Analgosedation before Less Invasive Surfactant Administration: a systematic review

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Abstract

Background

Surfactant therapy is the cornerstone of respiratory distress syndrome management. “Less invasive surfactant administration (LISA)” is now recommended for spontaneously breathing preterm infants. Analgosedation remains controversial as 52% of European neonatologists don’t use any. This systematic review aims to describe the efficacy and safety of different drugs for analgosedation during LISA.

Methods

Medline via Ovid, Embase, Scopus and Cochrane Library of Trials were searched independently by 2 reviewers for studies on sedation or analgesia for LISA, without filters or limits.

Results

Eight studies (1 RCT) recruiting 945 infants were included. Infant pain was significantly reduced, with more infants evaluated as comfortable. Failure, defined as need for intubation or for a second dose of surfactant, was not different between sedated and unsedated groups. Analgosedation was associated with a higher occurrence of desaturation and need for positive pressure ventilation during procedure, but the need for mechanical ventilation within 24 or 72 hours of life was not significantly different. There does not seem to be any difference in clinical tolerance and complications (e.g. hypotension, mortality, air leaks…).

Procedural conditions were evaluated as good or excellent in 83% after sedation.

Discussion and conclusion

Analgesia or sedative drugs increase infant comfort and allow good procedural conditions, with a limited impact on the clinical evolution. Questions remain about best choice of drugs and dosage, with the constraint to maintain spontaneous breathing and have a rapid offset. Further

good quality studies are needed to provide additional evidence to supplement those limited existing data.

Introduction

Respiratory distress syndrome (RDS) remains a significant problem in preterm infants. Surfactant is the cornerstone of its management and its modes of administration have been extensively studied.

In recent years, alternatives to endotracheal intubation for surfactant administration have been developed, especially the "less invasive surfactant administration (LISA)" method. This involves the tracheal insertion of a small-diameter catheter to instil surfactant while the infant breathes spontaneously on nasal Continuous Positive Airway Pressure (nCPAP). Several studies and meta-analyses have demonstrated the effectiveness of this technique in reducing mechanical ventilation (MV), bronchopulmonary dysplasia (BPD) and mortality [1, 2]. In 2019, the European Consensus Guidelines on the Management of RDS updated its recommendations to state that "it is reasonable to recommend (LISA) as the optimal method of surfactant administration for spontaneously breathing infants who are stable on nCPAP" [3]. However, many questions remain and current studies still explore appropriate treatment thresholds for different gestational ages, ideal catheter/device for administration, or the suitable type of surfactant [4]. The issue of analgesia and sedation during the procedure also remains controversial [1, 4–6].

Prior to the 2000s, tracheal intubation was usually performed on awake neonates, despite several studies having revealed its association with deleterious physiological effects including bradycardia, hypertension and intracranial hypertension [7–9]. Premedication─attenuates physiological responses to intubation, shortens procedure time and makes it easier [9]. A 2001 consensus statement for prevention and management of pain in the newborn advised for premedication in non-emergent intubation [10].

Evolutions in practices include new endotracheal tubes, use of video-laryngoscopes and an emphasis on safe laryngoscopy [11]. Specifically in LISA, lower pressures on laryngotracheal structures from the small-bore catheter may also reduce its physiological impact.

Recent surveys revealed that at least 52% of neonatologists in Europe and 94% in US do not use analgosedation for LISA [12, 13]. Some centres have policies restricting drugs for specific indications (e.g. second attempt, more mature babies…) or individualized approach [4, 14]. Procedure performed early after vaginal birth benefit from endogenous analgesia related to high vasopressin levels [15]. A survey in Spain highlighted that all participants considered that sedative medications reduce experience of pain and discomfort and 54% believed that it improved procedural conditions and shortened the duration of the procedure [16]. Non-pharmacological measures for analgesia (sucrose, swaddling, environmental control,…) were used in all hospitals in Spain [16] and were preferred by 55% of physicians in the UK [17].

Specific conditions may explain high rates of awake laryngoscopy for LISA. An important limit is the need to maintain cardiorespiratory stability and to have a minimal impact on the respiratory drive centres. Spontaneous breathing is considered important during LISA procedure to assure the surfactant dispersion from the trachea and to allow the infant to stay on CPAP [5, 6]. The first large RCT, the Avoidance of Mechanical Ventilation study [18] investigating LISA allowed for sedation at the discretion of the caregiver. In supplementary material, they briefly reported that rates of failure in infants who were actually treated with LISA were higher when premedication was used. The populations were not further described. Thereafter most studies investigating the LISA were performed without systematic analgosedation, and it was still proved to be beneficial. Adding analgosedation could therefore potentially change the beneficial outcomes. Klotz et al. hypothesized that, compared to invasive intubation, LISA was perceived to be less traumatic or that the maintenance of spontaneous breathing was considered paramount [12].

The aim of this systematic review is to describe the efficacy and safety of different drugs regimen for analgosedation during less invasive administration surfactant (LISA).

Methods

1. Research protocol

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for meta-analysis in health care interventions [19].

The protocol was registered in advance of data extraction with the Prospective Register of Systematic Reviews (registered September, 2020; CRD42020205365).

The initial protocol was modified on 26 February 2021. The focus shifted to LISA rather than both LISA and INSURE because of important differences between these procedures and their physiology. In addition, retrospective studies were included for a broader over-view of practices.

2. Criteria of Eligibility

All clinical studies of LISA procedure after analgosedation were considered eligible.

We included randomised controlled trials (RCTs), prospective and retrospective cohorts published in English as well as in non-English language. In studies comparing LISA with another method of surfactant administration, the LISA arm was included if the procedure was performed after sedation.

Studies on animal models, review articles, editorials, comments and case reports were excluded.

3. Information sources and search strategy

Medline via Ovid, Embase, Scopus and Cochrane Library of Trials were searched between inception and July 26, 2021 without any language restriction, filter or limit. The search included Mesh/Emtree terms as well as free language. Search strategies are available in online supplementary material. Subsequently, Google Scholar was searched for grey literature. Reference lists of publications eligible for full-text review and systematic review about LISA procedure allowed for an additional "snowball search".

4. Selection process

Rayyan QCRI web app (rayyan.qcri.org) was used for a 2 steps study selection. After exclusion of duplicates, two reviewers independently screened titles and abstracts for potentially relevant studies.

Full texts were then independently reviewed for eligibility by two reviewers. Conflicts at any step of the selection process were resolved by a third reviewer.

5. Data extraction and analysis

Relevant data were independently extracted in predetermined tables by 2 reviewers. We extracted data about the reports, the study design, the population and the intervention. Authors were contacted for additional data, if necessary.

6. Data items

The selection and the importance rating of patient-oriented outcomes were determined in advance through discussion.

Main outcomes were procedure failure, defined by the intubation rate and/or the need of a second dose of surfactant, and infant's comfort or pain.

Secondary outcomes focused on clinical tolerance of the procedure: occurrence of desaturation $SpO_2 < 85\%$, bradycardia and hypotension (defined as a mean arterial blood pressure (MABP) in mmHg below the number of weeks of gestational age).

Respiratory outcomes and complications were also retrieved: air leaks, need for MV and duration thereof, oxygen therapy requirements and duration.

Markers of procedural conditions were analysed, namely duration of procedure and number of attempts of laryngoscopy or catheterization.

Finally, surrogate markers of immediate impact on the brain, specifically cerebral oxygenation and electrical cerebral activity, were searched.

