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MIST or INSURE in Preterm Infants with Respiratory Distress Syndrome

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Abstract

Premature infants with respiratory distress syndrome (RDS) are typically administered surfactant via the intubation and extubation procedure (INSURE). A variety of surfactant administration practices are available today. The term "SURE" (surfactant without endotracheal intubation) refers to any approach that requires direct laryngoscopy but uses a narrow catheter instead of an endotracheal tube. They include Take Care, LISA (least invasive surfactant administration), and MIST (minimally invasive surfactant therapy). MIST approaches avoid intubation while minimizing airway damage and barotrauma. This study sought to determine the practicality, effectiveness, and security of using the MIST approach to administer surfactant to premature infants with RDS. The study examined 90 preterm infants who were born before 36 weeks with respiratory distress and were able to breathe on their own. They were divided into two groups of 45 infants each: the MIST and INSURE groups. Both surfactant administration procedures were tested to determine their impact on morbidity and mortality in newborns. The study revealed no noticeable differences between both groups in maternal or newborn factors. Still, the MIST group exhibited a significantly decreasing necessity of mechanical ventilation (MV), had shorter MV and continuous positive airway pressure durations, and significantly reduced periventricular–intraventricular hemorrhage (PIVH) and death. The MIST procedure is pragmatic and reliable, and it decreases the need for MV and mortality in preterm infants who need surfactant treatment. It decreases the occurrence of PIVH in susceptible subgroups.

Keywords
- bronchopulmonary dysplasia
- minimally invasive surfactant therapy
- respiratory distress syndrome
- surfactant
- preterm

Surfactant therapy is a fundamental component of treating preterm infants, and it has proven to be effective when administered as a preventative therapy in the delivery room or as a rescue therapy for infants already suffering from respiratory distress syndrome (RDS).[1] Implementing exogenous surfactant therapy in newborn medicine throughout the early 1990s led to a substantial decrease in infant mortality rates.[2] The role of exogenous surfactant therapy has recently been altered while critical care for preterm newborns continues to advance and improve. Nasal continuous positive airway pressure (nCPAP) is becoming more widely used as the main method of respiratory support. Consequently, a significant number of premature infants experiencing respiratory distress no longer necessitate intubation either immediately after birth or during the early postnatal period.[3] This additionally entails the postponement or avoidance of surfactant usage. Nevertheless, a significant proportion of newborns who initially received CPAP subsequently needed intubation due to escalating oxygen needs and/or respiratory acidosis, which were the most prevalent factors. RDS caused by a lack of surfactant is the most common reason for CPAP failure in premature

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newborns.[4] The study conducted by Dargaville et al,[5] utilizing CPAP shortly after birth followed by selective surfactant administration is seen as an alternative approach to the standard practice of intubation with prophylactic or early surfactant treatment in premature neonates.[6] The utilization of the intubation, surfactant, and extubation (INSURE) method has demonstrated a decrease in the requirement for mechanical ventilation (MV).[7] However, positive pressure ventilation (PPV) and tracheal tube placement are necessary actions in the INSURE technique. This will be linked to a range of acute and chronic morbidities, including bronchopulmonary dysplasia (BPD).[2]

Consequently, throughout the past 30 years, significant efforts have been made to develop less intrusive alternative techniques for delivering surfactants. The primary objective is to provide a sufficient dose of surfactant without requiring PPV or intubation. Currently, there are various techniques for delivering surfactants. They can be more precisely classified into two main types based on the level of invasiveness. The techniques that require direct laryngoscopy but substitute the endotracheal tube (ETT) with a thin catheter, such as a flexible feeding tube or a semirigid angiocath, are collectively known as "SURE." This acronym encompasses LISA (less invasive surfactant administration), MIST (minimally invasive surfactant therapy), and Take Care.[8] This not only avoids intubation but also enables uninterrupted use of CPAP, which maintains a stable functional residual capacity (FRC) in the lungs of premature infants. LISA is gaining popularity in neonatal intensive care units (NICUs) worldwide because it reduces the need for MV. LISA differs from other methods of surfactant delivery by allowing the newborn to continue spontaneous breathing and use the physiological function of the larynx.[9] The outcomes obtained from studies conducted in advanced economies on the efficiency of the least-invasive surfactant therapy technique cannot be generalized to countries with middle and low incomes. Thus, we conducted this randomized trial aiming to evaluate the efficacy of LISA/MIST by comparing the INSURE approach to a thin catheter approach for surfactant treatment in spontaneously breathing premature neonates with RDS.

