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Original Research Article

Comparison of INSURE and LISA techniques in preterm neonates with respiratory distress

Chaitra Reddy Molugu[1]*, Molugu Hemanth Reddy[2], Ramisetti Manikanta[3]

[1]Kamineni Academy of Medical Sciences and Research Centre, L. B. Nagar, Hyderabad, Telangana, India
[2]Apollo Institute of Medical Sciences and Research, Jubilee Hills, Film Nagar, Hyderabad, Telangana, India
[3]Konaseema Institute of Medical Sciences (KIMS), Chaitanya Health City, Amalapuram, Andhra Pradesh, India

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***Correspondence:**
Dr. Chaitra Reddy Molugu,
E-mail: research.nmch@rediffmail.com

ABSTRACT

Background: Respiratory distress syndrome (RDS) is a major cause of morbidity in preterm neonates. Aim of the study is to compare respiratory outcomes, procedure-related complications, neonatal morbidities, and hospitalization outcomes following surfactant administration by Less Invasive Surfactant Administration (LISA) versus INSURE in preterm neonates with RDS.
Methods: This comparative clinical cohort study included 100 preterm neonates diagnosed with RDS. Fifty neonates received surfactant by LISA and 50 by INSURE. In the LISA group, surfactant (200 mg/kg) was administered through a 5F thin catheter while spontaneous breathing was maintained on non-invasive respiratory support. In the INSURE group, surfactant was administered following endotracheal intubation, followed by positive-pressure ventilation and extubation. Demographic characteristics, respiratory outcomes, procedure-related complications, neonatal morbidities, and duration of respiratory support and hospitalization were compared.
Results: Mean gestational age was 30.35±3.12 weeks in the LISA group and 31.50±4.26 weeks in the INSURE group (p=0.127), and mean birth weight was 1952.8±750.92 g and 1968.5±850.88 g, respectively (p=0.956). Desaturation during surfactant administration was significantly less frequent with LISA than INSURE (20% vs. 40%; p=0.029). LISA also showed lower rates of intubation within 72 hours, mechanical ventilation, repeat surfactant administration, and several neonatal complications, although these differences were not statistically significant. Hospital stay was significantly shorter with LISA (9.1±2.1 vs. 12.6±3.2 days; p<0.001).
Conclusion: LISA was associated with significantly less procedure-related desaturation and shorter hospitalization than INSURE. LISA may be a feasible alternative for surfactant administration in spontaneously breathing preterm neonates with RDS.

Keywords: Respiratory distress syndrome, Preterm neonates, Less invasive surfactant administration, INSURE, Surfactant therapy, Non-invasive ventilation

INTRODUCTION

Respiratory distress syndrome (RDS) is one of the most important respiratory disorders affecting preterm neonates and results primarily from pulmonary surfactant deficiency and structural immaturity of the developing lung. Surfactant deficiency increases alveolar surface tension, promotes alveolar collapse, impairs lung compliance and gas exchange, and contributes to progressive respiratory failure. Despite substantial advances in antenatal care, neonatal respiratory support, and surfactant therapy, RDS remains an important contributor to respiratory morbidity and the need for intensive care among preterm infants.[1,2] Exogenous surfactant therapy has been one of the major advances in neonatal medicine and has substantially improved the

survival of preterm infants with RDS. Surfactant replacement reduces alveolar surface tension, improves pulmonary compliance and oxygenation, and decreases the need for invasive mechanical ventilation and the risk of air-leak syndromes. However, the method by which surfactant is delivered has become increasingly important because endotracheal intubation and positive-pressure ventilation themselves may contribute to lung injury in the immature preterm lung.[2-4] Current international recommendations emphasise maintaining spontaneous breathing and minimising exposure to invasive mechanical ventilation whenever clinically feasible.[2,5] INSURE technique was developed to reduce the duration of invasive ventilation. In this approach, the infant is briefly intubated for surfactant administration, receives short-term positive-pressure ventilation, and is subsequently extubated to non-invasive respiratory support.[3,6] Less invasive surfactant administration (LISA) involves placement of a thin catheter into the trachea while the infant remains spontaneously breathing on CPAP or another form of non-invasive respiratory support. Surfactant is then administered gradually without routine mechanical ventilation.[5,7]

