



Less Invasive Surfactant Administration Versus Intubation for Surfactant Delivery in Very Low Birth Weight Infants

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ABSTRACT

Aim: Routes for surfactant administration for respiratory distress syndrome (RDS) has changed from bolus endotracheal administration together with ongoing mechanical ventilation, to intubation-surfactant administration and rapid extubation (INSURE) method and finally to less invasive surfactant administration (LISA). In this study our aim was to compare respiratory outcomes of LISA and INSURE methods for surfactant delivery in very low birth weight (VLBW) infants.

Materials and Methods: This retrospective, single-center study was performed in a one year period in between March 2014-2015. Data of VLBW infants who had diagnosis of RDS and received surfactant treatment via LISA or INSURE techniques were analyzed. Primary outcome of the study was failure of non-invasive respiratory support. Secondary outcomes were bronchopulmonary dysplasia diagnosis and its severity, duration of mechanical ventilation via endotracheal tube, total number of surfactant administered, duration of hospitalization and duration of all sorts of non-invasive respiratory support. Non-invasive ventilatory support failure incidences of LISA group according to gestational ages were also analyzed.

Results: Fifty-nine VLBW infants in LISA group and 55 VLBW infants in INSURE group were analyzed. Need for intubation/reintubation (non-invasive ventilatory support failure) was significantly lower in LISA group (31.6% vs 49%, $p=0.043$). Duration of intubation was significantly longer in INSURE group [0 vs 4 days (median), $p=0.001$]. Both LISA and INSURE treated infants had similar moderate to severe BPD ratios (26.6% vs 32.7%, $p=0.306$). We did not observe any reported complications during application of both methods. Intubation ratios were lowest in the group with gestational ages 28-29 weeks (25%).

Conclusion: LISA technique for surfactant delivery to preterms with RDS is a safe method ending with lower rates of need for intubation/reintubation. Even if no difference in BPD incidences in between the two groups was observed at the 36th corrected gestational week, intubation duration of infants was significantly lower in LISA group.

Keywords: LISA, INSURE, surfactant, preterm infant

Introduction

Respiratory distress syndrome (RDS) is a common morbidity experienced in premature infants, having the major etiology of surfactant deficiency (1). This deficiency

was described nearly 60 years ago and treatment of preterm infants with exogenous surfactant preparations has been one of the most important milestones in neonatology (2). Surfactant treatment, as the most effective evidence-based

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therapy for RDS, has been shown to reduce the risk of death and bronchopulmonary dysplasia (BPD) in preterm infants (3,4). Since its first use, routes for surfactant administration have changed from bolus endotracheal administration together with ongoing mechanical ventilation, to the intubation-surfactant administration and rapid extubation (INSURE) method and finally to less invasive surfactant administration (LISA) which enables infants to go on spontaneous breathing whilst having non-invasive respiratory support without facing the consequences of intubation (1,5). Even if infants are extubated shortly after receiving surfactant by the INSURE method, there is still a brief time of positive pressure ventilation (1). However, ventilator-induced lung injury poses many risks for the vulnerable lungs of preterm infants (6-10). Non-invasive ventilation is better compared to mechanical ventilation via endotracheal tube in terms of causing less alveolar injury (11-13).

A variety of guidelines in Europe indicate LISA to be the method of choice for surfactant administration (14-16). Additionally, there is significant interest in LISA worldwide with an increasing number of studies (17-22). Furthermore, LISA is a holistic non-invasive approach which aims to support the maximum capacity of the preterm to fulfill its potential during the adaptation period to extrauterine life (1). With the results of several randomized controlled trials, the need for mechanical ventilation was shown to decrease as a result of LISA (23-25). Not only intubation rates, but also the rate of BPD in LISA-treated preterm infants is low compared to international standards (1).

With all this knowledge, the aim of our study was to compare the respiratory outcomes of the LISA and INSURE methods for surfactant delivery in VLBW infants in a single center during a 1-year period.

