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Pichler, K.; Kuehne, B.; Dekker, J.; Stummer, S.; Giordano, V.; Berger, A.; ... ; Klebermass-Schrehof, K.

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Assessment of Comfort during Less Invasive Surfactant Administration in Very Preterm Infants: A Multicenter Study

Karin Pichler[a] Benjamin Kuehne[b] Janneke Dekker[c] Sophie Stummer[a] Vito Giordano[a] Angelika Berger[a] Angela Kribs[b] Katrin Klebermass-Schrehof[a]

[a]Division of Neonatology, Pediatric Intensive Care and Neuropediatrics, Department of Pediatrics, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria; [b]Division of Neonatology, Department of Paediatrics, University of Cologne, Cologne, Germany; [c]Division of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

Keywords
Preterm infants · Comfort · Less invasive surfactant administration · Respiratory distress syndrome

Abstract

Introduction: This study was set up to investigate if and to what extent non-pharmacological analgesia is able to provide comfort to very preterm infants (VPI) during less invasive surfactant administration (LISA). ***Methods:*** This was a prospective non-randomized multicenter observational study performed in level IV NICUs. Inborn VPI with a gestational age between $22^{0/7}$ and $31^{6/7}$ weeks, signs of respiratory distress syndrome, and the need for surfactant replacement were included. Non-pharmacological analgesia was performed in all infants during LISA. In case of failure of the first LISA attempt, additional analgosedation could be administered. COMFORTneo scores during LISA were assessed. ***Results:*** 113 VPI with a mean gestational age of 27 weeks (+/− 2.3 weeks) and mean birth weight of 946 g (+/− 33 g) were included. LISA was successful at the first laryngoscopy attempt in 81%. COMFORTneo scores were highest during laryngoscopy. At this time point, non-pharmacological analgesia provided adequate comfort in 61% of the infants. 74.4% of lower gestational aged infants (i.e., 22^0–26^6 weeks) were within the comfort zone during laryngoscopy compared to 51.6% of higher gestational aged infants (i.e., 27^0–32^0 weeks) ($p = 0.016$). The time point of surfactant administration did not influence the COMFORTneo scores during the LISA procedure. ***Conclusion:*** Non-pharmacological analgesia provided comfort in as much as 61% of the included VPI during LISA. Further research is needed to both develop strategies to identify infants who, despite receiving non-pharmacological analgesia, are at high risk for experiencing discomfort during LISA and define patient-tailored dosage and choice of analgosedative drugs.

karger@karger.com
www.karger.com/neo

Correspondence to:
Katrin Klebermass-Schrehof, katrin.klebermass-schrehof@meduniwien.ac.at

Introduction

Respiratory distress syndrome (RDS) remains the major cause of neonatal respiratory morbidity and mortality. Half of all preterm infants with RDS require surfactant [1]. In 2019, the European Consensus Guidelines on the Management of RDS updated its recommendations to state that less invasive surfactant administration (LISA) is the optimal method for surfactant administration [1]. The LISA approach avoids exposure to positive pressure ventilation and has been shown to reduce the need for mechanical ventilation, the incidence of bronchopulmonary dysplasia (BPD), and death in meta-analyses and randomized controlled trials [2–5]. Still, major uncertainties about the necessity, feasibility, and the nature of administering premedication before LISA remain as painful and distressing stimuli are known to have a negative effect on the developing nervous system of a preterm infant [6]. Surveys revealed that at least 52% of the neonatologists in Europe and 94% in the USA do not use analgosedation for LISA but adopted non-pharmacological measures for analgesia, based on the assumption that procedures performed early after birth may additionally benefit from endogenous analgesia related to high vasopressin levels [7–9]. Although LISA has been reported to be perceived as less traumatic than invasive intubation [8], it has not been investigated so far if and to what extent non-pharmacological measures are sufficient to provide comfort to infants during the procedure.

The aim of this multicenter study was to analyze whether non-pharmacological analgesia is suitable to provide comfort in very preterm infants (VPI) during LISA. Furthermore, we addressed the questions of whether comfort during LISA varied based on the gestational age (GA) of the infant and/or the time point of surfactant administration.

Methods

Study Population

This prospective non-randomized multicenter observational study was conducted in two level IV neonatal centers (Medical University of Vienna, Austria, and Medical University of Cologne, Germany). Inborn VPI (GA between $22^{0/7}$ and $31^{6/7}$ weeks) with signs of RDS and the need for surfactant replacement were recruited from February 1, 2020, to August 31, 2021, after obtaining parental consent. Written parental consent was obtained before or immediately after birth. Exclusion criteria were major congenital malformations, intubation before the study entry, and neonatal acute RDS[10]. Neonatal acute RDS is characterized by extensive lung inflammation and surfactant catabolism, leading to lung dysfunction. These mechanisms can occur simultaneously with other mechanisms typical of neonatal age (i.e., quantitative surfactant deficiency and lack of alveolarization) [10]. The study was conducted according to the guidelines of the Declaration of Helsinki, approved by the Local Ethics Committees (EK Nr. 2291/2019/EK Nr. Z. 20-1087) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00022317).

