (Apnoea* OR loss of respiratory

drive OR Intervention Or Intubation OR Failure OR Bradycardia) were searched secondly then added to the first search with the Boolean operator AND to get the final results from the data base search.
A search was carried out on the National Institute for Health and Care Excellence (NICE) 2022[14] and the British Association of Perinatal Medicine (BAPM) 2021 websites.[15] Reference lists of all key papers were also manually searched.

Eligibility criteria

This systematic review included all quantitative studies. Qualitative articles were excluded as data are immeasurable. Only peer-reviewed studies published in English were included, with a date restriction of 2012-2022. Only infants under 37 weeks' gestation who required LISA within the first 72 hours of life were included.

Study selection

Of 119 articles identified, only 15 were eligible after title and abstracts were analysed and duplicates removed. Of these 15 papers, only eight studies were included after the inclusion/exclusion criteria had been applied. All of the studies used the quantitative research paradigm and were evaluated using the CASP checklist.[16]

Analysis

Design of studies

The majority of studies identified were cohort studies, four being prospective[11,19,21,22] and two retrospective.[17,18] Only two studies were randomised controlled trials (RCTs).[20,23]

Study population statistics and sample size

The number of infants included in the studies ranged from 29 to 495. Only two studies used a population of over 100.[21,22] All were receiving some form of non-invasive respiratory support with an oxygen requirement as part of their inclusion criteria.[11,17-23] All those included were classed as preterm with the gestational age ranging from 24^{+0} to 36^{+6} weeks, giving a median gestational age of 30^{+5} weeks. Nevertheless, only one study observed infants over 34^{+0} weeks gestation[17] thus giving a two week upper age limit that would affect confidence intervals. If infants over 34^{+0} weeks were excluded, the mean gestational age would become 29^{+0} weeks, which is important to consider as analgesics/sedatives prior to LISA can increase the rate of apnoea and decreased blood oxygenation, especially in the preterm infant.[5] In view of the wide gestational age, the range of weights was also considerably varied from 635-2,350g, giving an overall mean weight of 1,493g. This is also important to consider, as drugs like fentanyl, that rapidly distribute into muscle, remain in the plasma compartment for longer if the percentage of fat and muscle mass is lower.[24] Both these factors are more pronounced in the premature neonate.[25]

Outcomes measured

All of the studies in this review[11,17-23] measure the incidence of intubation during LISA, however, only four of them[11,18,19,22] considered this as the primary outcome. Vital parameters during LISA were only measured as secondary outcomes in seven out of the eight studies.[11,17-21,23] Pain scores were measured in four studies[17,19,20,23] as primary outcomes, two of these were RCTs.[18,23] Only two studies[19,23] considered mortality rates. The incidence of IVH, NEC, PDA were measured in five studies,[19-23] with four of these[19,22] including the incidence of retinopathy of prematurity (ROP) and four studies[18,21] including the incidence of pulmonary haemorrhage and pneumothorax.

Sedation vs non-sedation in LISA

Three studies used ketamine as their sedation drug.[18,19,22] Two used propofol[17,20] and one used fentanyl.[23] The large multicentre study[21] used a combination of medications including ketamine, propofol, fentanyl, midazolam, phenobarbital, sufentanil and thiopental, depending on the unit and its protocol. The volume of sedation administered also varied, with dosage depending on level of activity. Four studies compared use of sedation with a control group that did not receive sedation.[17,20,21,23] Three of the studies did not have a control group, observing LISA under sedation only.[18,19,22] The remaining study observed LISA under no sedation.[11] Ketamine was the preferred method of sedation used in three studies.[18,19,22] It has rapid onset and peak effect, followed by a relatively short duration of action. However, it is also known as a potent anaesthetic that has received minimal study in neonates.[25] Propofol was used in two studies.[17,20] It has a rapid onset and recovery.[26] Propofol is known to affect blood pressure.[25-27] One study used fentanyl, which again has a rapid onset and shorter duration of action. However, clearance is substantially prolonged in the preterm or critically ill neonate.[27] One study[21] used mixed sedation methods, including propofol and ketamine, with ketamine being the main sedative. Despite extensive research, the optimal approach to assessment, nonpharmacologic care, and pharmacotherapy remains vague in the neonatal setting.[28] The remaining study[11] did not use any sedation for LISA. However, they did use nonpharmacological methods of analgesia such as swaddling, containment holding or sucrose. Only two of the other studies[17,11,23] mention that they used nonpharmacological methods of analgesia. Evidence suggests nonpharmacological methods are effective and easily applied.[29]