Materials and Methods

This retrospective, single-center study was performed in the Izmir Medical Park Hospital Neonatal Intensive Care Unit (Izmir, Turkey). The medical records of preterm inborn or outborn infants who had been hospitalized in a one year period between March, 2014 and March, 2015 were reviewed for eligibility in this study. Data of VLBW infants who had received a diagnosis of RDS and received surfactant treatment via the LISA or INSURE techniques were analyzed. A flowchart of the included and excluded infants is shown in Figure 1. The RDS diagnosis and surfactant indications were made according to the guidelines of Turkish Neonatal Society (TNS) (26). Preterm infants who exhibited symptoms such

as tachypnea, grunting, need for oxygen supplementation, and/or retractions were diagnosed as RDS. This diagnosis was confirmed by typical X-ray and blood gas findings. Surfactant was administered if the patient required ≥ 0.40 FiO_2 to maintain the target oxygen saturation level of 90-95% along with these signs and symptoms.

According to the individual guidelines of the unit, the decision for which technique to use was given by the attending physician. As an inclusion criterion, only those infants who received Poractant Alfa with a dose of 200 mg/kg and who had reached the 36th postmenstrual age were accepted. Infants with major congenital anomaly, who had received another type of surfactant preparation, who could not be extubated shortly after surfactant administration and/or whose digital medical records could not be obtained were excluded. This study was approved by Institutional Ethical Committee conducted in Buca Seyfi Demirsoy Training and Research Hospital (approval no: 2021/4-39 dated on 28.04.2021).

Both inborn and outborn infants were supported by delivery room teams who were experienced regarding pregnancy, and which risks needed to be identified before each delivery. Each unit had a checklist of materials which were required in the premature infants' delivery room for stabilization and/or resuscitation and the members of each team were competent in performing the recommended neonatal resuscitation program. Preterm infants with findings of respiratory insufficiency received non-invasive ventilatory support by NCPAP with at least 5 $\text{cm-H}_2\text{O}$ through binasal prongs in the delivery room and during the transportation in cases where no urgent intubation indication emerged. Hypothermia was prevented and all of the preterm infants were monitored both clinically and by pulse-oximeters. All infants received prophylactic caffeine treatment according to the institutional guidelines and both the LISA and INSURE techniques were performed by the same team, similar to the methods described in the study conducted by Kanmaz et al. (21). In this technique, a 5F sterile and flexible nasogastric tube is used. The tube is shortened at 33 cm depth from the catheter hub. For the insertion depths, the gestational age of the infant is determinative. When the catheter is inserted through the vocal cords, 1.0, 1.5 and 2.0 cm insertions are performed for infants of 25-16, 27-28 and 29-32 gestational weeks, respectively. Standard laryngoscope and Miller 00 blade are used for direct laryngoscopy and catheter placement. The surfactant is drawn into a 5 mL syringe before direct laryngoscopy is performed. At this step, a

standard laryngoscope with a straight blade is used and the catheter is immediately removed as the planned amount of surfactant and 1 mL of air is applied. All throughout this procedure, the infants is kept on non-invasive ventilation support. As a standard policy, none of the infants receive premedication. The Jobe and Bancalari classification is used for BPD diagnosis and classification (22).

The primary aim of this study was to investigate the failure of non-invasive respiratory support. The secondary outcomes were BPD diagnosis and its severity, the duration of mechanical ventilation via endotracheal tube, the total amounts of surfactant administered, the duration of hospitalization and the duration of all sorts of non-invasive respiratory support. The non-invasive ventilatory support failure incidences of the LISA group according to gestational ages were also analyzed.

Statistical Analysis

Statistical analysis was conducted using the SPSS software for Windows version 25.0 (IBM, Armonk, NY: IBM Corp.) Descriptive statistics were used including mean (with standard deviations) and median [minimum-maximum (min.-max.)] for continuous variables, and counts (proportions) for categorical variables. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Student's t-test and the Mann-Whitney U test compared continuous variables for parametric and non-parametric variables, respectively. The chi-square test was used for categorical variables. Statistical significance was considered if the p-value was <0.05.

