Analgo-sedation before Less-Invasive Surfactant Administration: A Systematic Review

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Keywords

Surfactant administration · Less-invasive surfactant administration · Sedation · Analgesia

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. Analgo-sedation remains controversial as 52% of European neonatologists do not use any. This systematic review aims to describe the efficacy and safety of different drugs for analgo-sedation 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 randomized controlled trial) 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. Analgo-sedation 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 h 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, etc.). 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 the best choice of drugs and dosages, 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.

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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, espe-

cially 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. 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 (GAs), 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 the USA do not use analgesia for LISA [12, 13]. Some centres have policies restricting drugs for specific indications (e.g., second attempt, more mature babies, etc.) or individualized approach [4, 14]. Procedure performed early after vaginal birth benefits 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, etc.) 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 their online 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 LISA were performed without systematic analgesia, and it was still proved to be beneficial. Adding analgesia could therefore potentially change the beneficial outcomes. Klotz et al. [12] hypothesized that compared to invasive intubation, LISA was perceived to be less traumatic or that the maintenance of spontaneous breathing was considered paramount. The aim of this systematic review was to describe the efficacy and safety of different drug regimens for analgesia during LISA.

Methods

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 on September 2020; CRD42020205365).

The initial protocol was modified on February 26, 2021, before extracting data. The focus shifted to LISA rather than both LISA and INSURE (intubation-surfactant-extubation) because of important differences between these procedures and their physiology. In addition, retrospective studies were included for a broader overview of practices.

Criteria of Eligibility

All clinical studies of LISA procedure after analgesia were considered eligible. We included randomized controlled trials (RCTs) and 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.

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

Fig. 1. Flow diagram of study selection.

available in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000521553). Subsequently, Google Scholar was searched for the grey literature. Reference lists of publications eligible for full-text review and systematic review about LISA procedure allowed for an additional “snowball search.”

Selection Process

The 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.

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.

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 ($\text{SpO}_2 < 85\%$), bradycardia, and hypotension (defined as a mean arterial blood pressure in mm Hg below the number of weeks of GA). 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 the 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.

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 randomized trials or the Newcastle Ottawa Scales

Table 1. Features of included studies

Study	N	Study population (intervention/control)	Intervention versus control	Inclusion criteria	Exclusion criteria	Main outcomes	Secondary outcomes
RCT							
Dekker et al. [20] Monocentric	78	n: 42/36 Mean±SD BW (g): 1,475±575/1,502±606 (p = 0.837) Median (IQR) GA (weeks): 29 ⁺⁰ (27 ⁺⁵ –32 ⁺⁰) versus 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 cm H ₂ O)	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 24 h) Number of catheterization attempts Duration of procedure Desaturation, hypotension, bradycardia, and nasal haemorrhage Pneumothorax Pulmonary haemorrhage Resuscitation IVH ≥3 – death
Prospective studies							
Bourgoin et al. [21] Monocentric	29	Median (IQR) BW (g): 1,290 (945–1,600) Median (IQR) GA (weeks): 29.6 (28.6–30.9)	Ketamine IV (titration by 0.5 mg/kg steps (3–5 min) Max 3 mg/kg Median: 1.5 mg/kg + atropine 15 mcg/kg + caf- feine 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 mm Hg) Pneumothorax Hypotension (MABP < wGA): capillary refill time >3 s Apnoea requiring bag-mask ventilation before the start score	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 , MABP/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 h Pneumothorax Selective administration Mortality, BPD, IVH, NEC, and ROP
Krajewski et al. [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): 1,749±570/1,332±512 (p < 0.001)	Any analgesics/sedatives in mono- or polytherapy (ketamine, thiopental, midazolam, propofol, morphine, sufentanil, and 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, and O ₂ desaturation)	Changes in oxygenation status (SpO ₂ /FiO ₂) Need for MV at <24 h of life Difficulty of procedure Number of catheterization attempts	
Retrospective studies							
Dekker et al. [23] Monocentric	38	n: 23/15 Mean±SD BW (g): 1,312±483/1,469±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 cm H ₂ O)	Imminent need of intubation because of respiratory insufficiency (apnoea/acidosis)	Stress and comfort (COMFORTneo score <14)	Need of PPV Intubation rate (within 24 h) During procedure: desaturation, hypotension, and bradycardia (HR <80/min)
Descamps et al. [24] Monocentric	35	Mean (range) BW (g): 1,334 (635–2,350) 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 et al. [25] Monocentric	114	n: 62/52 Median (IQR) BW (g): 950 (825–1,140)/897 (780–1,150) (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 cm H ₂ O, 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 h following the procedure	Need for MV within 24 and 72 h Procedure tolerance Mortality and morbidity at 36 weeks GA Duration of MV and NIV Neonatal comfort (FANS) Drug tolerance Cardiorespiratory parameters (HR, FiO ₂ , and MABP)