Discussion

This literature review was conducted to determine whether use of sedation during LISA increases the risk of intervention and intubation due to apnoea and loss of respiratory drive. Dekker et al's RCT[17] was the first to be conducted on the use of sedation with LISA and was carried out in view of their previous retrospective study two years prior. Results show that more infants required intubation in the non-sedated group compared to sedated. However, it also showed that more infants in the sedated group needed intervention with PPV compared to the non-sedated group.

Although a single RCT is unlikely to prove causality, randomisation reduces bias and provides a rigorous tool to examine cause-effect relationships between intervention and outcome.[30,31] However, the results of this and Sk et al's[23] RCT may not be a reliable source, as the primary outcomes for both studies assessed COMFORT score and not rate of intervention or intubation during LISA. In Sk et al's RCT, only one of the fentanyl group was intubated during LISA, while none of the infants were intubated in the non-fentanyl group. The rate of intubation within the first 72 hours was similar in both groups and no data were provided as to whether PPV was used.

The rates of intubation being required following LISA with the two prospective studies only using sedation were similar. Bronte et al's[22] intubation rates were not

Author Year Citation	Study design	Study group statistics receiving LISA	Intervention	Primary and secondary outcomes	Key findings
Dekker et al (2016)[17]	Retrospective cohort study	n=38 26^{+0}-36^{+6} weeks' gestation	Group 1 (n=23) received propofol during LISA Group 2 (n=15) no sedation during LISA	Primary outcome: COMFORT (pain assessment) score during LISA Secondary outcomes: vital parameters during LISA, the need of PPV, the incidence of intubation	COMFORT score during LISA: 56% sedated vs 11% non-sedated (p<0.05) Mean length of desaturation higher in the sedated group 2-4 minutes vs 0-2 minutes non-sedated (p<0.01) 33% of the non-sedated, required PVV vs 100% sedated 2 infants sedated required intubation vs 0 non-sedated **Risks for validity and bias** Sample size small Individual carrying out LISA and NICU nurse assessing the COMFORT score were not blinded
Descamps et al (2017)[18]	Retrospective cohort study	n=35 24^{+0}-33^{+0} weeks' gestation	All (n=35) received sedation of ketamine	Primary outcomes: failure rate of procedure and the incidence of intubation Secondary outcomes: vital parameters during LISA	5 (14%) failed LISA attempts with 7 (20%) of 35 infants needing intubation for the second surfactant dose. Desaturation below 85% noted in 21 cases but reported as 100%. 4 (17%) experienced bradycardia and 3 (14%) had low mean blood pressure during the procedure. **Risks for validity and bias** Inaccurate true percentages reflected Small sample size No specific statistics mentioned
Bourgoin et al (2018)[19]	Prospective cohort study	n=29 27^{+0}-33^{+1} weeks' gestation	All (n=29) received sedation of ketamine	Primary outcomes: FANS score during LISA and the incidence of intubation with sedation Secondary outcomes: vital parameters during LISA, number of attempts at LISA, incidence of NEC, IVH, ROP, outcomes at discharge and mortality	56% scored a FANS score of <4 after ketamine. 41% were intubated immediately, or within 72 hours post LISA. Rate of desaturation and apnoea 52%, Cannula used to deliver PPV instead of face mask. **Risks for validity and bias** No control group Participants show regret bias when stating use of PVV instead of cannula to improve quality outcome. Small study sample
Dekker et al (2018)[20]	Randomised controlled trial	n=78 27^{+5}-32^{+0} weeks' gestation	Group 1 (n=42) received propofol during LISA Group 2 (n=36) no sedation during LISA	Primary outcome: COMFORT score during LISA Secondary outcomes: vital parameters during LISA, the need of PPV, the incidence of intubation, IVH, pneumothorax, pulmonary hemorrhage and mortality	COMFORT score lower for sedated 76% vs 22% non-sedated (p<0.001) Length of desaturations for sedated 91% vs 69% non-sedated (p=0.023) Heart rate significantly lower in both groups before and after the procedure. In sedated, difference in HR was greater before, during and after LISA compared with the non-sedated group (p=0.002) 93% in the sedated group needed PPV during LISA vs 47% non-sedated (p<0.001) Only one infant in the sedated group was intubated, compared to four infants non-sedated 2% vs 11% (p=0.175) No significant difference in incidences of IVH, pneumothorax, pulmonary hemorrhage and mortality between groups **Risks for validity and bias** Individual carrying out LISA not blinded, may have intervened earlier with the sedated group affecting rates of PPV