Data Collection

Basic patient characteristics and clinical data were collected from medical records: mode of delivery, 5-min APGAR score, GA at birth, birth weight (BW), and gender. The following complications of LISA were recorded: need for intermittent positive pressure ventilation, need for mechanical ventilation during LISA or within 24 h after completion of LISA, occurrence of desaturation (oxygen saturation <80%) or bradycardia (heart rate <80 bpm), number of laryngoscopy attempts to insert the catheter between the vocal cords, pneumothorax, and pulmonary hemorrhage. In the case of absence of any respiratory or hemodynamic complications, the infant was considered to have "stable vital signs." Assessed complications of preterm birth included severe intraventricular hemorrhage ([IVH] grade 2 or higher, according to Deeg et al. [11]), cystic periventricular leukomalacia, moderate or severe BPD [12], and death during birth hospitalization.

LISA Procedure and Non-Pharmacological Strategies to Provide Comfort

Participants' clinical management followed institutional guidelines with strong focus on developmental care. All infants received caffeine in the delivery room or at admission to the NICU. Non-pharmacological analgesia was performed in all infants and included physiologic positioning, holding ("facilitated tucking") and/or swaddling, nonnutritive sucking, and eventually the application of sucrose 24% solution. Infants <$28^{0/7}$ weeks at birth were stabilized using high-flow CPAP (20 L/min, approximately generating 25–30 cm H_2O PEEP [13]) via a nasopharyngeal tube (Vygon Aachen, Germany) and Benveniste® valve (Dameca, Rødovre, Denmark) with heated and humidified air. In infants, ≥$28^{0/7}$ weeks at birth, it was left to the discretion of the treating physician whether to apply the high-flow or a binasal CPAP system (Infant Flow®, CareFusion, San Diego, CA, USA; Fabian®, ACUTRONIC Medical Systems, Hirzel, Switzerland; or Leonie Plus®, Loewenstein Medical, Bad Ems, Germany) with a PEEP level of 6–8 cm H_2O. Surfactant (CUROSURF: 200 mg/kg, Chiesi Pharmaceuticals Parma, Italy) was administered over 2–5 min via a thin catheter {either a gastric tube (CH 04 [= 1.3 mm diameter], Metric; Unomedical, Birkerød, Denmark), the Surfcath™ (Vygon, Aachen, Germany), or the LISAcath® (Chiesi, Parma, Italy)} if reduction of PEEP level <6 cm H_2O failed. This was defined by an increase in the Silverman Andersen Respiratory Severity Score [14] to >6 and/or FiO_2 ≥0.3 to target SpO_2 89–93%. The increase in the Silverman Andersen Respiratory Severity Score to >6 and/or FiO_2 ≥0.3 to target SpO_2 89–93% also remained the criteria for giving surfactant later than in the first hour of life. In case surfactant was administered in the first hour of life, this was referred to as delivery room LISA, while surfactant administration at a later time point was referred to as rescue LISA.

In case of failure to insert the catheter through the vocal cords at the first attempt, the decision whether to give a low dose of analgosedation before the next LISA attempt was left to the

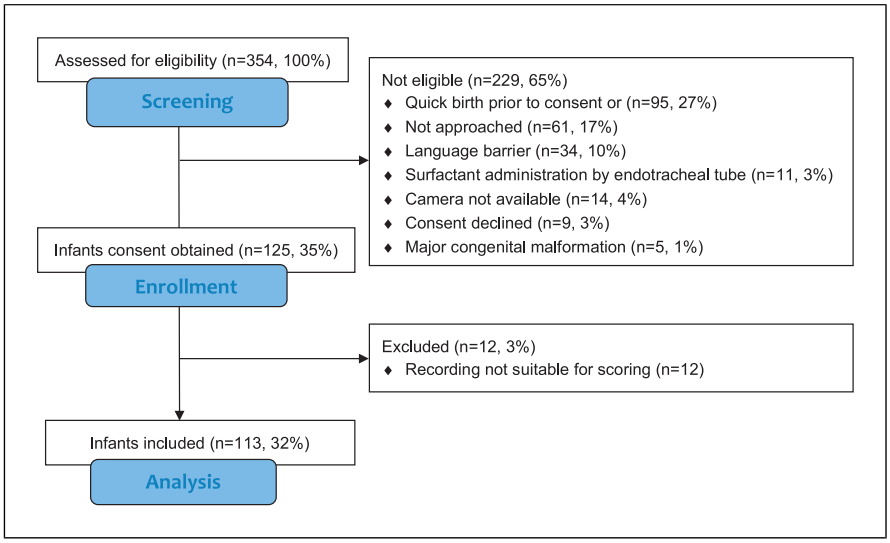

Fig. 1. Patient flowchart.

discretion of the attending neonatologist. The type of analgosedation was not predefined. LISA procedures were audio- and videorecorded. The recordings were used for the assessment of comfort.

