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ORIGINAL ARTICLE

Less invasive surfactant administration versus intubation-surfactant-extubation in preterm infants: a retrospective study

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ABSTRACT

Aim To compare the need for intubation and mechanical ventilation after surfactant delivery between less invasive surfactant administration (LISA)-treated and intubation-surfactant-extubation (INSURE)-treated premature infants with respiratory distress syndrome (RDS).

Methods Retrospective registry-based cohort study enrolled 36 newborns admitted to the Neonatal Intensive Care Unit of the "Santa Maria" Hospital of Terni between 2016 and 2023. As a primary outcome, the need for intubation and mechanical ventilation within 72 hours of life was followed, and major neonatal morbidities and death before discharge as the secondary outcome.

Results The LISA group and the INSURE group included 13 and 23 newborns, respectively. Demographic features showed no significant differences between the two groups. The need for mechanical ventilation in the first 72 hours of life was similar in both groups ($p>0.99$). There were no significant differences in morbidities.

Conclusion LISA and INSURE are equally effective modalities for surfactant administration for the treatment of RDS in preterm infants.

Keywords: newborn, respiratory distress syndrome, surfactant

INTRODUCTION

Respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in preterm infants (1). Early nasal continuous positive airway pressure (nCPAP) and selective administration of surfactant via the endotracheal tube are widely used in the treatment of RDS in preterm infants (2). Although treating RDS with surfactant improves clinical outcomes, mechanical ventilation (MV) can cause lung injury in preterm infants with RDS and contribute to the development of bronchopulmonary dysplasia (BPD) (3,4). The intubation-surfactant-extubation (INSURE) technique was introduced in 1992 by Verder et al. (5) to reduce the duration of MV. However, the INSURE method does not allow to completely avoid MV and poses a potential risk of iatrogenic laryngeal or tracheal damage. On the other hand, during the "less invasive surfactant administration" (LISA) technique, surfactant is instilled into the trachea of a spontaneously breathing neonate on nCPAP, via a thin catheter placed in the trachea (6).

The LISA method is becoming increasingly popular in neonatology departments. In a recent systematic review, Isayama et al. have found that LISA decreased the need for MV, as well as reduced the incidence of intraventricular haemorrhage (IVH) and BPD (7).

Comparing outcomes between the two methods of surfactant administration is crucial, as understanding the best strategy for pulmonary surfactant administration may improve the future quality of life of preterm infants.

The aim of this study was to evaluate the effect of administering surfactant by LISA method using an orogastric

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feeding tube over the traditional INSURE method on the duration of MV and other modalities of respiratory support.

PATIENTS AND METHODS

Patients and study design

This retrospective cohort study was performed in the level III Neonatal Intensive Care Unit (NICU) of "Santa Maria" Hospital (Terni, Italy). Medical records of preterm infants, who were born between 25 to 36 weeks of gestation from January 2016 to December 2023, were collected from the hospital database. Newborns with major congenital anomalies, as well as infants who required intubation in the delivery room, were excluded from the study.

Methods

The diagnosis of RDS was based on clinical symptoms (tachypnoea, grunting, subcostal and intercostal retractions, nasal flaring, and/or cyanosis), and a chest radiograph consistent with a reticulogranular appearance to the lung fields (8). Preterm infants with RDS were initially stabilized on non-invasive ventilation (NIV) in the form of nCPAP.

The technique for surfactant administration was chosen at the physician's discretion. Patients who received surfactant via the INSURE technique were first orally intubated with a single lumen appropriate sized endotracheal tube, and poractant alfa (Curosurf; Chiesi Farmaceutici, Parma, Italy) at a dose of 200 mg/kg was instilled to the trachea in 30 seconds. Manual lung inflation by using a T-piece device (Neopuff Infant Resuscitator; Fisher and Paykel, Auckland, New Zealand) at 20/5 cm H_2O pressure was performed during the surfactant instillation, and then the patient was rapidly extubated. After extubation, nCPAP support was maintained.

The LISA method was performed as follows: a 5 Fr, flexible, sterile nasogastric tube was inserted through the vocal cords under direct vision using a laryngoscope, without the need for Magill forceps and any sedation; porcine surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) at a dose of 200 mg/kg, which was previously prepared by drawing up in a 5-mL syringe with an additional 1 mL of air for dead volume of the instillation catheter, was administered in bolus in 30 to 60 seconds. The catheter was immediately removed and non-invasive respiratory support was continued.

Neonatal outcomes. The primary outcome of the study was the need for MV in the first 72 hours of life. Secondary outcomes were the requirement of ≥2 doses of surfactant, rates of hemodynamically significant patent ductus arteriosus (hsPDA), pneumothorax (PNX), IVH (grade ≥2) - Papile classification (9), retinopathy of prematurity (ROP) stage >2 as defined in the international classification (10), necrotizing enterocolitis (NEC) modified Bell's stage ≥2 (11), BPD as defined by Jobe and Bancalari (12), as well as sepsis, duration of hospital stay, and mortality before discharge. PNX was diagnosed via chest X-ray (13). When the clinical team suspected sepsis based on perinatal risk factors or clinical signs a sepsis screen was performed. Echocardiography was done for suspected patent ductus arteriosus and treated if hemodynamically significant.