Patients and Methods

Methodology

We conducted a randomized clinical trial (RCT) on preterm infants with gestational ages (GAs) between 28 and 36 weeks, spontaneous breathing infants, and respiratory distress necessitating surfactant therapy. Infants who had major birth abnormalities, abnormal heart structure, or required intubation at birth were not included. People who needed more than 30% fraction of inspired oxygen (FiO_2) on CPAP (7 cm H_2O) to keep their oxygen saturation between 90 and 94% in 6 hours after birth were randomly given either the MIST or INSURE techniques to apply surfactant. Every infant was closely observed until they were discharged from the NICU or until they reached 36 weeks of postmenstrual age, whichever came later. A 16-gauge angiocath or a 6-French feeding tube, depending on individual preference and accessibility, was prepared. In the NICU, two competent specialists performed the procedure. Prior to the procedure, no sedation was given. A direct laryngoscopy took place, and the catheter was inserted below the vocal cords with the CPAP prongs in position. Once the catheter had been inserted, the laryngoscope was withdrawn. Either the surfactant, beractant (Survanta), was administered at a dose of 100 mg/kg, requiring a volume of 4 mL/kg or alternatively, based on availability, bovactant (Alveofact) was given at a dose of 50 mg/kg with a volume of 1.2 mL/kg. A 5- to 10-mL syringe containing the surfactant was filled up with an extra 1 mL of air to compensate for the dead volume of the catheter. The tracheal catheter was promptly removed after the surfactant was administered in a single bolus over a 60- to 90-second period. Infants who had a heart rate of 100 beats per minute or less, oxygen saturation of 80% or less, or apnea that lasts more than 20 seconds had PPV. If the patient's need for oxygen concentration (FiO_2) remained above 30% 6 hours after surfactant delivery, a second dose of surfactant was delivered in a similar way. Intubation was indicated if there was respiratory acidosis with a pH below 7.2 and/or partial pressure of carbon dioxide (PCO_2) levels over 60 mm Hg. Additionally, recurrent apnea requires PPV despite the patient receiving caffeine. The use of CPAP was discontinued if the infant did not exhibit any signs of difficulty breathing and remained free from apnea for a minimum of 24 hours while being treated with CPAP settings of 5 or less and FiO_2 levels of 25% or below. During INSURE technique, sedation was optional; however, analgesia and nonpharmacological pain management had been used, infants underwent intubation using an ETT of suitable size and were administered a dosage of 100 mg/kg of surfactant. After the delivery of surfactant, neonates are either ventilated using bag valve masks or connected to a mechanical ventilator that provides gas volumes with positive pressure for a short duration. The patient received nCPAP treatment following extubation. If a FiO_2 level more than 30% was necessary to maintain arterial oxygen saturation between 90 and 94% after 6 to 12 hours, they administered a second dosage of surfactant (►**Fig. 1**).

Randomization

Randomization is generated by a computer, which produces random and distinct sequences of consecutive numbers. During the whole trial, from the intervention phase to the evaluation of outcomes and analysis of collected data, there was no intervention with the aim of ascertaining the undisclosed fundamental principle of the treatment being administered.

Ethical Approval

The ethical committee of the Faculty of Medicine, Assiut University approved the study (IRB: 04-2024-100255). Informed written consent was obtained from the parents of all participant newborns before recruitment in the study after explaining the objectives of the work.