The qualification of the physician performing the LISA procedure was documented. No pre-specifications were made in the study protocol in this regard, but the choice of the physician was left to the description of the participating study centers.

Assessment of Comfort during LISA

For the assessment of comfort during LISA, the COMFORTneo score was used. COMFORTneo is a validated pain score for very premature neonates, consisting of 6 behavioral items (alertness, calmness/agitation, crying/breathing, body movement, facial tension, and body muscle tone) [15]. A COMFORTneo score <14 indicates adequate pain control [15–17]. It was assessed at the following time points of the LISA procedure: before intervention, during laryngoscopy, during surfactant administration, and after intervention. In order to allow correct assessment of body movement and muscle tone, one extremity of the infant was excluded from measures of non-pharmacological analgesia such as facilitated tucking and holding.

A subgroup analysis was performed, comparing infants of low GAs (i.e., 22^0–26^6 weeks) with infants of higher GAs (i.e., 27^0–32^0 weeks). The recordings were scored by three independent observers: two fellows in neonatology and one attending. They were blinded regarding the application of analgosedative medication and regarding the number of preceding laryngoscopy attempts. The observers assessed 10 LISA procedures, after which inter-rater reliability was analyzed by Cohen's κ, where 0 means no agreement and 1 means total agreement. A Cohen's $\kappa > 0.4$ was considered reasonable. When reasonable Cohen's κ was achieved within the observers, the remaining LISA procedures were subdivided for assessment.

Statistical Analysis

Statistical analysis was performed using SPSS® Statistics for Mac version 27.0 (Armonk, NY: IBM Corp.). Demographics between the groups were compared by χ^2 test and Student's *t* test. Linear study parameters that were assessed once per infant were compared by a two-way factorial analysis of variance or a linear mixed-effect regression model in multiple assessments, including both the randomization and stratification group. Categorical outcomes were assessed by Fisher's exact test. Two-sided *p* values < 0.05 were considered statistically significant. Figures were prepared using GraphPad Prism® 9.

Results

Study Population

A total of 113 infants were included in the study. 75 (66%) infants were recruited in Vienna, Austria, and 38 (34%) infants were recruited in Cologne, Germany. Further details are given in the study flowchart (Fig. 1). Characteristics of infants who received non-pharmacological analgesia for LISA are given in Table 1. Given the limited number of 8 (7%) out of 113 infants, who received pharmacological analgesia, characteristics are reported in online supplementary Table 2 (for all online suppl. material, see https://doi.org/10.1159/000530333).

LISA Procedure

In our study, cohort delivery room LISA was performed more frequently than rescue LISA (75% vs. 25%). The number of attempts to insert the catheter into the trachea was higher in the infants, who received rescue LISA ($p = 0.006$, Table 1). In 81% of all infants, LISA was successful at the first laryngoscopy attempt. Pharmacological analgesia was used primarily during rescue LISA.

Table 1. Characteristics of infants who received non-pharmacological analgesia for LISA