Statistical analysis

Qualitative data were presented as frequencies and percentages. Quantitative data were expressed as mean (standard deviation; SD) or median (interquartile range). Pearson's χ^2 test or Fisher's exact test was used to compare categorical variables. To compare numerical variables, independent samples t-test or Mann–Whitney U-test was used. $p<0.05$ was considered significant.

RESULTS

A total of 36 infants, who were stabilized by nCPAP at birth and were administered surfactant via INSURE or LISA method were enrolled. Twenty-three infants received surfactant by INSURE and thirteen by LISA method. Demographic and clinical characteristics of the infants in the LISA and INSURE groups were similar (Table 1).

A total of 32 newborns were delivered by cesarean section. The mean birth weight (BW) of infants who received the surfactant by the INSURE method was 1554 g±502, with a minimum of 805 g and a maximum of 2805 g. In the LISA group, gestational age ranged from 25^{+5} to 35^{+0} weeks, and the BW ranged from 760 to 3075 g.

The MV was required in nine (out of 23; 39.1%) infants in the INSURE group and in five (out of 13; 38.4%) in the LISA group. Among the secondary outcomes, the prevalence of BPD was higher in the INSURE group, three (13%) and zero (0%), respectively, without statistical significance (p=0.288). No differences were observed between the two groups for IVH, NEC ≥ Bell stage 2, hsPDA, ROP requiring treatment, sepsis, and mortality before hospital discharge (Table 2).

There was no statistically significant difference in the total duration of respiratory support in both groups (p=0.454) (Figure 1).

The median (IQR) duration of MV was similar in both groups. The median (IQR) duration of hospital stay was 38 (24-49) days in the INSURE group and 27 (15-46) days in the LISA group (p=0.328). LISA reduced the median duration of hospital stay although the result was not statistically significant.

Table 1. Baseline characteristics of 36 infants enrolled in the study

Variable	INSURE (n=23)	LISA (n=13)	p
Gender (No; %)			
Male	8 (34.7)	5 (38.5)	0.825
Female	15 (65.2)	8 (61.5)	
Birth weight mean (±SD) (g)	1554 (±502)	1718 (±717)	0.428
Gestational age mean (±SD) (weeks)	30.78 (±2.50)	31.46 (±2.75)	0.456
SGA (No; %)	1 (4.3)	2 (15.3)	0.539
Delivery mode (No; %)			
Vaginal	1 (4.3)	3 (23)	0.124
C-section	22 (95.6)	10 (76.9)	
Apgar score median (IQR)			
1 min	7 (7-8)	7 (7-8)	0.488
5 min	9 (8-9)	9 (8-9)	0.582

INSURE, intubation-surfactant-extubation; LISA, less invasive surfactant administration; SGA, small for gestational age; IQR, interquartile range.

DISCUSSION

The management of RDS aims to provide interventions to maximize survival whilst minimizing potential adverse effects including BPD. For a long time, the standard approach to treating RDS involved surfactant therapy administered during intermittent positive pressure ventilation (IPPV). However, since MV has been identified as a risk factor for BPD due to potential airway and lung injuries (barotrauma/volutrauma), different strategies have been developed over time to address this issue (14,15). Although the INSURE procedure has been standard since the 1990s, it involves short-term endotracheal intubation followed by a brief period of MV. To avoid the negative effects of intubation and MV, less invasive procedures of surfactant replacement with thin catheters have emerged. The LISA method delivers the surfactant via a thin catheter while the infant is spontaneously breathing directly into the proximal airway (16). Multiple randomized, controlled trials suggest that, compared to more invasive methods like INSURE, LISA reduces the need for MV at 72 hours of life, and may potentially reduce the risk of BPD and mortality (17,18). LISA was also associated with reduced duration of hospital stay, reduced duration of oxygen supplementation, lower rates of other common neonatal morbidities, such as IVH, and lower rate of interventions for ROP (19). Despite these findings supporting the feasibility and safety of LISA, some relevant adverse events of LISA have been reported, including tracheal surfactant reflux, bradycardia, hypoxia, need for intubation, unilateral deposition of the surfactant, and mucosal bleeding (20).

Regarding the primary outcome of the present study, we found no significant difference in the need for MV within 72 hours of birth between the two groups. This is similar to findings from earlier studies (21–23). A single-centre randomized controlled trial in China among 90 spontaneously breathing preterm infants (from 28 to 32 weeks of gestational age) found no significant differences in the rate of MV in the first 72 hours of life (21). This aligns with the findings of a multicenter RCT from Iran involving 38 preterm infants (22). Another recent single-centre RCT by Gupta et al., comparing INSURE and minimally invasive surfactant therapy (MIST), also did not find any difference in the need for MV in the first 72 hours (23).