Results

A total of 383 preterm infants were hospitalized during the period of this study and 189 of them were very low birth weight (VLBW) infants. The data of the VLBW infants who had RDS diagnoses and who received

surfactant treatment via the LISA or INSURE methods were analyzed. Of the 130 infants who were treated via these two methods, 16 had insufficient medical records and finally, 59 VLBW infants in the LISA group and 55 VLBW infants in the INSURE group were analyzed (24-32 weeks) (Figure 1). The demographic characteristics and antenatal steroid rates of the infants in the two groups were similar (Table I).

The need for intubation/reintubation (non-invasive ventilatory support failure) was significantly lower in the LISA group (31.6% vs 49%, $p=0.043$). The total amount of surfactant administered was similar between the two groups ($p=0.492$). The duration of intubation was significantly longer in the INSURE group [0 vs 4 days (median), $p=0.001$]. The median duration of non-invasive ventilation was 11 (0-180) days for the LISA group and 20 (0-76) days for the INSURE group but this did not reach statistical significance ($p=0.035$). Both LISA and INSURE treated infants had similar moderate to severe BPD ratios (26.6% vs 32.7%, $p=0.306$) (Table II). The median duration of total oxygen support was similar in both groups at 37 (2-250) days for the LISA group and 48 (0-219) days for the INSURE group ($p=0.039$). However, there was a statistically significant difference regarding the duration of hospitalization between the two groups, being longer in the INSURE group (62.4 ± 28.9 vs 87.5 ± 46.4 , $p=0.001$). We did not observe any reported complications during the application of either method. None of the infants experienced adverse events such as air leak, significant surfactant reflux, unilateral administration of surfactant or deterioration in vital signs leading to an interruption of the application.

When we performed subgroup analysis, classifying the LISA group according to their gestational ages, the intubation ratios were similar between the 3 subgroups (Table III).

Table I. Basic demographic characteristics of the infants

	LISA n=59	INSURE n=55	p-value
Gestational age, (weeks, mean±SD)	28.14±1.95	27.5±2.07	0.140
Birth weight (gr, mean±SD)	1106±292	1009±291	0.089
Maternal age, (years, mean±SD)	29.8±5.1	29.4±8.3	0.784
Antenatal steroid, n (%)	35 (59.3)	32 (58.2)	0.541
Gender, female, n (%)	27 (45.8)	27 (49)	0.739
Caesarean delivery, n (%)	50 (84.7)	45 (83.3)	0.842

LISA: Less invasive surfactant administration, INSURE: Intubate-Surfactant-Extubate

Table II. Incidence of short and long term respiratory morbidities

	LISA n=59	INSURE n=55	p-value
Need for intubation/reintubation, n (%)	19 (31.6)	27 (49)	0.043
Total number of surfactant administration (mean±SD)	1.7±1.5	2.02±2.3	0.492
Duration of intubation (days, mean±SD)	3.68±11.3	15.7±23.7	0.001
Duration of noninvasive ventilation [days, median (min-max)]	11 (0-180)	20 (0-76)	0.035
Total duration of oxygen support [days, median (min-max)]	37 (2-250)	48 (0-219)	0.039
BPD (moderate, severe), n (%)	16 (26.6)	18 (32.7)	0.306
Duration of hospitalization (days, mean±SD)	62.4±28.9	87.5±46.4	0.001

LISA: Less invasive surfactant administration, INSURE: Intubate-Surfactant-Extubate, BPD: Bronchopulmonary dysplasia

