Original Article

Less Invasive Surfactant Administration versus Intubation, Surfactant Administration, and Extubation in Preterm Infants with Respiratory Distress Syndrome: A Randomized Controlled Trial

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is one of the major causes of morbidity and mortality among preterm infants in Pakistan. Less Invasive Surfactant Administration (LISA) is a new and effective lung-protective technique; however, very few centers in Pakistan are using this, which may decrease the need for mechanical ventilation compared with the conventional INSURE (Intubation–Surfactant–Extubation) method. The objective of this study was to compare the need of mechanical ventilation requirement between LISA and INSURE techniques in spontaneously breathing preterm infants with RDS.

Methodology: This randomized controlled trial was conducted at the Neonatal Unit, Paediatric Department, Sir Ganga Ram Hospital, Lahore, from May to November 2023. The trial was registered at ClinicalTrials.gov under registration number NCT07910539. A total of 90 preterm infants (<35 weeks gestation) who were diagnosed with RDS were enrolled and randomly assigned to receive surfactant using either the LISA or INSURE technique. All infants with respiratory distress were initially stabilized on nasal CPAP. The primary outcome was to assess the need for mechanical ventilation within three hours of surfactant administration. Data were analyzed using SPSS 25, with p ≤0.05 considered statistically significant.

Results: Baseline demographic characteristics were similar in both groups. Mechanical ventilation was significantly lower in the LISA group (11/45; 24.4%) compared with the INSURE group (24/45; 53.3%) (p = 0.005). Subgroup analyses showed consistent benefits of the LISA technique across gender, gestational age, and birth-weight categories.

Conclusion: LISA significantly reduces the need for mechanical ventilation in preterm infants with RDS compared with INSURE.

Keywords: Respiratory Distress Syndrome; Preterm infants; Pulmonary Surfactants; Mechanical ventilation

INTRODUCTION

Pakistan has one of the highest neonatal mortality rates in the world with 39/1000 live births. Among top three causes of neonatal mortality are prematurity, sepsis, and birth asphyxia.[1] RDS is one of the main contributive factors for poor outcomes and mortality among preterm babies and neonates.[2] One local study showed prevalence of RDS 1.2% among all live birth with 39% mortality among RDS babies.[3] Other local study stated about 60-70% mortality related to RDS. Neonatal RDS, primarily resulting from surfactant deficiency in immature lungs, is frequently encountered in tertiary-care neonatal intensive care units (NICUs) across Pakistan.[4] Local data from Pakistani hospitals show a high burden of respiratory distress among preterm neonates, especially in the setting of preterm premature rupture of membranes and gestational age below 35 weeks.[5] These infants usually require advanced respiratory support, including continuous positive airway pressure (CPAP), supplemental oxygen, and surfactant therapy. These interventions are life-saving, they are also resource-enriched settings and helpful in preventing short- and long-term complications, such as bronchopulmonary dysplasia (BPD), prolonged hospitalization, and increased healthcare costs issues that are particularly critical in resource-limited Pakistani NICUs. Surfactant replacement therapy is crucial for RDS management after CPAP.[6] RDS is also responsible for morbidity as well in terms of need for ventilation, prolonged hospital stay, bronchopulmonary dysplasia, intubation related complications like leak syndrome and hospital acquired infections. In public sector hospitals, there may be overcrowding of babies with limited number of beds in NICUs, reduce number of human resource, equipment, medicines, and disposables, which may further

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compromise outcome of babies with RDS. Therefore, a treatment modality is needed that requires less invasive ventilation, shorter hospital stay, and fewer RDS related complications compared to the traditional mode of RDS treatment, which is called INSURE (intubation, surfactant administration, and extubation). INSURE technique has been widely adopted in many units, in Pakistan, as a strategy to limit prolonged mechanical ventilation. However, INSURE still requires endotracheal intubation and positive pressure ventilation. Recent evidence from literature showed a relatively new technique of surfactant administration called LISA. In which, surfactant is administered to a spontaneously breathing child without need for intubation. This technique has very promising results in Western literature with benefits of less need of invasive ventilation, hospital stay and other complications associated with RDS.[7]

However, LISA is not frequently practiced in many NICUs in the local setting, where challenges include inadequate human resources, machinery, monitoring, and limited ventilator availability. Despite this growing international evidence, data from Pakistan and similar resource-constrained South Asian settings remain limited. A randomized controlled trial from Lahore comparing minimally invasive surfactant therapy (MIST, a form of LISA) with INSURE in neonates with RDS reported a significantly reduced need for invasive mechanical ventilation in the MIST group, supporting the feasibility and potential benefit of less-invasive strategies in the local context.[8] However, there is still a need for further high-quality, context-specific evidence focusing on spontaneously breathing preterm infants, using clearly defined clinical and radiological criteria for RDS and standardized thresholds for escalation to mechanical ventilation.