7. Bias and quality assessment

Two independent authors evaluated the risk of bias (RoB) and assessed quality in individual studies using the Revised Cochrane Risk-of-Bias for randomised trials (RoB2) or the Newcastle Ottawa Scales (NOS) for cohort studies. For RCT, the following domains were assessed: randomisation process, deviation from intended intervention, missing outcome data, measurement of outcome and selection of reported results. For cohort studies, quality of selection, comparability and outcomes were evaluated.

Assessments are available in supplementary information.

8. Synthesis methods

Meta-analyses could not be undertaken given the limited number of RCT's and studies with comparative arms.

We detailed data in a predefined table, according to main and secondary outcomes of each study.

Results

1. Literature search and study selection

The search strategy produced 1555 records. After accounting for 452 duplicates, 1041 records were screened by title and abstract and led to explore 24 full-text articles. Eleven references met inclusion criteria. Three were duplicate publications (one scientific abstract and 2 protocols), leaving 8 studies for analysis (See PRISMA flowchart in Figure 1).

Nine ongoing studies were also referenced.

2. Study Characteristics

Characteristics of the included studies are summarised in Table 1.

Only one study was randomised and controlled [20]. Dekker et al. studied propofol versus no sedation during LISA, with infant comfort and pain as primary outcomes.

Two prospective studies were included [21, 22]. Bourgoin et al. [21] studied the impact of ketamine on technical conditions and pain scores during LISA, without comparison. Krajewski et al. [22] conducted a nationwide cohort study and compared analgesics and sedatives as ketamine, midazolam, propofol, sufentanil, morphine, thiopental, phenobarbital in mono or polytherapy to no analgosedation. Their main outcome was the safety of sedation by assessing the occurrence of pre-specified adverse events during LISA (surfactant reflux, need for rescue intubation, bradycardia, apnoea, desaturation).

Three retrospective observational studies were included [23–25]. All used propofol as sedative drug, in comparison once with ketamine [25] and once with no sedation [23], at the discretion of the caregiver. The third study [24] was a preliminary study without a comparative arm, prior to a multicentric RCT currently recruiting [26].

Finally, two RCT comparing INSURE (intubation-surfactant-extubation) and LISA with fentanyl [27] or ketamine [28] premedication were included. The LISA arms of those studies were assessed as prospective cohorts

All studies but one [22] were monocentric.

3. Patient characteristics

In total, 945 newborns were included, with study recruitments ranging from 24 to 500 infants (78 in the RCT). Three studies focused on extremely and very preterm infants [24, 25, 28], one on moderate and late preterm [27], while the 4 others included preterm infants of all gestational ages.

In the RCT by Dekker et al. [20] and in cohort studies by Dekker et al. [23] and Brotelande et al. [25], groups were matched in terms of gestational age (GA), birth weight (BW) and sex. Krajewski et al. [22] reported statistically significant differences in terms of GA and BW ($p<0,001$) with older and bigger infants in the analgosedation group.

4. RoB and quality assesment

The RoB of the RCT of Dekker and al. [20] was evaluated as low.

Quality of the cohort studies were assessed as good, excepted Krajewski [22] where differences between groups decreased their comparability. Assessments are summarized in Figure 2.

There was obviously no unsedated arm in the LISA vs INSURE studies. Two other studies didn’t have comparative arm either.

5. Outcomes analysis

Results of the systematic review are detailed in Table 2 and summarized in Figures 3 and 4.

RCT

Dekker et al. [20] found a significant reduction in the mean COMFORTneo score ($p<0,001$) and a higher proportion of infants evaluated as comfortable during the procedure ($p<0,001$) after propofol compared to no analgosedation. Intubation rates were not different between groups.

Among markers of clinical tolerance, a significantly higher incidence of desaturation ($p=0,023$) is described in the propofol group. Occurrence of hypotension and bradycardia did not differ between sedated and unsedated groups. More infants in the propofol group needed non-invasive positive pressure ventilation (PPV) during procedure ($p<0,001$). Incidence of pneumothorax, pulmonary haemorrhage, IVH ≥ 3 or mortality were not different. The number of attempts for catheter insertion and the total duration of procedure were comparable.

Cohort studies

Respiratory outcomes

Intubation during or within one or two hours of the procedure was often assessed as "failure" in studies. Its rates ranged from 2,3 to 24% [21–25], with no significant difference between sedated and unsedated groups [22, 23].

Need for MV within 24 hours was not different between awake and sedated infants [22, 23]. Brotelande et al. reported rates of 16 and 19% for propofol and ketamine groups respectively [25]. Intubation rate within 72 hours of life reached 21% after propofol [25], 18-41% in ketamine studies [21, 25, 28] and 29% after fentanyl analgosedation [27]. Four studies without an unsedated arm described second dose of surfactant requirements from 6,4 to 37,5%, irrespectively of the choice of drug used (ketamine [25, 28], propofol [24, 25] or fentanyl [27]). The duration of MV and oxygen therapy was reported in 3 [25, 27, 28] and 2 studies [27, 28]

respectively, but lack of awake comparative precluded further interpretation. Pneumothoraxes occurred in 0% in Bourgoin et al.[21], 3% in Berneau et al. [28] and 4% in Olivier et al. [27],

Comfort and pain

Three studies described infant comfort or pain with different scales [21, 23, 25]. Dekker reported a significant reduction in the COMFORTneo score with analgosedation [23]. Bourgoin et al. and Brotelande et al. evaluated pain with the Faceless Acute Neonatal Scale (FANS) score. Median scores were 1 to 2 [21, 25], when a score below 4 indicates comfort.

Clinical tolerance

Krajewski et al. reported for the analgosedation group a higher drop in oxygenation evaluated by changes in the SpO_2/FiO_2 ratio during LISA compared to baseline ($p < 0.001$) [22]. Procedural desaturation lasted significantly longer in the sedation group (p<0,001) in Dekker et al. [23]. Bradycardia did not occur more frequently in analgosedation groups [22, 23]. Hypotension has been reported in 3 retrospective studies [23–25] using propofol. Dekker found no difference between sedated and unsedated patients [23]. When comparing propofol and ketamine, comparable drops of MABP occurred but remained within physiological range [25]. Descamps et al. reported hypotension in 14% of cases, which were transient and self-resolving [24]. Incidence of apnoea and need for PPV during and immediately after procedure were significantly higher in sedated patients (p=0,009 and p<0,001) [22, 23]. Two cases of thoracic rigidity after fentanyl administration were reported [27]. Mortality rates before discharge ranged from 0 to 8% [21, 25, 28].

Technical conditions

Bourgoin et al. reported excellent or good quality in 83% of procedures after ketamine sedation [21], while in contrast Krajewski noted no significant difference in the difficulty of the procedure between the sedated and unsedated groups [22]. The duration of the procedure, as well as the number of attempts of catheter insertion were similar in both groups [22, 23, 25].

Long-term outcomes

Evidence regarding intermediate- or long-term outcomes of analgosedation during LISA remains limited. Few data on the comorbidities of prematurity (such as BPD, ROP, PDA, NEC, cPVL) are available [21, 25, 28]. These are detailed in Table 2.

No study described the impact of the procedure on cerebral oxygenation or electrical brain activity.

Discussion

This systematic review, including 1 RCT and 7 cohort studies addressing analgosedation during LISA procedure, highlighted that analgesic or sedative drugs increased infant comfort with a limited impact on the clinical evolution. A higher occurrence of desaturation and need of positive pressure ventilation during procedure were reported in the only RCT [20] and in two cohorts studies [22, 23]. Rates of intubation and need for MV were similar to the non-sedated arm when available. Caution is required when analysing this result. The largest prospective study described in this review reported a non-significant increase (2.3% from 1%) of treatment failure with analgosedation even if exposed infants had a GA that was two weeks higher (31 4/7 vs 29 5/7) [22].