Accumulating evidence supports the use of LISA in appropriately selected spontaneously breathing preterm infants with RDS. Randomized trials and systematic reviews have reported reductions in the requirement for invasive mechanical ventilation with LISA compared with more invasive surfactant administration strategies.[7-9] In particular, a systematic review and meta-analysis of randomized trials comparing LISA with INSURE reported lower requirements for mechanical ventilation and reductions in several clinically important outcomes with LISA, although the magnitude of benefit varied across individual studies.[7] More recent evidence continues to support an association between LISA and reduced need for invasive respiratory support compared with INSURE, while also highlighting variation according to gestational age, treatment protocols, and clinical setting.[10]

The OPTIMIST-A randomized clinical trial evaluated minimally invasive surfactant therapy in 485 infants born at 25–28 weeks' gestation who were receiving CPAP and required an inspired oxygen concentration of at least 0.30. Although the primary composite outcome of survival without BPD was not significantly improved, the trial provided important evidence regarding the effects of selective minimally invasive surfactant administration on respiratory outcomes and demonstrated the feasibility of this approach across multiple tertiary neonatal centres.[11]Recent safety evidence suggests that most acute adverse events are broadly comparable between LISA and INSURE/endotracheal techniques, although surfactant reflux may occur more frequently with LISA.[12] In this context, comparison of LISA with the established INSURE technique remains clinically relevant. Both approaches aim to provide timely surfactant replacement while reducing prolonged exposure to invasive ventilation, but they differ substantially in the degree of airway instrumentation and respiratory support required during surfactant administration. Comparative assessment of respiratory outcomes, subsequent need for intubation and mechanical ventilation, repeat surfactant therapy, procedure-related complications, neonatal morbidities, duration of respiratory support, and length of hospital stay may therefore provide useful evidence for selecting an appropriate surfactant delivery strategy.[7,10] The present study was undertaken to compare the clinical and respiratory outcomes of LISA and INSURE in preterm neonates of 28–36 weeks' gestation diagnosed with RDS at a tertiary-care neonatal centre.

METHODS

Study design

The present study was a prospective, hospital-based comparative observational study. Study was conducted over a period of 18 months from June 2022 to December 2023.

Study setting

The study was conducted among a cohort of 100 preterm neonates admitted to the NICU, Department of Pediatrics, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad. The study was initiated after obtaining approval from the Institutional Ethics Committee/Institutional Review Board. Written informed consent was obtained from the parent or legally authorized guardian of each neonate before enrollment in the study. All information collected during the study was kept confidential.

Sample size

The sample size was calculated to compare the intervention and control groups based on the difference in the mean duration of NICU hospitalization. The mean difference and standard deviation were obtained from the study by Mishra et al with a considered value of 3.2±1.7.[15] The sample size was calculated using the following formula.

$$n= (Z\ 1- \alpha/2 +Z1-\beta)\times(\delta12+\delta12)2/ (\mu1-\mu2)2$$

Based on the calculated sample size, a total of 100 neonates were included in the study, with 50 neonates in the LISA group and 50 neonates in the INSURE group.

Sampling technique

A simple random sampling technique was used for allocation of eligible consecutive cases into the two study groups.

Study place

Study conducted at Department of Pediatrics, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad.

Inclusion criteria

Preterm neonates born at 28–36 weeks of gestation, admitted the NICU, and diagnosed with RDS requiring exogenous surfactant therapy were eligible for inclusion in the study.

Exclusion criteria

Neonates with major or multiple congenital anomalies, those who required endotracheal intubation and mechanical ventilation in the delivery room, and those with a 5-minute Apgar score ≤4 were excluded from the study.

Study procedure

Eligible neonates were those who were clinically considered suitable for surfactant administration by either the less invasive surfactant administration (LISA) or intubation–surfactant–extubation (INSURE) technique according to the treating neonatologist's assessment and institutional protocol. The chest X-ray was performed as clinically indicated. Written informed consent was obtained from the parent or legally authorized guardian before enrollment.