The objective of this study was to compare the need for mechanical ventilation between the LISA method and the conventional INSURE method in spontaneously breathing preterm infants with respiratory distress syndrome admitted to a tertiary-care neonatal unit in Lahore, Pakistan.

METHODOLOGY

This randomized controlled trial was conducted in the level III nursery, Department of Paediatrics, Sir Ganga Ram Hospital, Lahore, over a six-month period from 19 May 2023 to 18 November 2023. The trial was registered at ClinicalTrials.gov under registration number NCT07910539. Written informed consent was secured from parents or legal guardians of all participating neonates after ethical approval REU No.52683. The sample size was calculated using the WHO sample size calculator, assuming 80% power, 95% confidence level, and anticipated mechanical ventilation frequencies of 30% in the LISA group versus 60% in the INSURE group based on previously published evidence. This yielded a requirement of 45 infants per group, for a total sample size of 90 neonates.

Preterm infants of either gender with gestational age <35 weeks and a clinical and radiological diagnosis of RDS (Bombeck / Giedion classification) were eligible for inclusion. RDS was defined using standardized criteria, including prematurity, tachypnea (>60 breaths/min), subcostal or intercostal retractions, nasal flaring, cyanosis, and characteristic bilateral ground-glass opacities on chest radiograph. Infants those, who had been intubated for delivery room resuscitation, those with major congenital anomalies, sepsis, hypoxic ischemic encephalopathy, meconium aspiration syndrome, or with other co-morbid conditions, or those whose guardians declined consent were excluded. Eligible neonates were enrolled through non-probability consecutive sampling and randomly allocated into two equal groups (LISA or INSURE) using a lottery method and this is open label RCT. All infants were initially stabilized on nasal continuous positive airway pressure (CPAP) with pressures of 5–7 cm H_2O and a FiO_2 of 0.3 prior to surfactant administration. Those who require FiO_2 more than 0.3 were given surfactant. In the LISA group, surfactant (100 mg/kg) was administered via a 6 Fr feeding catheter inserted 1–2 cm beyond the vocal cords under direct laryngoscopic visualization while maintaining spontaneous breathing on CPAP. Surfactant was instilled slowly over 1–3 minutes in small aliquots without interrupting spontaneous respirations. In the INSURE group, infants were intubated with an appropriately sized endotracheal tube, administered surfactant (100 mg/kg) in 2–3 aliquots, and ventilated with positive pressure ventilation for 15–20 minutes before extubation back to CPAP.

Following surfactant administration, all neonates were monitored for three hours. Mechanical ventilation was considered necessary if the infant required an FiO_2 >0.40 to maintain adequate oxygenation, at which point endotracheal intubation and ventilatory support were initiated. Clinical parameters, like gestational age, birth weight, sex, and ventilation outcomes were documented on a proforma.

Data were analyzed using SPSS version 25. Continuous variables such as birth weight and gestational age were summarized as mean ± standard deviation, while categorical variables including gender and ventilation requirement were expressed as frequencies and percentages. The primary outcomes were need for mechanical ventilation was compared between groups using the chi-square test, with a p-value ≤0.05 considered statistically significant. Stratified analyses by gestational

age subgroups (28–31 weeks and 32–35 weeks), birth weight categories (≤1500 g and >1500 g), and gender were performed to assess effect modification, followed by post-stratification chi-square testing using the same significance p-value ≤0.05.