Included studies can be compared to LISA studies without sedation reporting on populations with similar mean GA (29-31 weeks) [29–31]. These studies reported rates for MV at 72 hours of life of 22-34%, comparable to those from analgosedation studies. The higher rate of intubations in Bourgoin et al. (41% in which 7/19 infants were intubated before LISA for apnoea or insufficient sedation) could be explained by high cumulative doses of ketamine (mean 1,8 ± 0,9 mg/kg). The need for additional doses of surfactant was not higher than in comparative studies (22-40%) [29–31]. Other clinical outcomes such as comorbidities of prematurity don’t seem influenced by analgosedation.

Up to now, the balance between long term impact of the potential pain from brief laryngoscopy and the potential long-term impact of medication remain unknown. Prolonged use of opioids or benzodiazepine over a week is associated with an increased risk of abnormal neurodevelopmental outcome at 2 years [32]. Even if analgosedation improves infant comfort, the question of the most effective drug remains. The ideal drug would suppress pain and discomfort, while maintaining cardiorespiratory stability and having a minimal impact on the respiratory drive. Moreover, it would allow a rapid onset and offset and be safe in long-term [6, 14, 33]. To optimise the effect of the chosen drug, the time interval before procedure varies according to its pharmacokinetics properties.

Multiple drugs have been studied for analgesia or sedation during LISA. Surveys revealed that the most common choices of premedication were opioids (23-63%), followed by propofol (5-23%), benzodiazepines (5-23%), ketamine (9%), and, surprisingly, muscle relaxants, either as mono or polytherapies [12, 16, 17, 34].

Fentanyl is the most commonly used opioid in NICU practice. It has analgesic, sedative and anaesthetic properties that are 50 to 100 times more potent than morphine [35]. It has a rapid onset of action and minimal effect on hemodynamic [35]. Remifentanil is another synthetic opioid with very rapid onset and offset of action [7, 9]. Both carry a risk of thoracic rigidity with rapid injection, which may limit their use [7, 9, 27]. Naloxone, their antagonist, could attenuate the respiratory drive depression generated by opioids. It had been used by Elmekkawi et al. to facilitated extubation in INSURE procedure with high efficacity and no adverse effects [36].

Propofol, used by Dekker, Brotelande and Descamps, is a purely sedative drug without specific analgesic effects. It is a common premedication for neonatal intubation or INSURE and still enable procedural pain control [37]. Propofol has a rapid onset with a short duration of action. It reduces airway reactivity and muscle tone in the upper respiratory tract [7]. It has

been associated with bradycardia, desaturations, and prolonged hypotension in neonates [9, 38], whereas the included studies reported limited incidence of those side effects. A recent RCT comparing propofol and atracurium-sufentanil for nasotracheal intubation of children reporting no difference in risk of neurodevelopmental delay at two-year follow-up [39].

Bourgoin, Brotelande and Berneau studied ketamine, which has both sedative and analgesic properties [5, 40]. It has rapid onset of action, short duration of action and relatively safe respiratory and hemodynamic profiles [40].

Benzodiazepines, most commonly midazolam, were reported in the prospective study from Krajewski et al, and are often been reported in surveys [12, 16, 34]. They have minor analgesic effect, along with potential respiratory depression and neurotoxicity and therefore could not be recommended [38, 41].

Non pharmacological measures to reduce pain have also been reported [5, 16, 17]. Oral sucrose or glucose, known to provide analgesia during minor neonatal procedures [38, 42], was reported by 18-20% of physicians [16, 17].

Postural control and swaddling have been widely used during procedure. They have shown variable effectiveness in reducing pain and stress behavioural pain responses associated with painful procedures [38, 43]. It is clear that other effective non-pharmacological measures including rocking/holding, skin-to-skin, breastfeeding could not be used during LISA procedure.

Technical conditions are often good or excellent with analgosedation. De Kort et al. studied quality and response to LISA without sedation and found a low success rate of the first attempt (52%) and frequently inadequate technical quality (41%) [44]. However, these results may also reflect a lack of experience, as suggested by 72% of first attempt successes for neonatologists [44].

This systematic literature research provides an overview of the premedication used for sedation for LISA with several methodological strengths. According to a predefined protocol registered in PROSPERO, we searched 4 databases with indexing terms as well as grey literature. There were no limitations for inclusion in terms of language or study design to complement the findings of RCTs and provide evidence based on real-world data. Some limitations remain. Different designs and inhomogeneity of the studies precluded the realisation of a meta-analysis. Second, most of the included studied did not have a comparative arm. While we compared their result with those of recent studies comparing LISA to INSURE, we could not control for unavoidable differences (such as population, technical conditions, type of surfactant used…). Moreover, the lack of study specifically designed for respiratory outcomes and the possibility that existing studies were underpowered to assess these outcomes should be taken into account when interpreting these results.

The representativeness of the population might be an issue, as extremely premature infants were under-represented despite the extensive use of LISA in this age group. Adverse effects of analgosedation for these infants may be different or even more important.

Finally, many studies are ongoing, as detailed in additional data. Seven are RCT using fentanyl, ketamine, remifentanil or propofol as analgosedative drugs. Study outcomes are very diverse. LISA limits the evaluation of facial expression and, regardless of pain, induces oxygen desaturation and sometimes bradycardia, therefore limiting the effectiveness of common pain scales. Milesi et al. developed the Faceless Acute Neonatal Scale (FANS) for use when the neonate's face is hidden by respiratory devices [45], but this scale also includes heart rate variations and oxygen desaturation. Other studies will compare sedation impact on stress, oxygenation changes and oxidative damage and cerebral oxygenation.

Conclusion

LISA without analgosedation improves clinical outcomes, but has the disadvantage of awake laryngoscopy. Concerns regarding analgosedation include respiratory depression, risk of failure and potential loss of benefits reported without it.

A significantly pain reduction with analgosedation was described in the only RCT addressing the question. Except for higher risks of oxygen desaturation and more positive pressure ventilation during procedure, clinical outcomes were not different. Observational studies also reported reduction in pain at the expend of a high procedural rate of desaturation, apnoea and ventilation.

Many questions remain about best drugs, optimal dosages and long-term impact of these drugs, but those questions are not resolved for intubation either.

Nine ongoing studies should provide welcome additional evidence to supplement the limited existing data.

Acknowledgment

Statement of Ethics

The research was conducted ethically in accordance with the Declaration of Helsinki ethical principles. The paper is exempt from ethical committee approval. All data were collected and synthesised from previous clinical trials for which informed consent had already been obtained by the trial investigators.

The protocol was registered in advance of data extraction with the Prospective Register of Systematic Reviews (registered September, 2020; CRD42020205365).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

ST, NH and DS contributed to the search strategy, data selection and analysis. ST drafted and revised the manuscript. CL cooperate to the revision of the draft. VR helped with data interpretation, writing and editing of the manuscript. All authors reviewed and approved the manuscript.

Data Availability Statement

All data generated or analysed are included in this article and its supplementary material. Further enquiries can be directed to the corresponding author.

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Figure legends

Fig. 1. Flow diagram of study selection.

Fig. 2. Risk of bias and quality assessment using RoB2 (Cochrane) and the Newcastle-Ottawa Scale respectively.

Fig. 3. Main outcomes: intubation rates and comfort and pain scores.