Preterm neonates born at 28–36 weeks of gestation, diagnosed with RDS and fulfilling the eligibility criteria, were enrolled in the study. The enrolled neonates were allocated to either the LISA group or the INSURE group, with 50 neonates in each group. Surfactant was administered at a dose of 100 mg/kg according to the assigned technique.

less invasive surfactant administration group

In the LISA group, surfactant was administered through a thin catheter while maintaining non-invasive respiratory support and spontaneous breathing, whenever clinically appropriate.

intubation–surfactant–extubation group

In the INSURE group, the neonate underwent endotracheal intubation, followed by surfactant administration and positive-pressure ventilation. The neonate was subsequently extubated when clinically appropriate and continued on non-invasive respiratory support. The clinical course of all enrolled neonates was monitored, and relevant respiratory and neonatal outcomes were recorded and compared between the two groups.

Outcome

The primary outcome measures were the requirement for endotracheal intubation within the first 72 hours of life following surfactant administration and the requirement for a second dose of surfactant in the LISA and INSURE groups. The secondary outcome measures included the incidence of major neonatal morbidities, duration of respiratory support, duration of mechanical ventilation, duration of hospitalization, and procedure-related complications. Neonatal morbidities assessed included intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC). All outcome measures were compared between the LISA and INSURE groups.

Statistical analysis

Data were entered and analyzed using SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were expressed as mean±standard deviation (SD), while qualitative variables were summarized as frequencies and percentages. The student's independent-samples t-test was used for comparison of continuous quantitative variables between the two groups. The Chi-square test was used to compare categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

Table 1 shows that the INSURE and LISA groups were comparable in baseline demographic and clinical characteristics. There were no statistically significant differences in gestational age, birth weight, maternal age, neonatal sex, 1- and 5-minute Apgar scores, or mode of delivery (all p>0.05). Mean gestational age was 31.50±4.26 weeks in the INSURE group and 30.35±3.12 weeks in the LISA group (p=0.127), while mean birth weight was 1968.50±850.88 g and 1952.80±750.92 g, respectively (p=0.956).

Table 2 shows that maternal characteristics and antenatal factors were comparable between the INSURE and LISA groups. Antenatal steroid administration was more frequent in the INSURE group than in the LISA group (68.0% vs. 52.0%), but the difference was not statistically significant (p=0.102). Gestational diabetes mellitus, preeclampsia, and chorioamnionitis were also distributed similarly between groups. Overall, the proportion of mothers with the listed maternal conditions was 34.0% in the INSURE group and 46.0% in the LISA group, with no significant difference (p=0.519).

A large number of participants answered 14 injections 46 (31.9%) followed by 7 injections 22 (15.2%), 5 injections 28 (19.4%). Similarly, about the site of administration for the vaccine to be given was abdomen 91 (65.9%), buttocks 22 (15.9%), shoulder 18 (13.04%), thigh 2 (1.4%), don't know 5 (3.6%). Table 3 demonstrates that the LISA group had numerically lower rates of intubation within 72 hours, second surfactant dose, mechanical ventilation, PDA, IVH, BPD, pulmonary hemorrhage, and NEC compared with the INSURE group, although none of these differences were statistically significant (all p>0.05). Intubation within 72 hours occurred in 20.0% versus 32.0% (p=0.171), while mechanical ventilation

was required in 22.0% versus 28.0% (p=0.488) in the LISA and INSURE groups, respectively. The requirement for a second surfactant dose was also lower with LISA (10.0% vs. 18.0%; p=0.249). Table 4 shows that surfactant administration-related adverse events were generally less frequent in the LISA group than in the INSURE group. The incidence of surfactant reflux, coughing, bradycardia, and pneumothorax was lower with LISA, although these differences were not statistically significant (p>0.05). Desaturation was significantly less frequent with LISA than with INSURE (20.0% vs. 40.0%; p=0.029). Apnea occurred at similar rates in both groups (20.0% vs. 18.0%; p=0.799).