	All patients (n = 105, 100%)	Delivery room LISA (n = 82, 78%)	Rescue LISA (n = 23, 22%)	p values	GA 22^0–26^6 weeks (n = 43, 41%)	GA 27^0–32^0 weeks (n = 62, 59%)	p values
GA (mean ± SD), weeks	27 (2.3)	26 (1.9)	29 (1.9)	<**0.001**	25 (1.3)	28 (1.5)	<**0.001**
BW (mean ± SD), g	946 (330)	864 (257)	1,239 (395)	<**0.001**	722 (192)	1,101 (316)	<**0.001**
Mode of delivery (C-section, *n*, %)	100 (95)	77 (94)	22 (96)	0.225	40 (93)	60 (97)	0.375
APGAR 5 min, median (IQR)	8 (8–9)	8 (7–9)	9 (8–9)	**0.016**	8 (7–9)	9 (8–9)	0.215
Gender (male, %)	62 (59)	50 (61)	12 (52)	0.448	29 (67)	33 (53)	0.145
Stable vital signs, *n* (%)	86 (82)	72 (88)	14 (60)	**0.003**	39 (90)	47 (76)	0.051
Desaturation, *n* (%)	14 (13)	9 (11)	5 (22)	0.180	4 (9)	10 (16)	0.312
Desaturation and bradycardia, *n* (%)	3 (3)	0 (0)	3 (13)	<**0.001**	0 (0)	3 (5)	0.143
IPPV necessary, *n* (%)	2 (2)	1 (1)	1 (4)	0.332	0 (0)	2 (3)	0.234
Attempts to insert the catheter into the trachea							
Median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	**0.022**	1 (1–1)	1 (1–1)	0.263
One attempt, *n* (%)	89 (85)	73 (89)	16 (70)		38 (89)	51 (82)	
Two attempts, *n* (%)	11 (10)	7 (9)	4 (17)		4 (9)	7 (11)	
More than 2 attempts, n (%)	5 (5)	2 (2)	3 (13)		1 (2)	4 (7)	
Neonatologist performs the first attempt, *n* (%)	50 (48)	43 (52)	7 (30)	0.101	22 (51)	28 (45)	0.713
Pneumothorax, *n* (%)	3 (3)	3 (4)	0 (0)	0.352	1 (2)	2 (3)	0.785
Pulmonary hemorrhage, *n* (%)	1 (1)	1 (1)	0 (0)	0.595	1 (2)	0 (0)	0.228
MV during LISA, *n* (%)	4 (4)	3 (4)	1 (4)	0.879	1 (2)	3 (5)	0.508
MV within 24 h after LISA, *n* (%)	13 (12)	12 (15)	1 (4)	0.186	8 (19)	5 (8)	0.107
Severe IVH, *n* (%)	11 (10)	10 (12)	1 (4)	0.277	8 (19)	3 (5)	**0.024**
cPVL, *n* (%)	1 (1)	1 (1)	0 (0)	0.495	1 (2)	0 (0)	0.231
BPD, *n* (%)	19 (18)	17 (21)	2 (9)	0.185	15 (35)	4 (7)	<**0.001**
Moderate BPD, *n* (%)	14 (13)	12 (15)	2 (9)	0.459	12 (28)	2 (3)	<**0.001**
Severe BPD, *n* (%)	5 (5)	5 (6)	0 (0)	0.225	2 (7)	2 (3)	0.375
Death, *n* (%)	5 (5)	5 (6)	0 (0)	0.225	3 (7)	2 (3)	0.375

GA, gestational age; BW, birth weight; IPPV, intermittent positive pressure ventilation; MV, mechanical ventilation; LISA, less invasive surfactant administration; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia; BPD, bronchopulmonary dysplasia.

The number of attempts to insert the catheter into the trachea was higher in these infants (online suppl. Table 2). Administered drugs for analgosedation during LISA were either ketamine (1 mg/kg i.v., n = 3) or the combination of midazolam (0.05–0.1 mg/kg i.v.) and ketamine (1 mg/kg i.v., n = 5). The LISA procedure was performed either by a neonatal fellow or a neonatologist. No differences between the groups were observed regarding the experience of the physician performing LISA (Table 1).

Complications

Infants who received delivery room LISA with non-pharmacological analgesia showed more stable vital signs (p = 0.003) and a lower incidence of the combined outcome of desaturation and bradycardia (p < 0.001) compared to infants who received rescue LISA with non-pharmacological analgesia (Table 1). A higher incidence of severe IVH (p = 0.024) and BPD (p < 0.001) was observed in the lower GA group of the infants who received non-pharmacological analgesia for LISA (Table 1). Complications of infants who received pharmacological analgesia are reported in online supplementary Table 2.

COMFORTneo Score

The course of the COMFORTneo scores during LISA for the study population and analyzed subgroups is given in Figure 2. COMFORTneo scores during LISA were the highest during laryngoscopy in all groups (Table 2). When comparing delivery room LISA with rescue LISA, we observed that a higher number of infants in the rescue LISA group had a COMFORTneo score <14 both before and after the intervention (p = 0.011 and p < 0.0001), but there was no difference during the procedure itself (Table 2).