Fig. 4. Trends of sedation during LISA: a summary (the results of the RCT appear in bold).

Table 1. Features of included studies.

	Study	N	Study population (Intervention/Control)	Intervention vs control	Inclusion criteria	Exclusion criteria	Main outcomes	Secondary outcomes
RCT	**Dekker 2019** [20] Monocentric	78	- n: 42/36 - mean ±SD BW (g): 1475±575/ 1502± 606 (p=0,837) - median (IQR) GA (weeks): 29^{+0} (27^{+5}-32^{+0}) vs 29^{+0} (28^{+0}-31^{+0}) (p=0,731) - male sex (%): 62/56 (p=0,647)	**Propofol** 1 mg/kg IV (+ caffeine) versus **no sedation** (+ caffeine)	- GA 26-36^{+6} weeks - RDS and need for surfactant (FiO_2 > 0,3 and PEEP ≥ 8 cmH_2O)	- imminent need of intubation because of respiratory insufficiency (apnoea/acidosis) - pneumothorax - pulmonary haemorrhage	Stress and comfort (COMFORTneo-score <14)	- occurrence of PPV - intubation rate (within 24h) - number of catheterisation attempts - duration of procedure - during procedure: desaturation, hypotension, bradycardia, nasal haemorrhage - pneumothorax - pulmonary haemorrhage - resuscitation - IVH ≥ 3 - death
Prospective studies	**Bourgoin 2018** [21] Monocentric	29	- median (IQR) BW (g): 1290 (945-1600) - median (IQR) GA (weeks): 29,6 (28,6-30,9)	**Ketamine** IV (titration by 0,5 mg/kg steps (3 to 5 min) – max 3 mg/kg – median: 1,5 mg/kg + atropine 15 mcg/kg + caffeine citrate 20 mg/kg	- GA 27-36 weeks - need for first surfactant administration (FiO_2 > 0,25 if < 30 weeks or > 0,3 if > 30 weeks)	- need for emergency intubation - hypercapnia (> 65 mmHg) - pneumothorax - hypotension (MABP < wGA)- capillary refill time > 3 sec - apnoea requiring bag-mask ventilation before start	Technical conditions (scale based on jaw relaxation, vocal cords opening, movement during catheter insertion and coughing) Pain scores with FANS score	- vital signs: HR, SpO_2, MBP/3 min, SpO_2 nadir, HR nadir and occurrence of SpO_2 < 80% - occurrence of apnoea ± intubation - number of laryngoscopy attempts - LISA duration - short term efficacy: need of second surfactant and intubation within 72 hours - pneumothorax - selective administration - mortality, BPD, IVH, NEC, ROP
	Krajewski 2020 [22] Multicentric	500	- n: 88/393 - mean ±SD GA (weeks): 31,6 ± 2,4/ 29,7 ± 2,7 (p<0,001) - mean ±SD BW (g): 1749 ± 570/1332± 512 (p<0,001)	**Any analgesics/ sedatives in mono or polytherapy** (ketamine, thiopental, midazolam, propofol, morphine, sufentanil, phenobarbital) versus **no sedation** **At discretion of the caregiver**	- RDS treated by LISA		Safety: occurrence of pre-specified adverse events during LISA (reflux, need for rescue intubation, bradycardia, apnoea, O_2 desaturation)	- changes in oxygenation status (SpO_2/FiO_2) - need for MV at < 24h of life - difficulty of procedure - number of catheterisation attempts

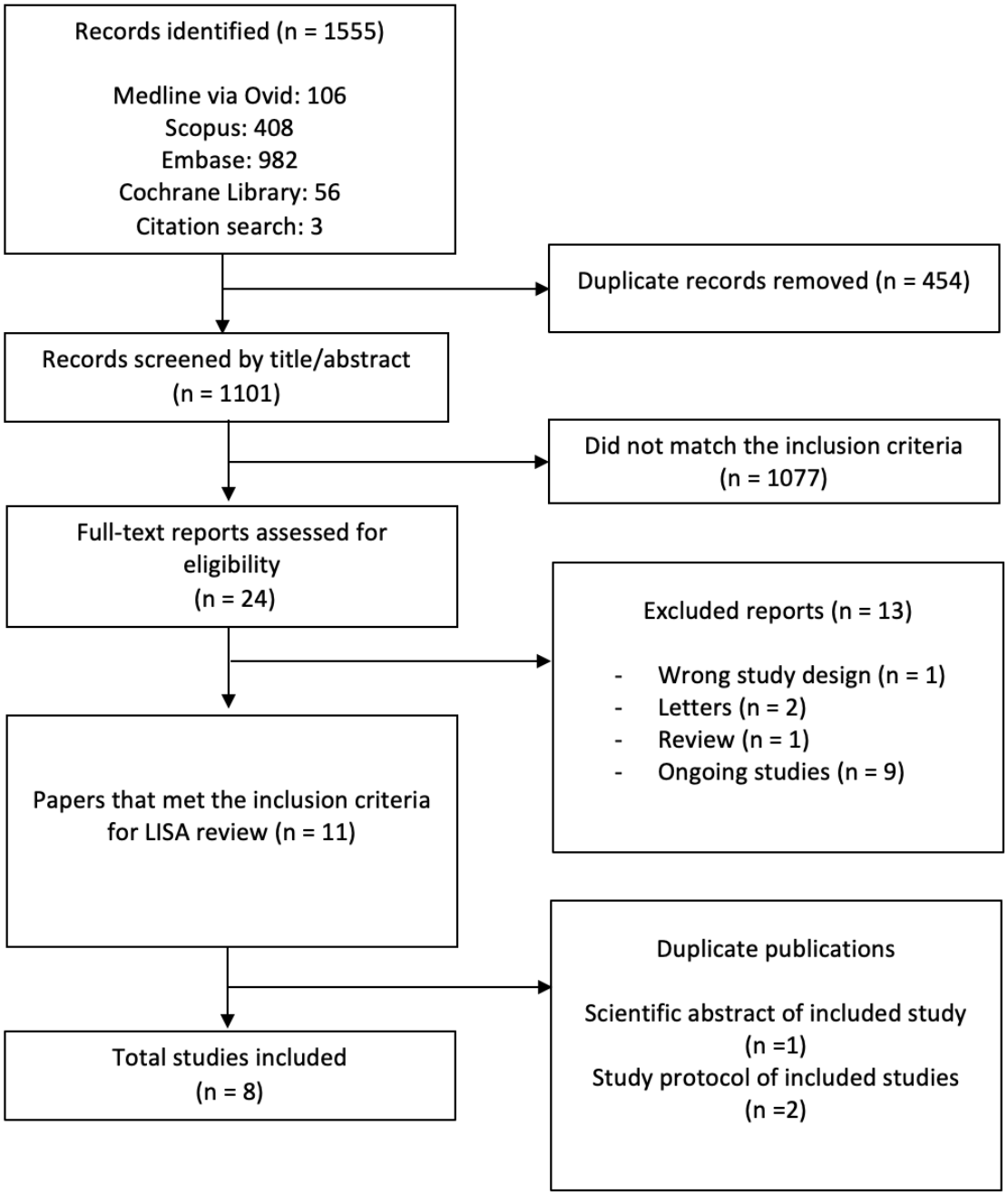
Retrospective studies	**Dekker 2016** [23] Monocentric	38	- n: 23/15 - mean ±SD BW (g): 1312±483/1469±588 - mean ±SD GA (weeks): 29±2 /29±3 - male sex (%): 61/73	**Propofol** 1 mg/kg IV (+ sucrose 24%) versus **no sedation** **At discretion of the caregiver**	- GA 26-36^{+6} weeks - need for first surfactant (FiO_2 > 0,3 and PEEP ≥ 8 cmH_2O)	- imminent need of intubation because of respiratory insufficiency (apnoea/acidosis)	Stress and comfort (COMFORTneo-score <14)	- need of PPV - intubation rate (within 24h) - during procedure: desaturation, hypotension, bradycardia (HR < 80/min)
	Descamps 2017 [24] Monocentric	35	- mean (range) BW (g): 1334 (635-2350) - mean (range) GA (weeks): 29,5 (24-33)	**Propofol** IV (titration started at 0,5 mg/kg - mean dose:1,5 mg/kg) + atropine 10 mcg/kg	- GA 24-33 weeks		Failure of procedure: need for intubation during the hour after the onset of LISA	Clinical tolerance: - HR < 80/min - hypotension - SpO_2 < 85%
	Brotelande 2021 [25] Monocentric	114	- n: 62/52 - median (IQR) BW (g): 950 (825-1140)/ 897 (780- 1150) (p=0,36) - median (IQR) GA (weeks): 27,4 (26,4-28,7)/ 27,8 (26,4-28,6) (p=0,96) - male sex (%): 50/62 (p=0,26)	**Propofol** 1 mg/kg IV versus **Ketamine** 0,5 mg/kg IV (second dose if necessary) **At discretion of the caregiver**	- GA < 30 weeks - need for first surfactant for RDS (PEEP 6 cmH_2O, Silverman-Anderson score >3 and FiO_2 > 0,3 if ≤ 26 weeks or FiO_2 > 0,4 if 27-30 weeks) - spontaneous breathing - available intravenous line	- imminent need for intubation	Failure of procedure: intubation for apnoea or need for a second dose of surfactant within 2 hours following the procedure	- need for MV within 24 and 72 h - procedure tolerance - mortality and morbidity at 36 weeks GA - duration of invasive and non-invasive ventilation - neonatal comfort (FANS) - drug tolerance - cardiorespiratory parameters (HR, FiO_2, MABP)
LISA arm of LISA vs INSURE studies	**Olivier 2017** [27] Multicentric	24	- mean GA (weeks): $34^{0/7}$± 1,4 - mean ±SD BW (g): 2157 ± 487 - male sex (%): 42	**Fentanyl** 1 mcg/kg IV + atropine 20 mcg/kg	- GA of $32^{0/7}$-$36^{6/7}$ weeks - PEEP 6 cmH_20 and FiO_2 > 35% for SpO_2 ≥ 90%	- lethal conditions or congenital malformations - intubation or pneumothorax prior to enrolment	- need for MV or pneumothorax (chest tube insertion) within 3 days. - respiratory failure: respiratory acidosis < 7,2 or pCO_2> 70 mmHg or non-improvement of FiO_2 in the 4 hours	- number of laryngoscopy attempts - adverse events (surfactant reflux, desaturations) - age at surfactant administration - duration of MV, NIV and O_2
	Berneau 2018 [28] Monocentric	127	- median (IQR) GA (weeks): 28,1 (27,0-29,2) - median (IQR) BW (g): 1045 (832-1238) - male sex (%): 53,5	**Ketamine** 0,5 mg/kg IV (repeat once if necessary) + atropine 20 mcg/kg	- GA < 30 weeks - spontaneously breathing infants on PEEP 5-6 cmH_2O who need surfactant	- congenital malformations - outborn patients	- failure: need of second dose of surfactant or intubation - survival without moderate to severe BPD - number of days on MV - age at O_2 withdrawal	- pneumothorax - IVH 3 or 4, cPVL - PDA needing surgical closure - surgery for NEC - late onset sepsis - ROP