Table 5 shows that the LISA group had numerically shorter durations of CPAP (7.5±2.1 vs. 8.2±2.2 days), mechanical ventilation (11.85±4.20 vs. 12.20±2.40 days), and oxygen requirement (85.2±14.5 vs. 86.5±18.5 hours) compared with the INSURE group, although these differences were not statistically significant (p>0.05). Time to first surfactant administration was also comparable (2.85±1.65 vs. 3.30±2.20 hours; p=0.250). In contrast, duration of hospitalization was significantly shorter with LISA (9.1±2.1 vs. 12.6±3.2 days; p<0.001). Overall, LISA was associated with a significantly shorter hospital stay, while other respiratory-support measures were comparable between groups.

Table 1: Baseline demographic and clinical characteristics of neonates and mothers.

Variable	INSURE (n=50)	LISA (n=50)	P value
Gestational age, weeks, Mean±SD	31.50 ± 4.26	30.35 ± 3.12	0.127
28–32 weeks, N (%)	32 (64.0)	30 (60.0)	0.680
33–36 weeks, N (%)	18 (36.0)	20 (40.0)	
Birth weight, g, Mean±SD	1968.50 ± 850.88	1952.80 ± 750.92	0.956
<2500 g, N (%)	34 (68.0)	36 (72.0)	0.663
≥2500 g, N (%)	16 (32.0)	14 (28.0)	
Maternal age (in years) Mean±SD	26.72 ± 4.60	25.98 ± 4.30	0.408
<25 years, N (%)	34 (68.0)	36 (72.0)	0.663
≥25 years, N (%)	16 (32.0)	14 (28.0)	
Male sex, N (%)	34 (68.0)	37 (74.0)	0.509
Female sex, N (%)	16 (32.0)	13 (26.0)	
Apgar score at 1 min, Mean ± SD	6.18 ± 1.06	5.98 ± 1.26	0.393
Apgar 4–6, N (%)	27 (54.0)	29 (58.0)	0.687
Apgar 7–8, N (%)	23 (46.0)	21 (42.0)	
Apgar score at 5 min, Mean ± SD	8.04 ± 0.40	7.84 ± 0.61	0.055
Apgar 7–8, N (%)	45 (90.0)	44 (88.0)	0.749
Apgar >8, N (%)	5 (10.0)	6 (12.0)	
Caesarean delivery, N (%)	31 (62.0)	32 (64.0)	0.836
Vaginal delivery, N (%)	19 (38.0)	18 (36.0)	

Table 2: Maternal characteristics and antenatal factors.

Variable	INSURE (n=50)	LISA (n=50)	P value
Antenatal steroids administered, N (%)	34 (68.0)	26 (52.0)	0.102
No antenatal steroids, N (%)	16 (32.0)	24 (48.0)	
Gestational diabetes mellitus, N (%)	5 (10.0)	6 (12.0)	0.519*
Preeclampsia, N (%)	6 (12.0)	12 (24.0)	
Chorioamnionitis, N (%)	6 (12.0)	5 (10.0)	
Patients with listed maternal conditions, N (%)	17 (34.0)	23 (46.0)	

*Statistically significant.

Table 3: Neonatal respiratory and major clinical outcomes.

Outcome	INSURE (n=50)	LISA (n=50)	P value
Intubation within 72 h, N (%)	16 (32.0)	10 (20.0)	0.171
Intraventricular hemorrhage, N (%)	3 (6.0)	2 (4.0)	0.646
Bronchopulmonary dysplasia, N (%)	5 (10.0)	4 (8.0)	0.727
Pulmonary hemorrhage, N (%)	3 (6.0)	2 (4.0)	0.646
Patent ductus arteriosus, N (%)	15 (30.0)	8 (16.0)	0.096
Retinopathy of prematurity, N (%)	1 (2.0)	2 (4.0)	0.558

Continued.

Outcome	INSURE (n=50)	LISA (n=50)	P value
Necrotizing enterocolitis, N (%)	3 (6.0)	2 (4.0)	0.646
Second surfactant dose required, N (%)	9 (18.0)	5 (10.0)	0.249
Mechanical ventilation required, N (%)	14 (28.0)	11 (22.0)	0.488
Mortality, N (%)	0 (0.0)	0 (0.0)	—

Table 4: Surfactant administration-related adverse events.