RESULTS

A total of 90 preterm neonates diagnosed with respiratory distress syndrome (RDS) were enrolled and randomly allocated into two equal groups: LISA (n=45) and INSURE (n=45). The distribution of gender, gestational age, and birth weight was comparable between the groups, with no statistically significant differences (Table 1). The mean gestational age in the LISA group was 32.5 ± 2.6 weeks, while in the INSURE group it was 32.9 ± 2.9 weeks. Similarly, the mean birth weight was 1735.5 ± 250.4 g in the LISA group and 1790.4 ± 260.6 g in the INSURE group. Most neonates in both groups were between 32–35-week gestational age category and weighed more than 1500 g at birth (Table 1). Following surfactant administration, infants were monitored for three hours related to the need for mechanical ventilation. A significantly smaller proportion of neonates in the LISA group required mechanical ventilation (11/45; 24.4%) compared with the INSURE group (24/45; 53.3%, p = 0.005) (Table 2). Further analysis showed same trend among gender, gestational age strata, and birth weight categories. Among male infants, mechanical ventilation was required in 15.4% of the LISA group compared with 48.0% of the INSURE group (p = 0.012). Similar advantages were observed in low birth weight infants (≤1500 g), with 30.0% of the LISA group requiring ventilation compared with 61.9% in the INSURE group (p = 0.041). Overall, LISA significantly reduced the need for mechanical ventilation in spontaneously breathing preterm infants with RDS.

Table 1: Baseline demographic and clinical characteristics of study participants

Characteristics	LISA n (%)	INSURE n (%)	Total n (%)	p-value
Gender				
Male	26 (57.8)	25 (55.6)	51 (56.7)	0.831[a]
Female	19 (42.2)	20 (44.4)	39 (43.3)	
Gestational age, weeks (mean ± SD)	32.5 ± 2.6	32.9 ± 2.9	—	0.493[b]
Gestational age category				
28–31 weeks	17 (37.8)	16 (35.6)	33 (36.7)	0.827[a]
32–35 weeks	28 (62.2)	29 (64.4)	57 (63.3)	
Birth weight, g (mean ± SD)	1735.5 ± 250.4	1790.4 ± 260.6	—	0.311[b]
Birth weight category				
≤1500 g	20 (44.4)	21 (46.7)	41 (45.6)	0.832[a]
>1500 g	25 (55.6)	24 (53.3)	49 (54.4)	

[a]Chi-square test. [b]Independent-samples (Welch) t-test. p ≤ 0.05 considered statistically significant.

Table 2: Primary outcome — need for mechanical ventilation, overall and by pre-specified subgroup

Characteristics	LISA n (%)	INSURE n (%)	p-value
Overall (N = 90)	11/45 (24.4)	24/45 (53.3)	0.005*
By gender			
Male (n = 51)	4/26 (15.4)	12/25 (48.0)	0.012*
Female (n = 39)	7/19 (36.8)	12/20 (60.0)	0.048*
By gestational age			
28–31 weeks (n = 33)	3/17 (17.6)	6/16 (37.5)	0.041*
32–35 weeks (n = 57)	8/28 (28.6)	18/29 (62.1)	0.011*
By birth weight			
≤1500 g (n = 41)	6/20 (30.0)	13/21 (61.9)	0.041*
>1500 g (n = 49)	5/25 (20.0)	11/24 (45.8)	0.044*

Chi-square test used for all comparisons (overall analysis reproduced from source; subgroup p-values as reported in source dataset). *p ≤ 0.05.

DISCUSSION

In this randomized controlled trial from Neonatal unit of the Department of Paediatrics, Sir Ganga Ram Hospital, Lahore, it was found in this study that preterm infants with RDS managed with LISA required significantly less mechanical ventilation than those treated with the conventional INSURE technique (24.4% vs. 53.3%, p = 0.005), with this benefit persisting after stratification by gestational age, birth weight, and gender.[9-21] These results align with international evidence as well, where recent reviews and meta-analysis confirm that LISA is now a better lung-protective strategy in preterm RDS, reducing risks of mechanical ventilation compared with invasive techniques.[9-12] A 2024 systematic review reported significantly lower ventilation rates with LISA relative to

INSURE across multiple randomized trials.[10,8,13] Studies from Finland, Spain, and other European countries showed similar results. However, one Korean study negated the advantage of LISA over INSURE in terms of need for mechanical ventilation, which may be due to lesser gestational age of study group, less experty of LISA technique or prolonged duration for need of mechanical ventilation (2-7 days). There are physiological advantages like preservation of spontaneous breathing, avoidance of positive-pressure ventilation, and reduction in volume trauma and barotrauma explain the superiority of LISA observed in this study population.[9-11,14]