RDS: respiratory distress syndrome – MV: mechanical ventilation – NIV: non-invasive ventilation – PPV: positive pressure ventilation – GA: gestational age – HR: heart rate – MBP: mean blood pressure - BPD: bronchopulmonary dysplasia – IVH: intraventricular haemorrhage – NEC: necrotising enterocolitis – ROP: retinopathy of prematurity – PDA: patent ductus arteriosus – cPVL: cystic periventricular leukomalacia

Table 2. Main results of included studies.

	Study	Intervention vs control	Main outcomes	Secondary outcomes
RCT	**Dekker 2019** [20] Monocentric N = 78	**Propofol** 1 mg/kg IV (+ sucrose 24%) versus **no sedation** (+ sucrose 24%)	Stress and comfort (COMFORTneo-score <14): 76 vs 22% (p<0,001) - mean ± SD COMFORTneo score: 12±3 vs 17±4 (p<0,001)	- occurrence of nasal PPV during and immediately after procedure: more frequent (93 vs 47% (p<0,001)) but no longer (median (IQR): 7 (3-21) vs 6 (3-12) min (p=0,274)) - intubation rate: 2 vs 11% (p=0,175) during procedure – similar in the first 24h (24 vs 17% (p=0,576)) - number of attempts: no difference (p=0,982) - duration of procedure: no difference (p=0,641) - during procedure: • desaturation: higher - 91 vs 69% (p=0,023) • MBP, hypotension, bradycardia: no difference • difference in HR between the periods before, during and after procedure higher (p=0,002) - pneumothorax: 7 vs 3% (p=0,620) - pulmonary haemorrhage: 2 vs 0% (p=1) - resuscitation, IVH ≥ III, death: no difference
Prospective studies	**Bourgoin 2018** [21] Monocentric N = 29	**Ketamine** IV (titration by 0,5 mg/kg steps (3 to 5 min) – max: 3 mg/kg – median: 1,5 mg/kg + atropine 15 mcg/kg + caffeine citrate 20 mg/kg	- technical conditions: 83% excellent or good quality - pain FANS score: median (IQR) 2 (2-4) with 56% score < 4 (norm recommended before intubation= 3) - intubation for sedation failure: 7%	- vital signs (median (IQR)): • HR nadir: 150 (133-160) bpm • SpO_2 nadir: 50 (33-72)% • patients SpO2 < 80% > 60 sec: 59% - occurrence of apnoea: 52% (15) - intubation rate: 41% (24% immediately + 17% within 72h) - number of laryngoscopies: median (IQR) 1(1-3) - LISA duration (min): median (IQR) 7 (4-13) - selective administration: none - pneumothorax, mortality, IVH, NEC: none - BPD: 10% - ROP: 3,4%
	Krajewski 2020 [22] Multicentric N = 500	**Any analgesics/ sedatives in mono or polytherapy** (ketamine, thiopental, midazolam, propofol, morphine, sufentanil, phenobarbital) versus **no sedation** **At discretion of the caregiver**	- occurrence of pre-specified adverse events during LISA: • reflux: 21,6 vs 17,6% (NS) • need for rescue intubation: 2,3 vs 1% (NS) • bradycardia: 3,4 vs 4,3% (NS) • apnoea: 9,1 vs 2,6% (p = 0,009) • O_2 desaturation: 28,4 vs 21,2% (NS) - changes in oxygenation status ($\Delta SpO_2/FiO_2$) during-before LISA: -55± 62 vs -32± 50 (p<0,001) - need for mechanical ventilation at < 24 h of life: 20,5 vs 14,3% (NS)	- difficulty of procedure: easy/very easy in 65,9 vs 69,1% (NS) - number of attempts of catheter insertion: median (IQR) 1 (1-1) vs 1 (1-1) (NS)