Table 1 (continued)

Study	N	Study population (intervention/control)	Intervention versus control	Inclusion criteria	Exclusion criteria	Main outcomes	Secondary outcomes
LISA arm of LISA versus INSURE studies	24	Mean GA (weeks): 34 ^{6/7} ± 1.4 Mean ± SD BW (g): 2,157 ± 487 Male sex (%): 42	Fentanyl 1 mcg/kg IV + atropine 20 mcg/kg	GA of 32 ^{0/7} –36 ^{6/7} weeks PEEP 6 cm H ₂ O 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: pCO ₂ > 70 mm Hg or non-improvement of FiO ₂ in the 4 h	Number of laryngoscopy attempts Adverse events (surfactant reflux and desaturations) Age at surfactant administration Duration of MV, NIV, and O ₂
Berneau et al. [28] Monocentric	127	Median (IQR) GA (weeks): 28.1 (27.0–29.2) Median (IQR) BW (g): 1,045 (832–1,238) Male sex (%): 53.5	Ketamine 0.5 mg/kg IV (repeated once if necessary) + atropine 20 mcg/kg	GA < 30 weeks Spontaneously breathing infants on PEEP 5–6 cm H ₂ O who need surfactant	Congenital malformations Outborn patients	Failure: need of a 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

NIV, non-invasive ventilation; HR, heart rate; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; cPVL, cystic periventricular leukomalacia; MABP, mean arterial blood pressure; MV, mechanical ventilation; BW, birth weight.

(NOSs) for cohort studies. For the RCT, the following domains were assessed: randomization 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 online supplementary information.

Synthesis Methods

Meta-analyses could not be undertaken given the limited number of RCTs and studies with comparative arms. We detailed data in a predefined table, according to main and secondary outcomes of each study.

Results

Literature Search and Study Selection

The search strategy produced 1,555 records. After accounting for 454 duplicates, 1,101 records were screened by the 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 Fig. 1). Nine ongoing studies were also referenced.

Study Characteristics

Characteristics of the included studies are summarized in Table 1. Only one study was randomized and controlled [20]. Dekker et al. [20] 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 such as ketamine, midazolam, propofol, sufentanil, morphine, thiopental, and 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, and desaturation).

Three retrospective observational studies were included [23–25]. All used propofol as the 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 studies comparing INSURE and LISA with fentanyl [27] or ketamine [28] premedication were

All arms of those trials were assessed as randomised. All studies but one [22] were mono-

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 pre-term infants [24, 25, 28], one on moderate and late pre-term [27], while the 4 others included preterm infants of all GAs.