Outcomes

The key finding was to detect the effect of MIST approach on the requirement for MV within the first 72 hours of life.

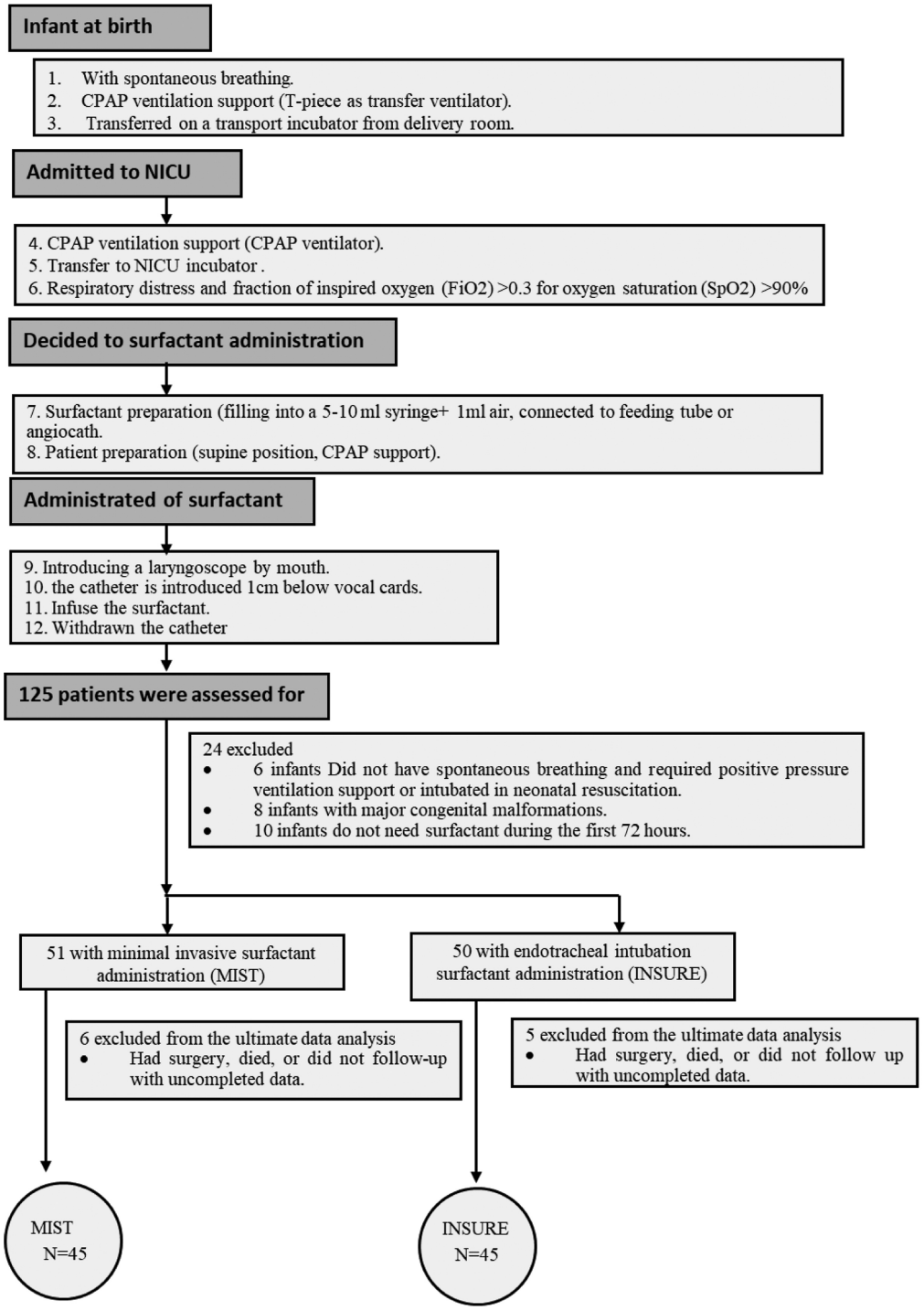

Fig. 1 Flowchart of the administration of surfactant. CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