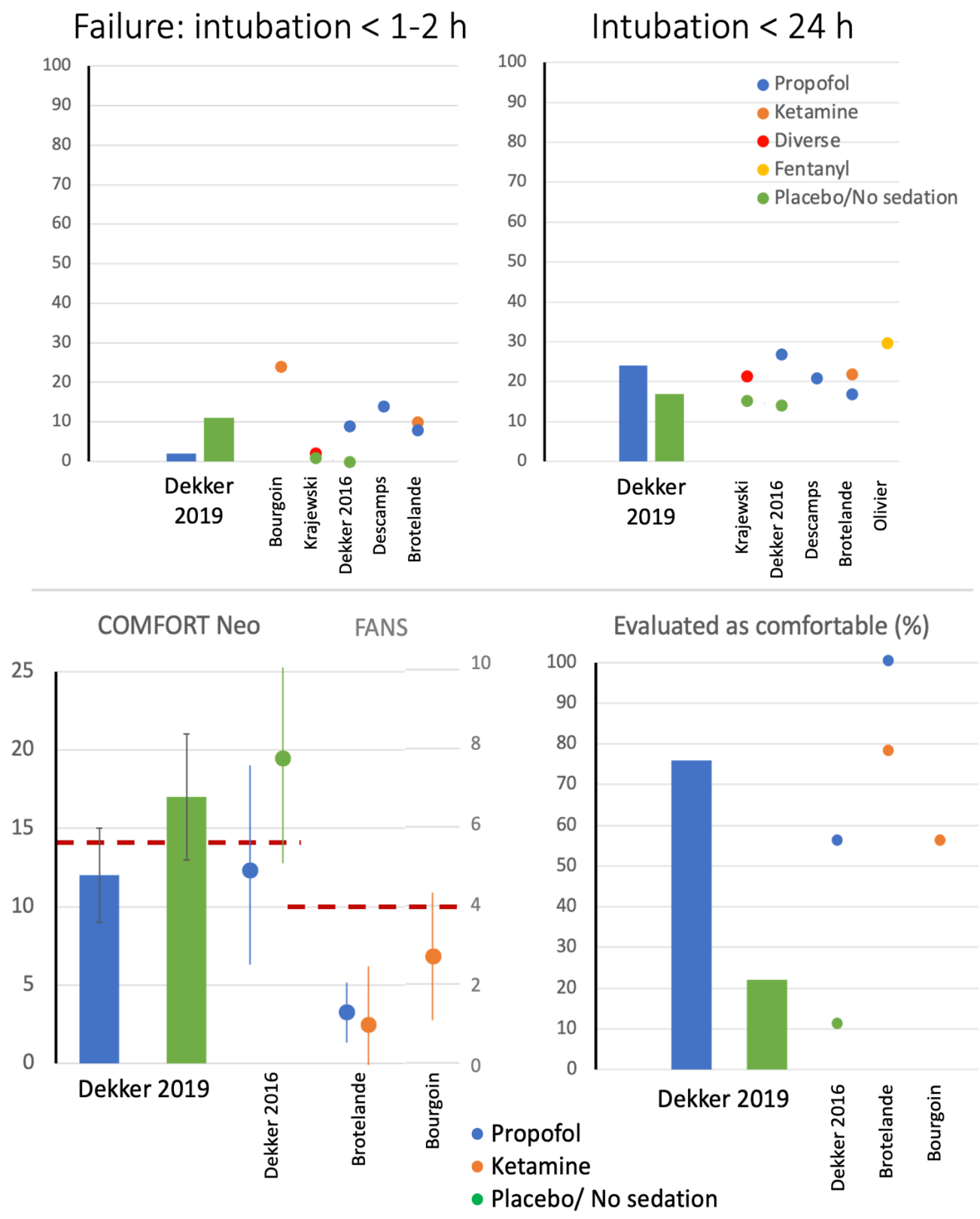
Retrospective studies	**Dekker 2016** [23] Monocentric N = 38	**Propofol** 1 mg/kg IV (+ sucrose 24%) versus **no sedation** **At discretion of the caregiver**	Stress and comfort (COMFORTneo-score): - same before and after - lower during procedure (median (IQR) 12 (9-17) vs 20 (15-23) - "comfortable score" (<14) during procedure: 56 vs 11% (p<0,05))	- need for PPV: 100% vs 33% (p<0,001) - intubation during procedure (for catheterization failure): 9 vs 0% (ns) - intubation rate within 24h: 26 vs 13% (ns) - duration of procedure (min): no difference - median (IQR) 2 (2-4) vs 3 (2-7) - during procedure: • duration (min) of SpO_2 <80% (median (IQR)): 3 (2-4) vs 1 (0-2) (p<0,01) • hypotension and bradycardia (HR < 80/min): no difference
	Descamps 2017 [24] Monocentric N = 35	**Propofol** IV (titration started at 0,5 mg/kg-mean dose:1,5 mg/kg) + atropine 10 mcg/kg	- failure (intubation during the hour after the onset of LISA): 14% - intubation for second dose of surfactant with MV maintained: 20%	- clinical tolerance: • HR < 80/min: 17% • hypotension: 14% • SpO2 < 85%: 100%
	Brotelande 2021 [25] Monocentric N = 77	**Propofol** 1 mg/kg IV versus **Ketamine** 0,5 mg/kg IV (repeat once if necessary) **At discretion of the caregiver**	Failure of procedure: - intubation for apnoea or need for a second dose of surfactant within 2 hours following the procedure): no difference (8% for propofol vs 10% for ketamine) - second dose of surfactant: 16 vs 19% (NS)	- need for MV within 24 and 72 h: no difference (16 and 21% for propofol vs 19 and 29% for ketamine) - procedure duration (min): median (IQR) 3,2 (2,8-3,6) vs 3,5 (3,1-4,0) - mortality (5 vs 8%) and morbidity (BDP moderate/severe (32 vs 35%), IVH III or IV (5 vs 3%), NEC (3 vs 2%), focal intestinal perforation (3 vs 12%), ROP (7 vs 6%), CPVL 3 or 4 (0 vs 0%)) - duration of MV (h): median (IQR) 96 (24-172) versus 150 (72-216) (p=0,1)) - duration of NIV (h): median (IQR) 1128 (912-1536) vs 1092 (792-1368) (p=0,27) - procedural pain (FANS): median (IQR) 1 (1-2) vs 1 (0-2) (p=0,61) - cardiorespiratory parameters: HR, FiO2 and MABP comparable
LISA arm of LISA vs INSURE studies	**Olivier 2017** [27] Multicentric N = 127	**Fentanyl** 1 mcg/kg IV + atropine 20 mcg/kg	- need for MV: 29% (7/24 – 2 for thoracic rigidity and 5 for non-improvement after MIST) - need for two or more doses of surfactant: 37,5% - pneumothorax requiring chest tube insertion within 3 days: 4% (1/24) - respiratory failure (pH < 7,2 and pCO_2> 70 mmHg or ↑ FiO_2): none	- number of laryngoscopy attempts: mean (± SD) 2,3±1,2 - adverse events: • surfactant reflux: 66% (direct vision by laryngoscopy) • desaturations: 58% moderate and 42% severe - duration of MV (days): median (IQR) 2,9 (1,2-4,0) - duration of NIV (days): median (IQR) 4,2 (2,8-5,4) - duration of oxygen administration (days): median (IQR) 2,4 (1,9-2,8)
	Berneau 2018 [28] Monocentric N = 24	**Ketamine** 0,5 mg/kg IV (repeat once if necessary) + atropine 20 mcg/kg	- failure: • need for second or more dose of surfactant or intubation: 6,4% • need for MV at 72 h: 18,1% - survival without moderate to severe BPD: 86,5% • mortality rate: 5,56% • BPD: no 63%, II or III 8,47% - number of days on MV: median (IQR) 0,0 (0,0-5) - postnatal age at O_2 weaning (weeks): 34,3 (31,6-36,7)	- air leak: 3,17% - IVH 3 or 4: no result - cPVL: 3,94% - surgical closure of PDA: 8,73% (all PDA: 27%) - surgery for NEC: 3,2% - late onset sepsis: 26,6% - ROP: no result