Adverse event	INSURE (n=50)	LISA (n=50)	P value
Surfactant reflux, N (%)	12 (24.0)	8 (16.0)	0.317
Coughing, N (%)	28 (56.0)	25 (50.0)	0.548
Bradycardia, N (%)	12 (24.0)	7 (14.0)	0.202
Desaturation, N (%)	20 (40.0)	10 (20.0)	0.029
Apnea, N (%)	9 (18.0)	10 (20.0)	0.799
Pneumothorax, N (%)	3 (6.0)	2 (4.0)	0.646

Table 5. Respiratory and hospitalization outcomes.

Outcome	INSURE (n=50), Mean±SD	LISA (n=50), Mean±SD	P value
Duration of CPAP, days	8.20±2.20	7.50±2.10	0.107
Time to first surfactant administration, hours	3.30±2.20	2.85±1.65	0.250
Duration of mechanical ventilation, days	12.20±2.40	11.85±4.20	0.610
Duration of oxygen requirement, hours	86.50±18.50	85.20±14.50	0.697
Duration of hospitalization, days	12.60±3.20	9.10±2.10	<0.001

DISCUSSION

Current European consensus recommendations support early non-invasive respiratory support and the use of thin-catheter surfactant administration in spontaneously breathing preterm infants when appropriate expertise is available.[1]

The present study compared LISA and INSURE in 100 preterm neonates with RDS between 28 and 36 weeks of gestation, with 50 infants in each group. The principal findings were that LISA was associated with a numerically lower requirement for intubation within 72 hours, second surfactant administration, mechanical ventilation, and several neonatal complications. However, most of these differences did not reach statistical significance. Two findings were statistically significant: desaturation during surfactant administration was lower with LISA, and duration of hospitalization was significantly shorter in the LISA group. These findings suggest that LISA may provide procedural and short-term clinical advantages while producing broadly comparable respiratory and neonatal outcomes to INSURE in this gestational-age population.

The two groups were comparable with respect to major baseline characteristics. These findings are consistent with the randomized clinical trial by Sabzehei et al in which gestational age and birth weight were also comparable between infants receiving MIST and INSURE.[13] The baseline comparability in the present study therefore supports a reasonable comparison of the two surfactant-delivery approaches. The mean time to first surfactant administration was 3.30±2.20 hours in the INSURE group and 2.85±1.65 hours in the LISA group. Although surfactant was administered somewhat earlier in the LISA group, the difference was not statistically significant (p=0.250). Thus, the two groups were broadly comparable with respect to timing of initial surfactant therapy.

Sabzehei et al similarly reported no significant difference in the timing of initial surfactant administration between MIST and INSURE groups.13 The comparable timing in the present study is relevant because delayed surfactant administration may independently influence respiratory outcomes. One of the important findings of the present study was the significantly lower incidence of oxygen desaturation during surfactant administration in the LISA group compared with the INSURE group (20% vs. 40%; p=0.029).

The finding is consistent with the randomized study of Sabzehei et al., which reported significantly less desaturation during MIST than INSURE (19.6% vs. 39.3%; p=0.023). The similarity between the magnitude of the difference in that study and the present investigation strengthens the observation that avoiding endotracheal intubation may reduce procedure-associated oxygen desaturation. Several mechanisms may contribute to this finding. LISA permits surfactant administration while spontaneous breathing and non-invasive respiratory support are maintained, whereas INSURE requires endotracheal intubation and positive-pressure ventilation.

Airway manipulation and interruption of spontaneous breathing may contribute to transient oxygen desaturation during INSURE. Sedation practices may also influence procedural tolerance and respiratory stability; therefore, differences in sedation protocols should be considered when comparing studies. Evidence regarding routine sedation during LISA remains uncertain, and practice varies between centres.[14]

The requirement for endotracheal intubation within the first 72 hours was 20% in the LISA group compared with 32% in the INSURE group. Although this represented a clinically relevant numerical reduction with LISA, the difference was not statistically significant (p=0.171).