The secondary outcomes were repeat doses of surfactant therapy, rates of hemodynamically significant patent ductus arteriosus (PDA), pneumothorax, intraventricular hemorrhage (IVH; ≥grade 2; Papile classification), necrotizing enterocolitis (NEC; modified Bell's stage ≥2),[10] BPD according to the 2018 National Institute of Child Health and Human Development's definition,[11] early-onset sepsis (EOS), oxygen duration, hospital stay, apnea, bradycardia, or desaturation during surfactant administration, and death.

Statistical Analysis

All statistical calculations were done using SPSS (statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, United States) version 22. Data were statistically described in terms of mean ± standard deviation, or median and range when not normally distributed, frequencies (number of cases), and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using Student's *t*-test for normally distributed data and Mann–Whitney's *U* test for nonnormally distributed data. For

comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. A *p*-value is always two-tailed set significant at 0.05 level.

Results

Every baseline variable was comparable between the two groups, as shown in ►**Table 1**. There was no difference in both maternal and neonatal clinical characteristics. There was a significant reduction in the need for MV in the MIST group ($p < 0.001$). Furthermore, the duration of MV and the duration of nCPAP, periventricular–intraventricular hemorrhage (PIVH), and death were significantly less in the MIST group (►**Table 2**). No difference was observed between the two groups in pneumothorax, EOS, PDA, NEC, or the duration of supplemental oxygen (►**Table 2**).

Discussion

In attempts to determine the necessity of MV during the first 72 hours of life as the primary outcome between both groups, the study found a statistically significant difference. The LISA group also had much shorter MV and CPAP durations compared with the INSURE group.

A new systematic review and meta-analysis of 16 RCTs that were released from 2012 to 2020 found that giving surfactant through the LISA technique cut down on the need

Table 1 Baseline characteristics of the studied patients

Variable name	MIST group ($n = 45$)	INSURE group ($n = 45$)	*p*-Value
Gestational age (wk)			
Mean ± SD	30.27 ± 2.14	30.44 ± 1.93	0.679
Range	28–34	28–34	
Birth weight (g)			
Mean ± SD	1,144.80 ± 225.15	1,149.11 ± 192.59	0.922
Range	830–1,700	850–1,600	
Gender, *n* (%)			
Male	22 (48.9%)	16 (35.6%)	0.200
Female	23 (51.1%)	29 (64.4%)	
Apgar score (first min)	4 (2–6)	4 (2–6)	0.630
Apgar score (fifth min)	7 (5–9)	8 (4–9)	0.379
IUGR, *n* (%)			
AGA	27 (60.0%)	34 (75.6%)	0.175
SGA	17 (37.8%)	11 (24.4%)	
LGA	1 (2.2%)	0 (0.0%)	
Mode of delivery, *n* (%)			
NVD	9 (20.0%)	9 (20.0%)	1
CS	36 (80.0%)	36 (80.0%)	
Multiple births, *n* (%)			
Single	37 (82.2%)	37 (82.2%)	1
Twin	8 (17.8%)	8 (17.8%)	
PROM, *n* (%)	13 (28.9%)	14 (31.1%)	0.818
Antenatal steroid, *n* (%)	19 (42.2%)	17 (37.8%)	0.667
Duration of steroid, *n* (%)3			
Full dose	13 (68.4%)	13 (76.5%)	0.717
Any doses	6 (31.6%)	4 (23.5%)	
Maternal illness, *n* (%)			
None	34 (75.6%)	37 (82.2%)	0.887
Diabetes	4 (8.9%)	2 (4.4%)	
Hypertension	5 (11.1%)	4 (8.9%)	
Chorioamnionitis	2 (4.4%)	2 (4.4%)	