Records identified (n = 1555)
Medline via Ovid: 106
Scopus: 408
Embase: 982
Cochrane Library: 56
Citation search: 3
Duplicate records removed (n = 454)
Records screened by title/abstract (n = 1101)
Did not match the inclusion criteria (n = 1077)
Full-text reports assessed for eligibility (n = 24)
Excluded reports (n = 13)
- Wrong study design (n = 1)
- Letters (n = 2)
- Review (n = 1)
- Ongoing studies (n = 9)
Papers that met the inclusion criteria for LISA review (n = 11)
Duplicate publications
Scientific abstract of included study (n =1)
Study protocol of included studies (n =2)
Total studies included (n = 8)

	Dekker 2019 [20]
Randomisation process	+
Deviations from the intended intervention	+
Missing outcome data	+
Measurement of the outcome	+
Selection of the reported result	+
	Low

		Bourgoin 2018 [21]	Krajewski 2020 [22]	Dekker 2016 [23]	Descamps 2017 [24]	Brotelande 2021 [25]	Olivier 2017 [27]	Berneau 2018 [28]
A	**Selection**							
	Representativeness of the exposed cohort	+	+	+	+	+	+	+
	Selection of the non-exposed cohort	/	-	+	/	+	NA	NA
	Ascertainment of exposure	+	+	+	+	+	+	+
	Demonstration that outcome of interest was not present at start of study	+	+	+	+	+	+	+
B	**Comparability**							
	Comparability of cohorts on the gestational age	/	-	+	/	+	NA	NA
	Comparability of cohorts for any additional factor	/	-	+	/	+	NA	NA
C	**Outcome**							
	Assessment of outcome	+	+	+	+	+	+	+
	Was follow-up long enough for outcomes to occur (intubation, pain…)	+	+	+	+	+	+	+
	Adequacy of follow up of cohorts	+	+	+	+	+	+	+
TOTAL		6	6	9	6	9	6/6	6/6

Figure 3. Intubation rates and impact of analgosedation before LISA on comfort and pain scores

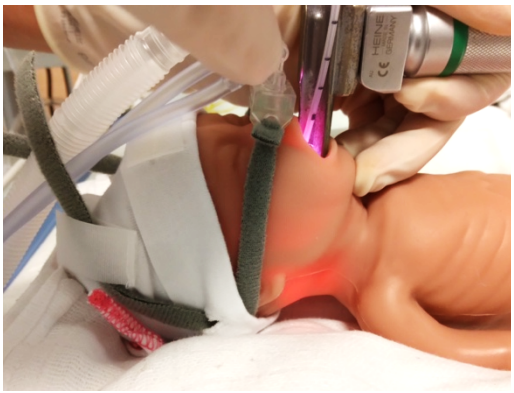


TRENDS OF SEDATION DURING LISA (the results of the RCT appear in bold)

Infant pain:
- **Significative reduction in scores**
- Comfortable in 56 to 100%

Procedural conditions:
- **No difference in number of attempts or duration of procedure**
- Excellent or good - easy

Respiratory outcomes:
- **Intubation:**
  - **< 1h: no difference**
  - **< 24h: no difference**
  - < 72h: same rates as in literature
- Need for second dose of surfactant: no difference
- **Air leaks: no difference**



Clinical tolerance:
- **Desaturation: ↑ incidence** and ↑ time of desaturation
- Larger drop in oxygenation
- **Apnoea: ↑ incidence**
- **Bradycardia: no difference**
- **Hypotension: no difference**
- **Need for PPV: ↑ occurrence, no difference of duration**
- Thoracic rigidity with fentanyl in 2/24

Long term (limited data):
- **Mortality: no difference**
- IVH, cPVL, BPD, ROP, PDA: no difference

Additional data: 1. Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 26, 2021>

Search Strategy:

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1 (infan* or Neonat* or Newborn* or Prematur* or Preterm or (low adj3 weight*)).ti,ab,kf. (970810)

2 exp Infant/ (1178811)

3 Surface-Active Agents/tu [Therapeutic Use] (829)

4 (surfactant or lisa or mist).ti,ab,kf. (55481)

5 analgesia/ or anesthesia/ or conscious sedation/ or deep sedation/ or neuromuscular blockade/ or preanesthetic medication/ (97599)

6 morphine/ or fentanyl/ or remifentanil/ or ketamine/ or propofol/ or midazolam/ or dexmedetomidine/ (87461)

7 (morphine or fentanyl or remifentanil or ketamine or propofol or midazolam or dexmedetomidine).ti,ab,kf. (118183)

8 (sedati* or analgesia or anesthes* or premedication or neuromuscular blocking).ti,ab,kf. (303389)

9 5 or 6 or 7 or 8 (414643)

10 1 or 2 (1646152)

11 3 or 4 (56051)

12 9 and 10 and 11 (106)

Database: Embase – July 27, 20121

#1. 'surfactant' OR 'surfactant'/exp OR surfactant 300,068

#2. 'fentanyl'/exp OR fentanyl OR 'remifentanil'/exp OR remifentanil OR 'ketamine'/exp OR ketamine OR 'morphine'/exp OR morphine OR 'propofol'/exp OR propofol OR 'midazolam'/exp OR midazolam OR 'dexmedetomidine'/exp OR dexmedetomidine 282,619

#3. 'sedation'/exp OR sedation OR 'analgesia'/exp OR analgesia OR 'anesthesia'/exp OR anesthesia OR (neuromuscular AND blocking) OR 'premedication'/exp OR premedication 774,621

#4. lisa OR mist 152,046

#5. infan* OR neonat* OR prematur* OR preterm OR 'infant' OR 'newborn' OR 'prematurity' 1,866,765

#6. #1 OR #4 451,019

#7. #2 OR #3 906,750

[Tapez ici]

#8. #5 AND #6 AND #7 982

Database: Scopus – July 27, 2021

(TITLE-ABS KEY (infan* OR neonat* OR newborn* OR prematur* OR preterm OR (low AND adj3 AND weight*)) AND TITLE-ABS-KEY (surfactant OR lisa OR mist) AND TITLE-ABS-KEY (fentanyl OR morphine OR remifentanil OR ketamine OR propofol OR midazolam OR dexmedetomidine OR sedati* OR analgesia OR anesthes* OR premedication OR (neuromuscular AND blocking)))