This direction of effect is consistent with evidence from systematic reviews and meta-analyses. A 2023 systematic review and meta-analysis including 16 randomized trials and 1,944 preterm infants reported that INSURE was associated with a higher risk of mechanical ventilation within the first 72 hours compared with LISA.10 Similarly, a more recent meta-analysis of 21 trials involving 2,656 infants found lower odds of intubation or mechanical ventilation with LISA compared with INSURE.[15]

A second surfactant dose was required in 10% of infants in the LISA group and 18% in the INSURE group. The difference was not statistically significant (p=0.249). Therefore, the present findings demonstrate a numerical reduction rather than a statistically confirmed advantage of LISA.

The findings are comparable with those reported by Sabzehei et al., who observed second-dose requirements of approximately 10.7% with MIST and 17.9% with INSURE. Differences between studies may reflect the initial surfactant dose, surfactant preparation, severity of RDS, criteria used for repeat dosing, and timing of administration. In the present study, poractant alfa was administered at 200 mg/kg, which is an important methodological consideration when comparing redosing rates with studies using lower initial doses.

Mechanical ventilation was required in 22% of infants in the LISA group and 28% of those in the INSURE group (p=0.488). Similarly, the mean duration of mechanical ventilation was 11.85±4.20 days with LISA and 12.20±2.40 days with INSURE (p=0.610). Thus, neither the proportion requiring mechanical ventilation nor its duration differed significantly between groups.

The numerical reduction in mechanical ventilation with LISA is consistent with previous evidence. Meta-analysis of randomized trials has demonstrated reduced exposure to mechanical ventilation with LISA compared with INSURE.[11,15] A randomized trial by Victor et al also reported significantly lower mechanical ventilation requirements with MIST than INSURE, although differences in duration of ventilation and CPAP were not statistically significant.[16]

The absence of statistical significance in the present study may again be related to the sample size and the relatively broad gestational-age range. Importantly, the present findings should not be interpreted as evidence that LISA eliminates the need for mechanical ventilation; rather, LISA may reduce the proportion of appropriately selected infants requiring invasive ventilation.

The mean duration of CPAP was 7.5±2.1 days in the LISA group and 8.2±2.2 days in the INSURE group (p=0.107). Although CPAP duration was numerically shorter following LISA, the difference was not statistically significant. Likewise, the duration of oxygen requirement was similar between groups (85.2±14.5 hours with LISA vs. 86.5±18.5 hours with INSURE; p=0.697). These findings indicate that the advantage of LISA in the present cohort was not demonstrated as a statistically significant reduction in the duration of respiratory support.

The direction of the findings is nevertheless consistent with the broader literature. A systematic review of randomized trials reported shorter CPAP and mechanical ventilation durations in many studies using LISA compared with INSURE.[10]

BPD occurred in 8% of infants in the LISA group and 10% in the INSURE group. The numerical difference was small and not statistically significant (p=0.727). Therefore, the present study does not demonstrate a significant reduction in BPD with LISA. The most prominent secondary finding in the present study was the significantly shorter duration of hospitalization among infants receiving LISA.

Limitations

Several limitations should be acknowledged. First, the study was conducted at a single centre and included only 100 infants, limiting statistical power for relatively infrequent outcomes such as IVH, NEC, pulmonary hemorrhage, pneumothorax, and ROP. Second, the study included infants from 28 to 36 weeks of gestation; therefore, the findings may not be directly generalizable to extremely preterm infants. Third, duration of hospitalization may be influenced by local discharge practices and non-respiratory factors. Fourth, the findings may depend on operator expertise with the LISA procedure.

CONCLUSION

LISA was a feasible and safe alternative to INSURE for surfactant administration in preterm infants with RDS. In the present study, LISA significantly reduced procedure-related oxygen desaturation and duration of hospitalization, while showing comparable rates of

intubation, mechanical ventilation, BPD, and other neonatal complications. Although several respiratory outcomes showed a favourable numerical trend with LISA, these differences were not statistically significant. LISA may therefore be considered an effective less-invasive approach for appropriately selected spontaneously breathing preterm infants with RDS.

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