TABLE 1 Key: FANS=Faceless Acute Neonatal Pain Score; NEC=necrotising enterocolitis; IVH=intraventricular haemorrhage; ROP=retinopathy of prematurity; PPV=positive pressure ventilation; R-PIPP=revised premature infant pain profile.

Author Year Citation	Study design	Study group statistics receiving LISA	Intervention	Primary and secondary outcomes	Key findings
De Kort, et al (2019)[11]	Prospective cohort study	n=86 26+6-32+0 weeks gestation	LISA performed with no sedation for all (n=86) infants Vital parameters only recorded for (n=37)	Primary outcomes: assess success rates, technical quality and vital parameters during LISA without sedative premedication Secondary outcomes: quality of technical conditions, vital parameters	LISA successful at the first attempt in 45 (52%) patients. In 32 (37%) patients, 2 attempts were required and in 9 (11%) patients, 3 attempts were needed 34% quality of technical conditions was inadequate Vital parameters only measured in 37 infants. Desaturations below 80% in 68%, with good quality conditions (47%) of patients with unacceptable quality p = 0.30 **Risks for validity and bias** The individual carrying out LISA not blinded No control group Data missing, not all vital parameters recorded
Krajewski et al (2020)[21]	Prospective cohort study	n=495 27^{+0}-33^{+1} weeks' gestation	Group 1 (n=102) received a form of sedation/ analgesia Group 2 (n=393-14) no sedation, however 14 received sublingual glucose for comfort	Primary outcomes: assess the safety of sedation/ premedication and their impact on easing the LISA procedure Secondary outcomes: vital parameters during LISA, the need of PPV, the incidence of intubation, IVH, pneumothorax pulmonary hemorrhage and mortality	Non-premedicated infants had the lowest maturity and the lowest birth weight. Premedication was more likely to be used by neonatal trainees 51 (47.7%) infants received ketamine Monotherapy was strongly predominant over polytherapy (98 vs 9 patients), with midazolam and sublingual 30% glucose being the second and third most frequent single agents 2 (2.3%) of the sedated group required intubation compared to 4 (1%) of the non-sedated group Desaturation rates between groups showed statistical difference Apnoea was more common in the sedated group 9.1 vs 2.6% (p= 0.009) **Risks for validity and bias** Large sample size could affect confidence intervals Different variety of sedation/analgesia used in study which could affect confounding variables
Brotelande et al (2021)[22]	Prospective cohort study	n=114 26^{+6}-29^{+0} weeks' gestation	108 received ketamine, while 6 received both ketamine and propofol	Primary outcomes: the incidence of intubation with sedation Secondary outcomes: baseline vital parameters before LISA, the need of PPV, IVH, NEC, ROP and mortality	Intubation rate not significantly different: 10 (19%) in the ketamine group and 10 (16%) in the propofol group MV required in 22 (42%) given ketamine and 21 (34%) patients given propofol (p=0.44) Baseline vital parameters before LISA in both groups are statistically similar. Incidence of PVV, IVH, NEC, ROP and mortality are all statistically similar **Risk of validity and bias** Individuals carrying out LISA not blinded, may have intervened earlier with the sedated group affecting rates of PPV No vital parameters measured during LISA
Sk et al (2022)[23]	Randomised controlled trial	n=34 28^{+0}-33^{+6} weeks' gestation	Group 1&3 (n=17) received fentanyl during LISA Group 2&4 (n=17) no sedation during LISA	Primary outcomes: R-PIPP score during LISA Secondary outcomes: vital parameters, the need for PPV, the incidence of intubation, IVH, NEC, significant PDA and mortality	Percentage with R-PIPP score <12 during LISA higher in the fentanyl group compared with the placebo group 88% vs 47% (p=0.025) Vital signs showed no statistical difference One of the fentanyl group was intubated during LISA, while none were intubated in the non-fentanyl group Rate of intubation in first 72 hours similar in both groups. No difference observed in PDA, IVH, NEC or duration of non-invasive ventilation days. **Risks for validity and bias** The individual carrying out LISA not blinded, may have intervened earlier with the sedated group affecting rates of PPV Small study size

significantly different between the ketamine and propofol group and MV was required by 38% in the overall study, but no data regarding PPV rates were given.