Database: Cochrane Library

Date Run: 27/07/2021 19:00:02

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#3	#1 OR #2	90412
#4	MeSH descriptor: [Surface-Active Agents] explode all trees	755
#5	(surfactant or lisa or mist):ti,ab,kw	2812
#6	(fentanyl or remifentanil or ketamine or propofol or midazolam or dexmedetomidine or morphine):ti,ab,kw	48361
#7	(sedati* or analgesia or anesthes* or premedication or neuromuscular blocking):ti,ab,kw	107033
#8	MeSH descriptor: [Deep Sedation] explode all trees	162
#9	MeSH descriptor: [Anesthesia and Analgesia] explode all trees	27801
#10	MeSH descriptor: [Premedication] explode all trees	4307
#11	MeSH descriptor: [Morphine] explode all trees	5093
#12	MeSH descriptor: [Fentanyl] explode all trees	5647
#13	MeSH descriptor: [Remifentanil] explode all trees	1783
#14	MeSH descriptor: [Propofol] explode all trees	5008
#15	MeSH descriptor: [Ketamine] explode all trees	2261
#16	MeSH descriptor: [Midazolam] explode all trees	3110
#17	MeSH descriptor: [Dexmedetomidine] explode all trees	1875
#18	MeSH descriptor: [Neuromuscular Blockade] explode all trees	500
#19	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	122333
#20	#4 or #5	3483
#21	#3 and #19 and #20	57

2. Features of ongoing studies.

	Intervention vs control	**Inclusion criteria**	**Outcomes**
Bohlin K. Stockholm (SE) RCT Monocentric NCT04445571	LISA with analgesia premedication (no precision) versus INSURE	- gestational age <32 weeks - RS and need for surfactant	Main - oxygenation 24 hours post-procedure - need for intubation and mechanical ventilation (MV) 48 hours post-procedure Secondary: - duration of ventilatory support (MV, CPAP, Oxygen) - incidence of air leaks, BPD, Systemic hypotension, ROP, NEC, IVH, PDA - death or composite outcome death/BPD - length of stay in NICU and total in neonatal care - time until surfactant administration - number of attempts before successful intubation/ placement of catheter - PPV during the procedure - yes/no/duration (minutes) - Stress and pain: changes in heart rate, blood pressure and BIIP-scales
Breseti I. Milan (IT) RCT Monocentric NCT03718507	Fentanyl (0,5-2 mcg/kg IV) + atropine (0,01-0,02 mg/kg) versus sucrose + atropine	- gestational age $27^{0/7}$ - $29^{6/7}$ weeks - need for non-invasive respiratory support (CPAP or nasal high flow) AND - need for surfactant according to unit guidelines	- PIPP SCALE scores - salivary cortisol levels as an indicator of stress - crSO2 values (NIRS) as indicators of cerebral oxygenation
Krajewski Warsaw (PL) RCT Monocentric NCT04409665	Ketamine (1 mg/kg IV) versus glucose 30%	- infant with established RDS or at risk for RDS - gestational age $28^{0/7}$ - $32^{6/7}$ weeks - non-invasive respiratory support with CPAP, BiPAP or NIPPV - need for surfactant	Main: - patient sedation changes before and after LISA using COMFORT scale and FANS scale Secondary: - incidence of complications: monitoring the possible side effects of used drugs
Carnielli Ancona (IT) RCT Monocentric NCT04073173	4 arms: - LISA after remifentanil (0,5-2 mgc/kg) - LISA without sedation - INSURE after remifentanil (0,5-2 mgc/kg) - INSURE without sedation	- gestational age $24^{0/7}$ - $31^{6/7}$ weeks - RDS (FiO_2 ≥0.30 (for ≤26 weeks) or ≥0.40 (for >26 weeks) to achieve a SpO_2 of 90-94%) within 24 hours of life and good respiratory drive	Main: - cortisol concentrations in saliva at 1, 3, 6 12, 24 hours after surfactant administration and then daily in the first week at the same time of the day (to avoid circadian variations). Secondary: - Galvanic Skin (conductance) Responses at 1, 3, 6 12, 24 hours after surfactant administration and then daily in the first week at the same time of the day (to avoid circadian variations). - heart rate (6 hours before and after surfactant therapy): average HR, tachycardia and bradycardia. - brain oxygenation (from admission to day 7) by near-infrared spectroscopy (NIRS). - oxygen saturation (SpO_2) (from admission to day 7) - markers of oxidative stress (at admission and at 6 and 12 hours after surfactant therapy): dosage of 8-isoprostane and nitrites/nitrates on urine samples.

Chevalier [24] Grenoble (FR) RCT Multicentric EUCTR2018-002876-41-FR NCT04016246	**Propofol** 0.5 mg/kg per dose (max two (before 28 wGA) or 3 (between 28 - 31 wGA)) (rescue treatment by Ketamine) versus **no sedation**	- gestational age <32 weeks - RDS in the first 48 hours of life treated by CPAP or BiPAP requiring surfactant ($FIO_2 \geq 0,3$ if 28-31 wGA or $\geq 25\%$ if < 28 wGA for a duration ≥ 10 min to obtain a $SpO_2 \geq 88$ and $\leq 95\%$ - available intravenous line - recipient of the French Social Security	Main: - need for mechanical ventilation up to 72 hours of life. Secondary: - need for MV in each GA strata up to 72 hours of life - FANS scores during LISA and 1h after - number of rescue ketamine administrations to obtain a FANS score <6 before procedure - number of laryngoscopies attempts - tolerance and efficacy: Apnea requiring bag mask ventilation, emergency intubation within 1h following the drug injection, Viby Mogensen score - BPD (bronchopulmonary dysplasia) at 36 weeks of GA - in-hospital morbidity and mortality: pneumothorax within 72hours, NEC, proven sepsis, ROP, cPVL, IVH 3 or 4, PDA needing treatment, mortality - at two years of corrected age: ASQ (Ages and Stages Questionnaire), Gross Motor Function Classification Scale (GMFCS), vision, audition
Marttila Oulu (FI) RCT Monocentric NCT03735563	**Ketamine** (1 mg/kg IV) versus **Fentanyl** (1 mcg/kg IV) (rescue Midazolam)	- gestational age ≥26 wGA - respiratory insufficiency managed with non-invasive respiratory support (nasal continuous positive airway pressure or high-flow) - requirement for oxygen to maintain oxygen saturation in the target range and need for surfactant treatment (according to clinician's assessment) If further doses of surfactant are needed, patient can be re-randomized	Main: - adverse event: need of PPV, intubation, heart rate below 80 per minute, mean arterial pressure change more than 20%, pH change more than 0.4, and CO_2 change more than 20%, and saturation <85 for more than 1 minute Secondary: - duration of the procedure - number of attempts to get the catheter intratracheally - pain score NIAPAS - need for additional dosing of study drug or midazolam (number of additional dosages) - Edi-signals (electrical activity of the diaphragm)
Patural Saint-Etienne (FR) Prospective Monocentric NCT03721640	**Propofol** before LISA or INSURE	- gestational age <33 weeks - breathing rate > 60 cycles/min - Silverman scale > 3 and < 6 - $FiO_2 > 30\%$ and < 60%	Main: - real-time low frequency values (represent the well-being sympathetic activity of the autonomic nervous system) measured with electrocardiogram Secondary: - heart rate measured with electrocardiogram - systolic arterial blood pressure measured with a blood pressure cuff - diastolic arterial blood pressure measured with a blood pressure cuff - oxygen saturation measured by pulse oximetry

? CTRI/2020/08/027144 **RCT**	**Fentanyl** (2 mcg/kg IV) **v**ersus **no sedation**	- gestational age 34-38 weeks - RDS who required FiO_2 > 30% on niPPV to maintain SpO2 90-95% in first 2 hours of life	Main: - percentage of infant with a Revised Premature Infant Pain Profile score < 10 during procedure. Secondary: - occurrence of positive PPV within 48h - intubation need during the procedure and within 24h - number of attempts of insertion of the orogastric catheter - duration of the procedure - complications occurring during the procedure - duration of respiratory support - length of stay