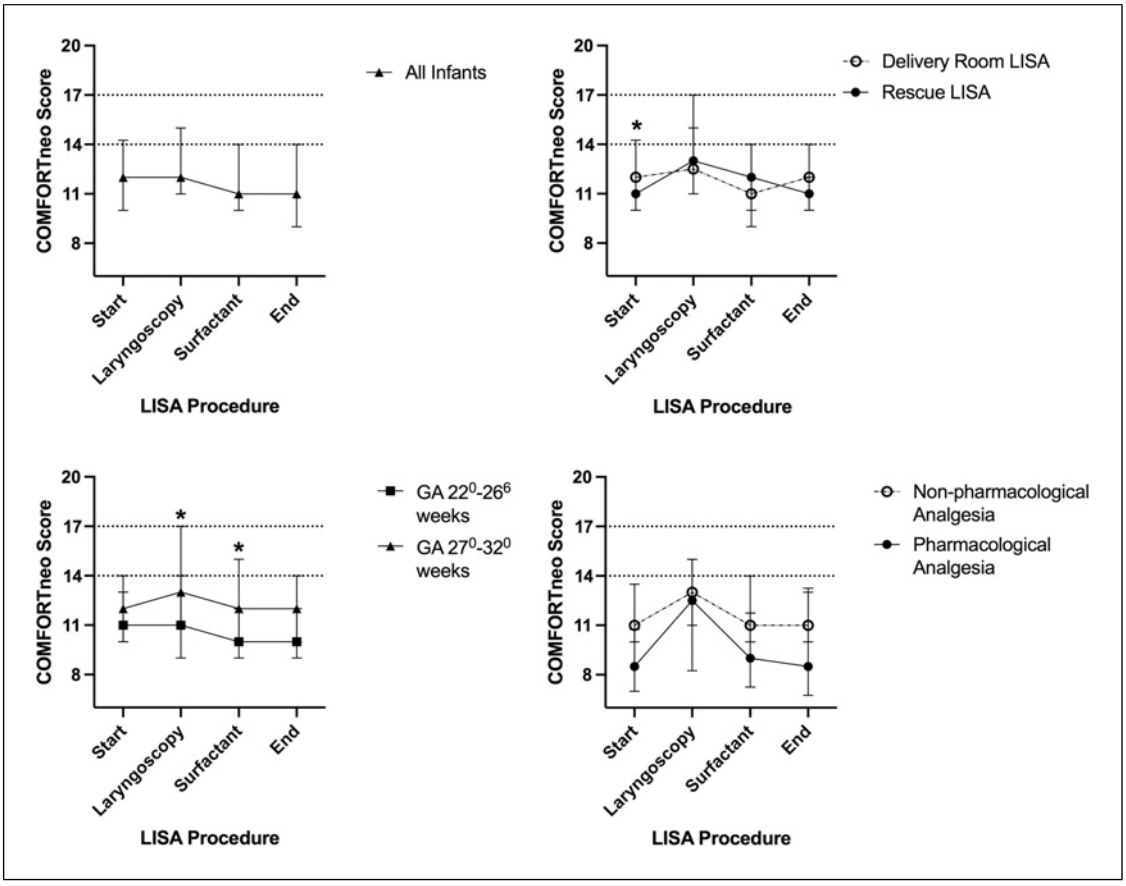

Fig. 2. COMFORTneo scores during LISA in the study population and analyzed subgroups. COMFORTneo scores are given as medians (IQR). Significant results ($p < 0.05$) are marked with an asterisk.

Table 2. COMFORTneo scores in infants receiving non-pharmacological analgesia during LISA

COMFORTneo score	All patients (*n* = 105, 100%)	Delivery room LISA (*n* = 82, 78%)	Rescue LISA (*n* = 23, 22%)	*p* values	GA 22^0–26^6 weeks (*n* = 43, 41%)	GA 27^0–32^0 weeks (*n* = 62, 59%)	*p* values
Before intervention							
Median (IQR)	11 (10–14)	12 (10–14)	11 (10–11)	**0.013**	11 (10–13)	12 (10–14)	0.307
Score <14, *n* (%)	79 (75.2)	58 (70.7)	21 (91.3)	**0.011**	35 (81.4)	44 (71.0)	0.215
During laryngoscopy							
Median (IQR)	13 (11–15)	13 (11–15)	13 (13–17)	0.802	11 (9–14)	13 (11–17)	**0.031**
Score <14, *n* (%)	64 (61.0)	51 (62.2)	13 (56.6)	0.626	32 (74.4)	32 (51.6)	**0.016**
During surfactant administration							
Median (IQR)	11 (10–14)	11 (10–14)	12 (9–14)	0.641	10 (9–12)	12 (10–15)	**0.004**
Score <14, *n* (%)	77 (73.3)	60 (73.2)	17 (73.9)	0.944	39 (90.7)	38 (61.3)	<**0.001**
After intervention							
Median (IQR)	11 (10–13)	12 (10–14)	11 (10–12)	0.665	10 (9–12)	12 (10–14)	0.100
Score <14, *n* (%)	66 (78.6)	49 (73.1)	23 (100)	<**0.001**	28 (90.3)	38 (71.7)	**0.027**

Table 3. COMFORTneo scores in infants receiving non-pharmacological versus pharmacological analgesia during LISA