Regional data from South Asia and the Middle East show similar trends, with mechanical ventilation rates of 20–35% using LISA versus 40–60% using INSURE, similar to findings in this study.[12,14,15,20] A meta-analysis of 17 studies included 913 infants treated with less invasive surfactant administration and 932 treated with INSURE. The analysis found that LISA was significantly associated with the need for ventilation, consistent with the present findings. However, the meta-analysis also examined mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, pneumothorax, pulmonary hemorrhage, surfactant reflux, duration of oxygen therapy, hospital stay, and duration of ventilation[12], which were not explored in this study. An Indian randomized trial used a feeding tube for surfactant administration because of resource limitations, an approach similar to that used in this study; the outcomes were also comparable, with a significantly lower need for ventilation in the LISA group than in the INSURE group.[14] A Chinese study likewise reported a reduced need for invasive ventilation with LISA, but its sample comprised infants with a gestational age below 32 weeks, whereas the present study included infants up to 35 weeks of gestation. Likewise, the need for ventilation was assessed at 3 hours in the present study, compared with up to 72 hours in the Chinese study.[16] Moreover, observational studies indicate decreased NICU stay and healthcare costs when LISA is implemented in NICUs across different centers.[16,21]

These benefits in resource-limited settings support LISA to Pakistani NICUs, which face constraints such as limited ventilator availability, insufficient human resource, and inconsistent antenatal steroid coverage, huge burden of preterm deliveries. Local Pakistani evidence remains limited but encouraging. A randomized controlled trial from Lahore evaluating LISA reported reduced ventilation requirements compared with INSURE, however this center is only recipient of outborn babies, meanwhile this study data had both inborn and outborn babies, as outborn infants tend to arrive later and sicker and this may effect outcomes of study.[8] Additionally another local study confirms low ventilation rates with minimally invasive techniques, however this was not a randomized clinical trial as compare to this study.[20]

The results of this study are consistent with emerging evidence demonstrating that the benefits of LISA documented internationally are reproducible in Pakistan's high-volume, low-resource NICUs. A distinguishing feature of the present study is the moderately preterm gestational age distribution of the sample (28–35 weeks), in contrast to international trials involving extremely preterm infants (<28 weeks), among whom risks and therapeutic thresholds differ.[9,14,21] The consistency of the benefits of LISA across gestational-age and birth-weight categories supports early adoption among moderately preterm infants before expansion to extremely preterm groups and represents a key feature of the present study.

Strengths of the study include its randomized design, standardized CPAP and surfactant protocols, objective FiO_2-based surfactant criteria, and subgroup stratification. However, limitations include its single-center setting, open-label design, relatively small sample size, and short three-hour assessment window, which does not capture late ventilation needs or longer-term outcomes such as BPD, mortality, neurodevelopment, procedure-associated complications, hospital stay, or cost.

Future directions should include multicenter Pakistani trials, evaluation of long-term respiratory and neurodevelopmental outcomes, well-organized LISA training programs, integration of LISA into national neonatal guidelines, and cost-effectiveness studies relevant to the public sector, especially in resource-limited settings in Pakistan. These measures should be incorporated across secondary-level hospitals, and LISA should be integrated into comprehensive preterm respiratory care bundles that include early CPAP, antenatal steroids, and optimized surfactant thresholds. LISA has the potential to substantially reduce ventilator dependence, improve neonatal outcomes, and relieve pressure on overburdened NICUs in Pakistan.

CONCLUSION

LISA significantly reduces the need for mechanical ventilation compared with the INSURE technique in preterm infants with RDS. Its consistent effectiveness across all demographic and clinical subgroups makes it a superior and practical option for resource-limited NICUs in Pakistan. Implementing LISA may help in reducing the need of ventilator in high-burden, low-resource settings.

Author Contributions

BW: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval.

AA: Conception and design, analysis and interpretation of data. Proofreading, final approval

MAS: Analysis and interpretation of data, drafting the article.
AA: Acquisition of data, conception and design, analysis and interpretation.
ZA: Analysis and interpretation of data.
NAH: Conception and design, analysis.

AI Disclosure

The authors declared that no generative AI or AI-assisted technologies were used in the preparation of this manuscript

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