In Bourgoin et al's[19] study, 41% of infants were intubated immediately, or within 72 hours post LISA. In Decamps et al[18] retrospective study, which used ketamine on all subjects, only 20% of infants needed intubation within the first hour. However, there are no data on rate of intubation after one hour or the incidence of PPV. Dekker et al's[17] retrospective study noted that 33% of the non-sedated group required PVV compared to 100% in the sedated group due to apnoea and desaturation; 5% in the sedation group required intubation. No infants in the non-sedated group required intubation.

Krajewski et al's[21] large prospective study showed 2.3% of the sedated group required intubation compared to 1% of the non-sedated group. De Kort et al's[11] non sedation approach study noted that LISA was successful in all infants. However, there are missing data and no further information to inform whether any of the subjects required intubation after the procedure.

The results of this systematic review show that intubation rates are not particularly different between groups. However, results do show the likelihood of infants requiring intervention with PPV is significantly higher in sedated infants. Nevertheless, the majority of the studies analysed were retrospective[17,18] and prospective[11,19,21,22] cohort studies. There are limitations with cohort studies as there is no randomisation to the subgroups of interest, hence cause and effect relationships cannot be determined, and relationships between variables must be stated as associations that may or may not be influenced by confounding factors.[32,33]

Conclusion

After extensively examining all of the literature, there is no evidence to support whether to give or withold sedation in the preterm neonate requiring LISA.

It is difficult to provide strong, conclusive, evidence-based recommendations as to which gestation a neonate requires premedication, and the risks associated with and without sedation during LISA.

Additional studies are needed to look at this question specifically, ensuring more RCTs with a wider sample size and adequate blinding that will impact and guide future practice.