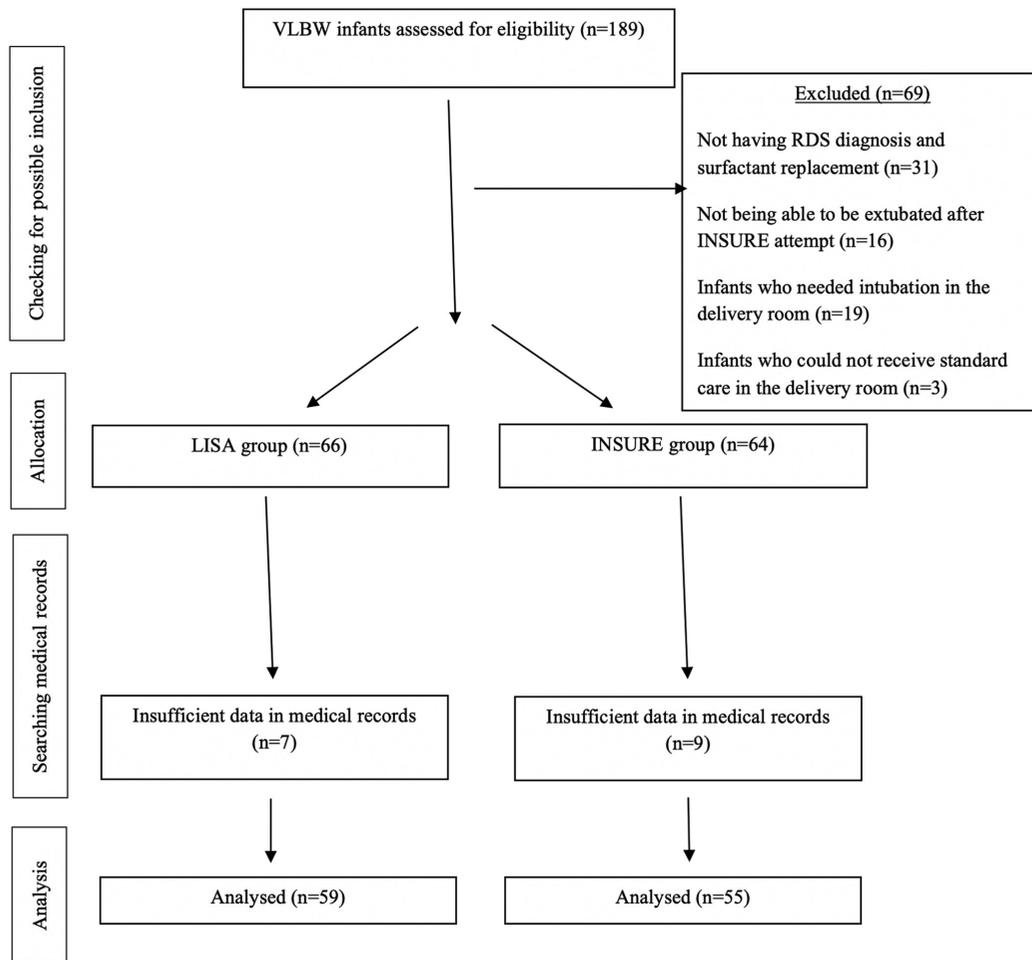


Figure 1. Flow diagram of included and excluded infants

Table III. Non-invasive ventilatory support failure incidences of LISA group according to gestational ages

	Total number of infants, n (%)	Intubation ratio (%)	p-value
<26 wk GA	4 (6.8)	50	0.617
26-27 ⁶ wk GA	19 (32.2)	42.4	
28-29 ⁶ wk GA	20 (33.9)	25	
30-32 wk GA	16 (27.1)	31	

GA: Gestational age, wk: Week

Discussion

In our study, we found lower intubation/reintubation rates with the LISA method compared to INSURE. In a meta-analysis comparing LISA with the standard method of surfactant delivery, data of 6 randomized controlled trials on 895 infants were evaluated and the LISA method was found to result in less need for mechanical ventilation, similar to the results of our study (27). In the same meta-analysis, BPD was evaluated together with death or the need for mechanical ventilation within 3 days of birth and it was seen that there was a reduction in these parameters with the use of LISA. In our study, moderate to severe BPD rates were less in the LISA group compared to the INSURE group. Our result is consistent with the findings of previous studies showing a reduction in BPD rates at the 36th week (21,28,29). As we did not include infants who died before the 36th gestational week and evaluated BPD rates among survivors, a composite outcome analysis was not possible in our study.