COMFORTneo score	Non-pharmacological analgesia (n = 105, 93%)	Pharmacological analgesia (n = 8, 7%)	p values
Before intervention			
Median (IQR)	12 (10–14)	9 (7–11)	0.132
Score <14, n (%)	79 (75.2)	7 (87.5)	0.438
During laryngoscopy			
Median (IQR)	13 (11–15)	13 (8–15)	0.772
Score <14, n (%)	64 (61.0)	5 (62.5)	0.932
During surfactant administration			
Median (IQR)	11 (10–14)	9 (7–12)	0.443
Score <14, n (%)	77 (73.3)	7 (87.5)	0.313
After intervention			
Median (IQR)	12 (10–14)	9 (7–13)	0.756
Score <14, n (%)	66 (78.6)	5 (83.3)	0.785

In the GA subgroup analysis, we found that infants with lower GAs (i.e., 22^0–26^6 weeks) displayed more frequent COMFORTneo scores <14 during laryngoscopy (74.4% vs. 51.6%, $p = 0.016$), surfactant administration (90.7% vs. 61.3%, $p < 0.001$), and after intervention (90.3 vs. 71.7%, $p = 0.027$) compared to higher GA groups (i.e., 27^0–32^0 weeks, Table 2). COMFORTneo scores for individual weeks of gestation are given in the online supplementary Table 1.

There was no difference in COMFORTneo scores between infants who received pharmacological and non-pharmacological analgesia (Table 3). As baseline characteristics of these infants were not comparable, a subgroup analysis was performed including only infants >29 weeks of gestation. Although in this analysis, infants who received pharmacological analgesia showed higher median COMFORTneo scores before LISA as well as during laryngoscopy and surfactant administration, there was no difference between the groups regarding the percentage of infants within the comfort zone throughout the LISA procedure. Detailed results of this subgroup analysis are given in online supplementary Table 3.

Discussion

Our study showed that in a cohort of 105 VPI, non-pharmacological analgesia provided adequate comfort in 61% of the infants during the most stressful part of LISA, which was laryngoscopy. This percentage is high and comparable to the sedated group of similar studies [17, 18]. In these studies, in contrast, only 11–22% of the non-sedated infants were within the designated comfort range. Similar to other studies, our results suggest a high effectiveness of non-pharmacological measures to reduce procedural pain and stress in preterm and term neonates [19–21]. In our study, we applied a bundle of non-pharmacological measures including optional application of sucrose 24% solution. Oral sucrose has been shown to alter behavioral response of infants undergoing painful procedures [20] but failed to have any significant impact on nociceptive brain activity [22]. If and to what extent other non-pharmacological measures influence the activation of pain networks in the brain has not been investigated so far and definitely warrants investigation.

In lower GAs <27 weeks, the percentage of infants in the comfort zone was highest with 74%. One could argue that it may be more difficult for the tiniest infants to express their discomfort. However, the COMFORTneo scale was adapted, especially in this regard, and is a well validated assessment tool from 24 weeks of gestation onward [23]. We also included infants <24 weeks of gestation (9 in total) into our study. The assessment of discomfort in these infants is particularly challenging as thalamocortical afferents, the structural basis for the perception of pain and discomfort, invade the cortical plate only around 25 weeks of gestation [24]. Thus, it is uncertain which tool is the appropriate to assess discomfort in these tiny infants and whether we even have one. However, by including these infants into the study, we overcame the limitation of representativeness of the population, which is an issue in many studies, despite the increasing use of LISA also in this age-group [25]. Importantly, overall results did not change when excluding these infants (data not shown).

A higher incidence of BPD and severe IVH were observed in the group of infants <27 weeks of gestation. As there was no difference in hemodynamic stability

during LISA compared to infants with higher GAs, we attribute these complications to the higher immaturity at birth and not the LISA procedure itself. In fact, recent data report that the LISA procedure is not associated with an elevated incidence of mortality and morbidity [5].

In our study, we did not observe any differences in comfort levels during delivery and rescue LISA. However, before and after LISA, more infants were within the comfort range in the rescue LISA group. The relevance of these findings remains unclear. We can only speculate that the immediate cardiorespiratory adaptations of a preterm infant in the first hour of life may contribute somehow to elevated levels of discomfort. Desaturation and bradycardia were more frequent in infants receiving rescue LISA, and more attempts were needed to insert the catheter into the trachea. We hypothesize that at the time point of rescue LISA, hemodynamic and respiratory responses may have been altered compared to the first hour of life, where vasopressin levels are high and contribute to endogenous analgesia [7–9]. This may have contributed to an increased number of respiratory complications. Besides the time point of LISA, the complications may also be related to the fact that infants in the rescue LISA group had a higher GA and BW and may have been more vigorous.