The MV has been associated with disruptions in the normal progression of alveolarization and pulmonary microvascular growth in preterm infants (24). Even brief periods of MV can activate complex inflammatory pathways and cause injury in preterm infants (25). Hence, minimizing the duration of MV is crucial to prevent damage and mitigate the risk of chronic lung disease. In presented study, the prevalence of BPD was lower in the LISA group, but without statistical difference. Similarly, a recent meta-analysis of three RCTs reported a lower risk of BPD with LISA compared to INSURE (26).

In the present study, the overall prevalence of ROP was very low with no baby requiring laser therapy or surgery for retinopathy of prematurity; the prevalence of PDA was similar in both study groups.

The length of hospital stay was similar in both the INSURE and LISA groups in our study, consistent with findings from a few other studies (27,28).

Table 2. Outcome parameters of infants with respiratory distress syndrome (RDS) after surfactant administration

Outcome	INSURE (n=23)	LISA (n=13)	p	Relative risk (95% CI)
Need for MV in the first 72 h (No; %)	9 (39.1)	5 (38.4)	>0.99	1.017 (0.432-2.394)
Median (IQR range)				
Duration of MV (days)	3 (2-6)	3 (2-10.5)	0.898	
Duration of NIV (days)	7 (4-23)	7 (4-30.5)	0.770	
Total duration of respiratory support (days)	7 (4-26)	9 (5.5-30.5)	0.454	
Length of hospital stay (days)	38 (24-49)	27 (15-46)	0.328	
No (%) of infants				
Repeat dose of surfactant	1 (4.3)	1 (7.6)	>0.99	0.565 (0.038-8.302)
Pneumothorax	2 (8.6)	3 (23)	0.328	0.377 (0.072-1.972)
Moderate-severe BPD	3 (13)	0	0.288	
Any sepsis	5 (21.7)	2 (15.3)	>0.99	1.413 (0.318-6.283)
ROP	0	0	NA	
hsPDA	4 (17.3)	0	0.274	
IVH > grade II	0	0	NA	
NEC ≥ stage II	0	0	NA	
Death	1 (4.3)	1 (7.6)	>0.99	0.565 (0.038-8.302)

INSURE, intubation-surfactant-extubation; LISA, less invasive surfactant administration; CI, confidence interval; MV, mechanical ventilation; NIV, non-invasive ventilation; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; IQR, interquartile range; NA, not applicable.

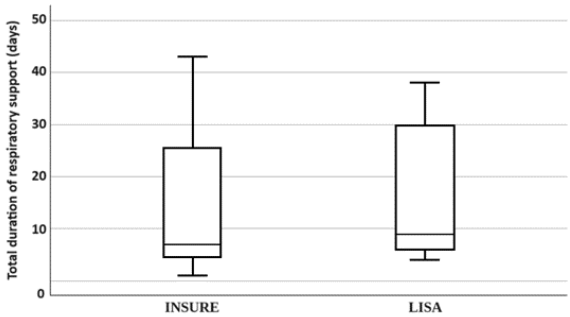

Figure 1. Comparison of the total duration of respiratory support (days) between INSURE and LISA groups (box plot)

However, Jena et al. reported a shorter duration of hospital stay in the LISA group, possibly linked to the lower rate of BPD in their study (18). The early discharge is influenced by several factors, including complications occurring during NICU stay (sepsis, feeding problems), social factors (parental presence and involvement), and public health factors. In this study, mortality rates were found to be similar in both groups, consistent with findings reported in existing literature (17,18,26).

In our retrospective study, the INSURE group had a relatively higher number of infants compared to the LISA group. This discrepancy could be attributed, at least in part, to the influence of doctors' attitudes, as suggested by findings in previous surveys (29,30).

One of the main limitations of the study was its retrospective design. In addition, the cohort was relatively small, and some patients were excluded due to inadequate data. Lastly, we only included patients who received poractant alfa. Therefore, the effects of other surfactant types were not analysed.

As a result, we found that the LISA method is safe and effective as much as the INSURE method. Future randomized controlled trials are needed to investigate the effect of these two methods on morbidities, particularly BPD.

In conclusion, we did not find any difference in the need for MV during the first 72 hours of life, the requirement of more than one dose of surfactant, duration of ventilator support, major complications, and mortality between the LISA and INSURE groups. The LISA procedure may be a good choice for spontaneously breathing infants with RDS. We believe that avoiding short-term intubation during surfactant administration could reduce the risk of BPD. The LISA method, involving surfactant instillation through a thin catheter, is a promising technique for achieving these positive effects and is considered a viable option for daily clinical practice in many NICUs.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare

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