RoB and Quality Assessment

Outcomes Analysis

Randomized Controlled Trial

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

Table 2. Main results of included studies

Study	Intervention versus control	Main outcomes	Secondary outcomes
RCT			
Dekker et al. [20] Monocentric N = 78	Propofol 1 mg/kg IV (+sucrose 24%) versus no sedation (+sucrose 24%)	Stress and comfort (COMFORTneo score <14): 76 versus 22% ($p < 0.001$) Mean $\pm$ SD COMFORTneo score: 12 ± 3 versus 17 ± 4 ($p < 0.001$)	Occurrence of nasal PPV during and immediately after procedure: More frequent (93 vs. 47% [$p < 0.001$]) but not longer (median [IQR]: 7 [3–21] vs. 6 [3–12] min [$p = 0.274$]) Intubation rate: 2 versus 11% ($p = 0.175$) during procedure – similar in the first 24 h (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 versus 69% ($p = 0.023$) MABP, hypotension, and bradycardia: no difference Difference in the HR between the periods before, during, and after procedure higher ($p = 0.002$) Pneumothorax: 7 versus 3% ($p = 0.620$) Pulmonary haemorrhage: 2 versus 0% ($p = 1$) Resuscitation, IVH $\geq$ III, and death: no difference
Bourgoin et al. [21] Monocentric N = 29 Prospective studies	Ketamine IV (titration by 0.5 mg/kg steps (3–5 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 SpO ₂ < 80% > 60 s: 59% Occurrence of apnoea: 52% (15) Intubation rate: 41% (24% immediately +17% within 72 h) Number of laryngoscopies: median (IQR) 1 (1–3) LISA duration (min): median (IQR) 7 (4–13) Selective administration: none Pneumothorax, mortality, IVH, and NEC: none BPD: 10% ROP: 3.4%
Krajewski et al. [22] Multicentric N = 500	Any analgesics/sedatives in mono- or polytherapy (ketamine, thiopental, midazolam, propofol, morphine, sufentanil, and phenobarbital) versus no sedation At discretion of the caregiver	Occurrence of pre-specified adverse events during LISA: Reflux: 21.6 versus 17.6% (NS) Need for rescue intubation: 2.3 versus 1% (NS) Bradycardia: 3.4 versus 4.3% (NS) Apnoea: 9.1 versus 2.6% ($p = 0.009$) O ₂ desaturation: 28.4 versus 21.2% (NS) Changes in oxygenation status (Δ SpO ₂ /FiO ₂) during before LISA: –55 $\pm$ 62 versus –32 $\pm$ 50 ($p < 0.001$) Need for MV at < 24 h of life: 20.5 versus 14.3% (NS)	Difficulty of procedure: easy/very easy in 65.9 versus 69.1% (NS) Number of attempts of catheter insertion: median (IQR) 1 (1–1) versus 1 (1–1) (NS)

Table 2 (continued)

Study	Intervention versus control	Main outcomes	Secondary outcomes
Retrospective studies			
Dekker et al. [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% versus 33% ($p < 0.001$) Intubation during procedure (for catheterization failure): 9 versus 0% (ns) Intubation rate within 24 h: 26 versus 13% (ns) Duration of procedure (min): no difference – median (IQR) 2 (2–4) versus 3 (2–7) During procedure: Duration (min) of SpO ₂ <80% (median [IQR]): 3 (2–4) versus 1 (0–2) ($p < 0.01$) Hypotension and bradycardia (HR <80/min): no difference
Descamps et al. [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 the second dose of surfactant with MV maintained: 20%	Clinical tolerance: HR <80/min: 17% Hypotension: 14% SpO ₂ < 85%: 100%
Brotelande et al. [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 h following the procedure: no difference (8% for propofol vs. 10% for ketamine) Second dose of surfactant: 16 versus 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) versus 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%], and 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) 1,128 (912–1,536) versus 1,092 (792–1,368) ($p = 0.27$) Procedural pain (FANS): median (IQR) 1 (1–2) versus 1 (0–2) ($p = 0.61$) Cardiorespiratory parameters: HR, FIO ₂ , and MABP comparable
LISA arm of LISA versus INSURE studies	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 mm Hg or FIO ₂): none	Number of laryngoscopy attempts: mean ($\pm$ SD) 2.3 $\pm$ 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 et al. [28] Monocentric N = 24	Ketamine 0.5 mg/kg IV (repeated once if necessary) + atropine 20 mcg/kg	Failure: Need for a 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

BPD, bronchopulmonary dysplasia; MABP, mean arterial blood pressure; cPVL, cystic periventricular leukomalacia; MV, mechanical ventilation; NIV, non-invasive ventilation; HR, heart rate; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus.