As practiced in many centers, the decision whether or not to give analgesia was left to discretion of the attending neonatologist, and the first LISA attempt was performed without analgesia [25]. This resulted in a very low number of infants in this group with a higher GA and BW compared to infants who received non-pharmacological analgesia. It may reflect the recent consensus guideline, which recommends sedation, particularly in infants of higher GAs [26]. Still, based on our results, we suggest [17, 18, 27] that leaving the decision whether or not to apply analgosedation to the treating physician may not be the adequate tool to identify those infants who may actually benefit from analgesia, and a more objective tool is warranted. It also remains unclear whether the used drugs may have been optimal. The drug of choice for analgosedation in our study was, similarly to others, ketamine, which has both sedative and analgesic properties and a relatively safe respiratory and hemodynamic profile [23, 25]. Further studies are definitely needed to investigate the potential of pharmacological analgesia to provide comfort during LISA. Overall, the group of infants who received pharmacological analgesia in our study was very small, and the baseline characteristics of the infants who did and did not receive pharmacological analgesia were, due to the study design, not comparable. This limits the possibility to interpret the results as a selection bias may be likely [23, 25].

Technical conditions are often reported as good or excellent with analgosedation [23]. Still, in our study, in as much as 81% of the infants, only one laryngoscopy attempt was necessary to perform LISA. This might be attributed to both the standardization of non-pharmacological treatment in our units and the experienced physicians who performed LISA, i.e., neonatal fellows and neonatologists. In a similar study, the success rate of LISA at the first attempt was comparable to our study for neonatologists, but the overall success rate at the first attempt was significantly lower [23]. This confirms previous data indicating that the level of experience of the operator is an important determinant of success [28]. More attempts to insert the catheter into the trachea were observed in the infants who received pharmacological analgesia in our study. This is attributable to the fact that, according to our protocol, the first attempt of LISA was performed without analgesia [17, 18]. Analgosedation was used primarily during rescue LISA. As discussed above already, besides analgosedation, the chosen time point of LISA may have eventually additionally contributed to hemodynamic and respiratory instability as these infants may benefit less from endogenous analgesia released immediately after birth [7–9].

In the infants who received non-pharmacological analgesia, the median increase in the COMFORTneo score from baseline to laryngoscopy was 1–-2 points, while it was 4 points in the sedated infants. The pathophysiological background for this is unknown. Further studies are needed to identify a cutoff level where to give analgosedation in order to guarantee infants being comfortable also during laryngoscopy.

Our study is limited by the above-mentioned fact that the COMFORTneo scale is validated from 24 weeks of gestation on only. A further limitation is, as repetitively mentioned, the small number of infants who received pharmacological analgesia. However, the assessment of comfort in infants who received pharmacological analgesia during LISA was not the aim of our study. Further studies are warranted to investigate the effect of the various analgosedative medications in the context of LISA. Theoretically, the LISA procedure would limit the evaluation of facial expression and, as a consequence, the effectiveness of the COMFORTneo scale. We tried to overcome this limitation by video recording the LISA procedure from a pre-specified perspective. Additionally, one extremity of the assessed infant was excluded from measures of non-pharmacological analgesia such as holding and facilitated tucking to evaluate body movements and muscle tone. This was done in accordance with

international experts in the field and seemingly did not alter the analgetic potential of these measures. The video recordings had the further benefit that they could be viewed multiple times. A strength of our study is the representative study cohort, including a relevant number of extremely preterm infants, which is the main population in which LISA is performed. Furthermore, to our knowledge, this is the largest cohort ever in which non-pharmacological analgesia for LISA has been investigated.

Conclusion

The results of our study encourage the use of non-pharmacological analgesia in VPI for LISA. Further research is needed to develop individualized treatment protocols, which allow the identification of infants who, despite receiving non-pharmacological analgesia, are at high risk for experiencing discomfort during LISA and would benefit from pharmacological interventions.

Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, approved by the Local Ethics Committees (EK Nr. 2291/2019/EK Nr. Z. 20-1087) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00022317). Inborn very preterm infants with signs of RDS and the need for surfactant replacement were recruited after obtaining written parental consent.

Conflict of Interest Statement

The authors do not have any conflicts of interest to report.