References

1. **Sweet DG, Carnielli V, Greisen G, et al**. European consensus guidelines on the management of respiratory distress. Neonatology 2019;115:432-50.
2. **Naseh A, Batool Ghorbani Yekta**. INSURE method (INtubation-SURfactant-Extubation) in early and late premature neonates with respiratory distress: factors affecting the outcome and survival rate. INSURE method (INtubation-SURfactant-Extubation) in early and late premature neonates with respiratory distress: factors affecting the outcome and survival rate. Turk J Pediatr 2014; 56:232-37.
3. **Keszler M, Sant'Anna G**. Mechanical ventilation and bronchopulmonary dysplasia. Clin Perinatol 2015;42:781-96.
4. **Verder H, Robertson B, Greisen G et al**. Surfactant Therapy and Nasal Continuous Positive Airway Pressure for Newborns with Respiratory Distress Syndrome. NEJM 1994;331:1051-55.
5. **Ng EH, Shah V**. Guidelines for surfactant replacement therapy in neonates. Paediatrics & Child Health 2021;26:35-41.
6. **Kribs A, Pillekamp F, Hunseler C et al**. Early administration of surfactant in spontaneous breathing with nCPAP: feasibility and outcome in extremely premature infants (postmenstrual age >27 weeks). Pediatric Anesthesia 2007;17:364-69.
7. **Bugter IA, Janssen LC, Dieleman J et al**. Introduction of less invasive surfactant administration (LISA), impact on diagnostic and therapeutic procedures in early life: A historical cohort study. BMC Pediatrics 2020;20:6-12.
8. **Herting E, Härtel C, Göpel W**. Less Invasive Surfactant Administration (LISA): Chances and limitations. Arch Dis Child Fetal Neonatal Ed 2019;104:665-59.
9. **Pareek P, Deshpande S, Suryawanshi P et al**. Less Invasive Surfactant Administration (LISA) vs. Intubation Surfactant Extubation (InSurE) in Preterm Infants with Respiratory Distress Syndrome: A Pilot Randomized Controlled Trial. J Trop Pediatr 2021;67(4).
10. **Ancora G, Lago P, Garetti E et al**. Evidence-based clinical guidelines on analgesia and sedation in newborn infants undergoing assisted ventilation and endotracheal intubation. Acta Paediatrica 2018;108:208-17.
11. **De Kort E, Kusters S, Niemarkt H et al**. Quality Assessment and response to less invasive surfactant administration (LISA) without sedation. Pediatric Research 2019;87:125-30.
12. **Beh A, Taylor E, Reynolds P**. Even less invasive: refinement of the LISA procedure improves success with less sedation. Infant 2018;15:1-3.
13. **Higgins JPT, Green S**. Cochrane Handbook for Systematic Reviews of Interventions. Chisester: Wiley-Blackwell; 2011.
14. **National Institute for Health and Care Excellence** 2022. NICE, The National Institute for Health and Care Excellence. [online] NICE. www.nice.org.uk
15. **BAPM.** 2020. British Association of Perinatal Medicine. [online] www.bapm.org
16. **Critical Appraisal Skills Programme**. CASP Checklists [Internet]. CASP. CASP; 2018. Available from: https://casp-uk.net/casp-tools-checklists.
17. **Dekker J, Lopriore E, Rijken M et al**. Sedation during Minimal Invasive Surfactant Therapy in Preterm Infants. Neonatology 2016;109:308-13.
18. **Descamps CS, Chevallier M, Ego A et al**. Propofol for sedation during less invasive surfactant administration in preterm infants. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2017;102:F465-5.
19. **Bourgoin L, Caeymaex L, Decobert F et al**. Administering atropine and ketamine before less invasive surfactant administration resulted in low pain scores in a prospective study of premature neonates. Acta Paediatrica 2018;107:1184-90.
20. **Dekker J, Lopriore E, van Zanten HA et al**. Sedation during minimal invasive surfactant therapy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2018;fetalneonatal-2018-315015.
21. **Krajewski P, Szpecht D, Hozejowski R**. Premedication practices for less invasive surfactant administration – results from a nationwide cohort study. J Matern Fetal Neonatal Med 2020;1-5.
22. **Brotelande C, Milési C, Combes C et al**. Premedication with ketamine or propofol for less invasive surfactant administration (LISA): observational study in the delivery room. Eur J Pediatr 2021;180(9):3053-58
23. **Sk H, Saha B, Mukherjee S, Hazra A**. Premedication with Fentanyl for Less Invasive Surfactant Application (LISA): A Randomized Controlled Trial. J Trop Pediatr 2022;68:fmac019.
24. **Allegaert K, Verbesselt R, Naulaers G et al**. Developmental pharmacology: Neonates are not just small adults. Acta Clinica Belgica 2007;63: 522-30.
25. **McPherson C, Ortinau CM, Vesoulis Z**. Practical approaches to sedation and analgesia in the newborn. J Perinatol 2020;41(3):383-95.
26. **Guaragni B, Howell A, Rehman FU et al**. Management of pain in ventilated neonates: current evidence. Paediatrics and Child Health 2014;24:32-37.
27. **Prins SA, Reiss IKM, Willemsen SP et al**. Propofol for endotracheal intubation in neonates: a dose-finding trial. Arch Dis Child Fetal Neonatal Ed 2020; 105:489-95.
28. **Carbajal R, Eriksson M, Courtois E, et al**. On behalf of the EUROPAIN survey Working Group. sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. Lancet Resp Med 2015;3:796-812.
29. **Queiros I, Moreira T, Pissarra R et al**. Non-pharmacological management of neonatal pain: a systematic review. Minerva Pediatr (Torino) 2023: 75(2):282-95
30. **Hassid S, Nicaise C, Michel F et al**. Randomized controlled trial of sevoflurane for intubation in neonates. Pediatric Anesthesia 2007;17:1053-58.
31. **Hariton E, Locascio JJ**. Randomised Controlled Trials - The Gold Standard for Effectiveness Research. BJOG 2018;125:1716.
32. **Norvell D**. Study types and bias – Don't judge a study by the abstract's conclusion alone. Evid Based Spine Care J 2010;1:7-10.
33. **Andrade C**. Research Design: Cohort Studies. Indian J Psychol Med 2022;44:105-06.