According to results of our study, the duration of mechanical ventilation was significantly lower in the LISA group. This finding was also consistent with the results of the studies conducted by Kanmaz et al. (21) and Göpel et al. (24) while several other studies reported similar durations of mechanical ventilation when the two groups are compared (15).

In our study, we preferred surfactant preparations of porcine origin with a starting dose of 200 mg/kg according to the recommendations of TNS and as a rescue treatment (26). There are different approaches in the literature such as using a whole vial of 120 mg, regardless of the infant's weight, or doses of 100 mg/kg or 200 mg/kg (24,25,30). In our experience, we know that reflux of surfactant during LISA is a common issue, experienced by many neonatologists. Due to this knowledge, we believe that following the recommendations of TNS is not only safe, but also offers the extra advantage of delivering the correct amount of surfactant to the lungs. According to results of our study, similar to previous studies, we also showed that the administration of surfactant by

LISA is a safe procedure. As LISA is not a common technique, the failure to insert the catheter, a deterioration of the vital signs during the application, a significant surfactant reflux when inserting the catheter to a single bronchus, and/or air leak syndromes are all examples of reported complications (18,19,24,31,32). We did not observe any complications during the process. This may be due to the experience and skill of the dedicated neonatologist/pediatrician performing this procedure as it is one of the most important factors in not experiencing such side effects.

In our study, when we divided the LISA group infants according to their gestational ages, the intubation rates were highest in the <26 gestational-week group and lowest in the 28-29⁶ gestational-week group but this did not reach statistical significance (p=0.617) (Table III). In one paper, where data of the German Neonatal Network was analyzed, it was reported that as the gestational age increased from the 22nd to the 30th weeks, the ratio of the need for mechanical ventilation within the first 3 days decreased (1). We still do not have evidence regarding the possible benefits of LISA for infants over 32 weeks but it is known that these more mature infants may have difficulty in tolerating the procedure without sedation/analgesia. We believe that a study including a larger population and also including >32 week infants will reveal more significant results regarding the sub-group differences relating to intubation needs.

Last but not least, we want to emphasize that LISA must be used as a component of multiple non-invasive/less invasive techniques in order to support the infant's adaptation to the world in a more natural and secure way. LISA should not be applied as an isolated method in order to achieve its maximum benefits. Starting in the antenatal periods, extending to the delivery room and neonatal intensive care units, avoiding all unnecessary procedures and manipulations is important. Otherwise, the LISA technique will not fulfill its potential.

Study Limitations

The main limitation of this study is that we only included infants who were able to survive until their date of evaluation for BPD so we could not make precise analyses about mortality. Another limitation is that medical records of some of the infants could not be accessed. Only one type of surfactant preparation was administered to the infants and no data regarding other types of preparations were available. However, rather than being a limitation, this may even be a positive aspect of our study. As a non-invasive respiratory support modality, we did not further analyze the infants according to mode and both nasal CPAP and nasal SIPPV methods were accepted as a single modality. However, as a standard of care, non-invasive ventilation support was initiated with NCPAP for all infants in the delivery room. The ventilator modality of the infant is chosen as either NCPAP or NSIPPV according to the preference of the attending physician.

Conclusion

The findings of our study have shown that the LISA technique for surfactant delivery to preterms with RDS is a safe method resulting in lower rates of the need for intubation/reintubation. Additionally, in cases where the need for intubation emerged, the intubation duration of those infants was significantly lower in the LISA group. Evaluated at the 36th corrected gestational week, we did not observe any difference in BPD incidences between the two groups. When sub-group analysis was performed according to 3 different gestational ages in the LISA group in order to compare intubation rates, even though differences were present, no statistical significance was observed between the sub-groups.

Ethics

Ethics Committee Approval: This study was approved by Institutional Ethical Committee conducted in Buca Seyfi Demirsoy Training and Research Hospital (approval no: 2021/4-39 dated on 28.04.2021).

Informed Consent: Retrospective, single-center study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: S.G., Design: S.G., Data Collection or Processing: S.G., S.Ş., Analysis or Interpretation: S.Ş., Literature Search: S.Ş., Writing: S.Ş.

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