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Author Contributions

K.P., B.K., S.S., and K.K. were involved in recruiting and collecting clinical data of the infants. K.P., J.D., and V.G. performed the statistical analysis and drafted the manuscript, helped by B.K., A.B., and A.K. K.K. and A.K. supervised the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European consensus guidelines on the management of respiratory distress syndrome 2019 update. Neonatology. 2019;115(4):432–50.
2 Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378(9803):1627–34.
3 Kribs A, Roll C, Göpel W, Wieg C, Groneck P, Laux R, et al. Nonintubated surfactant application versus conventional therapy in extremely preterm infants: a randomized clinical trial. Jama Pediatr. 2015;169(8):723–30.
4 Abdel-Latif ME, Davis PG, Wheeler KI, De Paoli AG, Dargaville PA. Surfactant therapy via thin catheter in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2021;5(5):CD011672.
5 Härtel C, Herting E, Humberg A, Hanke K, Mehler K, Keller T, et al. Association of administration of surfactant using less invasive methods with outcomes in extremely preterm infants less than 27 Weeks of gestation. Jama Netw Open. 2022;5(8):e2225810.
6 Knudsen K, Nilsson U, Högman M, Pöder U. Awake intubation creates feelings of being in a vulnerable situation but cared for in safe hands: a qualitative study. BMC Anesthesiol. 2016;16(1):71.
7 Kasser S, Hartley C, Rickenbacher H, Klarer N, Depoorter A, Datta AN, et al. Birth experience in newborn infants is associated with changes in nociceptive sensitivity. Sci Rep. 2019;9(1):4117.
8 Klotz D, Porcaro U, Fleck T, Fuchs H. European perspective on less invasive surfactant administration—a survey. Eur J Pediatr. 2017;176(2):147–54.
9 Kurepa D, Perveen S, Lipener Y, Kakkilaya V. The use of Less Invasive Surfactant Administration (LISA) in the United States with review of the literature. J Perinatol. 2019;39(3):426–32.
10 De Luca D, van Kaam AH, Tingay DG, Courtney SE, Danhaive O, Carnielli VP, et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. Lancet Respir Med. 2017;5(8):657–66.
11 Deeg KH, Staudt F, von Rohden L. Classification of intracranial hemorrhage in premature infants. Ultraschall Med. 1999;20(4):165–70.
12 Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. Am J Respir Crit Care Med. 2019;200(6):751–9.
13 Martherus T, Oberthuer A, Dekker J, Kirchgaessner C, van Geloven N, Hooper SB, et al. Comparison of two respiratory support strategies for stabilization of very preterm infants at birth: a matched-pairs analysis. Front Pediatr. 2019;7:3.
14 Silverman WA, Andersen DH. A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. Pediatrics. 1956 Jan;17(1):1–10.

15 van Dijk M, Roofthooft DWE, Anand KJS, Guldemond F, de Graaf J, Simons S, et al. Taking up the challenge of measuring prolonged pain in (premature) neonates the COMFORTneo scale seems promising. Clin J Pain. 2009;25(7):607–16.
16 Dekker J, van Zanten HA, Tan RNGB, Hooper SB, Te Pas AB, Lopriore E. A randomized controlled trial in low-dose sedation during minimal invasive surfactant therapy. Am J Perinatology. 2018;35(S 01):A040.
17 Dekker J, Lopriore E, Rijken M, Rijntjes-Jacobs E, Smits-Wintjens V, Te Pas A. Sedation during minimal invasive surfactant therapy in preterm infants. Neonatology. 2016;109(4):308–13.
18 Dekker J, Lopriore E, van Zanten HA, Tan RNGB, Hooper SB, Te Pas AB. Sedation during minimal invasive surfactant therapy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2019;104(4):F378–83.
19 Vento M, Bohlin K, Herting E, Roehr CC, Dargaville PA. Surfactant administration via thin catheter: a practical guide. Neonatology. 2019;116(3):211–26.
20 Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2016;7(7):CD001069.
21 Committee On Fetus And Newborn And Section On Anesthesiology And Pain Medicine. Prevention and management of procedural pain in the neonate: an update. Pediatrics. 2016;137(2):e20154271.
22 Slater R, Cornelissen L, Fabrizi L, Patten D, Yoxen J, Worley A, et al. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. Lancet. 2010;376(9748):1225–32.
23 de Kort E, Kusters S, Niemarkt H, van Pul C, Reiss I, Simons S, et al. Quality assessment and response to Less Invasive Surfactant Administration (LISA) without sedation. Pediatr Res. 2020;87(1):125–30.
24 Kostović I, Judaš M. The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatr. 2010;99(8):1119–27.
25 Tribolet S, Hennuy N, Snyers D, Lefèbvre C, Rigo V. Analgosedation before less-invasive surfactant administration: a systematic review. Neonatology. 2022;119(2):137–50.
26 Reynolds P, Bustani P, Darby C, Fernandez Alvarez JR, Fox G, Jones S, et al. Less-invasive surfactant administration for neonatal respiratory distress syndrome: a consensus guideline. Neonatology. 2021;118(5):586–92.
27 Krajewski P, Szpecht D, Hożejowski R. Premedication practices for less invasive surfactant administration — results from a nationwide cohort study. J Maternal-fetal Neonatal Med. 2022:35(24):4750–4754.
28 Foglia EE, Ades A, Sawyer T, Glass KM, Singh N, Jung P, et al. Neonatal intubation practice and outcomes: an international registry study. Pediatrics. 2019;143(1):e20180902.