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

procedure ($p < 0.001$) after propofol compared to no analgesedation. 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, intraventricular haemorrhage grade 3 or 4, or mortality was not different. The number of attempts for catheter insertion and the total duration of procedure were comparable.

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

Cohort Studies

Respiratory Outcomes. Intubation during or within 1 or 2 h 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 h was not different between awake and sedated infants [22, 23]. Brotelande et al. [25] reported rates of 16 and 19% for propofol and ketamine groups, respectively. The intubation rate within 72 h of life reached 21% after propofol [25], 18–41% in ketamine studies [21, 25, 28], and 29% after fentanyl analgesedation [27]. Four studies without an unsedated arm described the 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 Bourgoïn 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 et al. [23] reported a significant reduction in the COMFORTneo score with analgesedation. Bourgoïn et al. [21] and Brotelande et al. [25] evaluated pain with the Faceless Acute Neonatal Scale (FANS) score. Median scores were 1–2 [21, 25], when a score below 4 indicates comfort.

Clinical Tolerance. Krajewski et al. [22] reported for the analgesedation group a higher drop in oxygenation evaluated by changes in the SpO₂/FiO₂ ratio during LISA compared to baseline ($p < 0.001$). Procedural desaturation lasted significantly longer in the sedation group ($p < 0.001$) in Dekker et al. [23]. Bradycardia did not occur more frequently in analgesedation 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 mean arterial blood pressure occurred but remained within physiological range [25]. Descamps et al. [24] reported hypotension in 14% of cases, which were transient and

self-resolving. 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. [21] reported excellent or good quality in 83% of procedures after ketamine sedation, while in contrast, Krajewski et al. [22] noted no significant difference in the difficulty of the procedure between the sedated and unsedated groups. The duration of the procedure, as well as the number of attempts of catheter insertion was 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 bronchopulmonary dysplasia, retinopathy of prematurity, patent ductus arteriosus, necrotizing enterocolitis, and cystic periventricular leukomalacia) 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 PPV during procedure were reported in the only RCT [20] and in 2 cohort 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 2 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 h of life of 22–34%, comparable to those from analgosedation studies. The higher rate of intubations in Bourgoin et al. [21] (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 do not 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 the long term [6, 14, 33]. To optimize 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 50–100 times more potent than morphine [35]. It has a rapid onset of action and minimal effect on haemodynamic [35]. Remifentanyl is another synthetic opioid with a 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 Elmekawi et al. to facilitate extubation in INSURE procedure with high efficacy and no adverse effects [36].

Propofol, used by Dekker et al. [23], Brotelande et al. [25], and Descamps et al. [24], 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 2-year follow-up [39].

Bourgoin et al. [21], Brotelande et al. [25], and Berneau et al. [28] 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 haemodynamic profiles [40].

Benzodiazepines, most commonly midazolam, were reported in the prospective study from Krajewski et al. [22] 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, and breastfeeding could not be used during LISA procedure.

Technical conditions are often good or excellent with analgosedation. de Kort et al. [44] 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%). 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 pre-defined protocol registered in PROSPERO, we searched 4 databases with indexing terms as well as the 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 realization of a meta-analysis. Secondly, most of the included studies 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, etc.). 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 RCTs using fentanyl, ketamine, remifentanyl, 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. [45] developed the FANS for use when the neonate's face is hidden by respiratory devices, but this scale also includes heart rate variations and oxygen desaturation. Other studies will compare sedation impact on stress, oxygenation changes, 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 the benefits reported without it.

A significant pain reduction with analgosedation was described in the only RCT addressing the question. Except for higher risks of oxygen desaturation and more PPV during procedure, clinical outcomes were not different. Observational studies also reported reduction in pain at the expense of higher procedural rates 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.

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 synthesized 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

S.T., N.H., and D.S. contributed to the search strategy, data selection, and analysis. S.T. drafted and revised the manuscript. C.L. cooperated to the revision of the draft. V.R. helped with data interpretation and writing and editing of the manuscript. All the authors reviewed and approved the manuscript.

Data Availability Statement

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

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