(*Continued*)

Table 1 (*Continued*)

Variable name	MIST group ($n = 45$)	INSURE group ($n = 45$)	*p*-Value
Downes score before surfactant			
Median (range)	7 (5–8)	6 (5–8)	0.327
Serum glucose (mg/dL)			
Mean ± SD	69.04 ± 13.28	71.87 ± 10.89	0.273
Range	40–90	49–89	
Age at first-dose surfactant therapy (h)			
Mean ± SD	2.42 ± 1.07	2.10 ± 1.03	0.156
Range	1–4.5	1–4	
Number of surfactant doses, *n* (%)			
One dose (100 mg/kg)	30 (66.7%)	31 (68.9%)	0.200
Two doses (200 mg/kg)	15 (33.3%)	14 (31.1%)	
FiO_2 before PS administration			
Median (range)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.696

Abbreviations: AGA, appropriate for gestational age; CS, cesarean section; FiO_2, fraction of inspired oxygen; INSURE, intubation surfactant, and extubation; IUGR, intrauterine growth retardation; LGA, large for gestational age; MIST, minimally invasive surfactant therapy; NVD, normal vaginal delivery; PROM, premature rupture of membrane; PS, pulmonary surfactant; SD, standard deviation; SGA, small for gestational age.
Note: Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage), and significance is defined by $p < 0.05$.

Table 2 Outcome variables of the study group

Variable name	MIST group ($n = 45$)	INSURE group ($n = 45$)	*p*-Value
Duration of O_2 therapy (d)			
Mean ± SD	16.20 ± 6.45	16.71 ± 6.95	0.719
Range	6–30	6–32	
Need for MV <72 h	11 (24.4%)	30 (66.7%)	<0.001*
Duration of MV (d)			
Mean ± SD	4.91 ± 1.30	7.13 ± 2.97	0.022*
Range	3–7	3–13	
Duration of CPAP (d)			
Mean ± SD	6.67 ± 3.55	8.36 ± 2.96	0.016*
Range	1–14	1–14	
Death, *n* (%)	3 (6.7%)	11 (24.4%)	0.020*
BPD at 36 wk PMA, *n* (%)	6 (13.3%)	7 (15.6%)	0.764
IVH > grade II, *n* (%)	4 (8.9%)	11 (24.4%)	0.048*
Pneumothorax, *n* (%)	3 (6.7%)	6 (13.3%)	0.485
NEC > stage II, *n* (%)	3 (6.7%)	2 (4.4%)	1
Early-onset sepsis, *n* (%)	9 (20.0%)	17 (37.8)	0.063
PDA, *n* (%)	3 (6.7%)	7 (15.6%)	0.180
Pulmonary hemorrhage, *n* (%)	2 (4.4%)	4 (8.9%)	0.677
Duration of NICU stay, (d)	20 (7–36)	22 (7–38)	0.285

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; INSURE, intubation surfactant, and extubation; IVH, intraventricular hemorrhage; MIST, minimally invasive surfactant therapy; MV, mechanical ventilation; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PMA, postmenstrual age; SD, standard deviation.
Note: Qualitative data are presented as numbers (percentage), and *significance is defined by $p < 0.05$.

for MV in the first 72 hours of life, as well as BPD, PIVH, pneumothorax, and death rates in infants born before 36 weeks of gestation compared with INSURE.[12] Meta-analysis of Bellos et al concluded that compared with INSURE, surfactant administration via a thin catheter was associated with significantly lower rates of mortality, MV, BPD, and periventricular leukomalacia.[2] In the first 72 hours, the MIST group required much less intubation, according to the recently released OPTIMIST-A study by Dargaville et al.[13] A total of 350 infants with GA $\leq$ 34 weeks with RDS were studied by Jena et al, who randomized the patients between LISA and INSURE. According to their research, the LISA group required significantly less MV within the first 72 hours ($p < 0.01$).[14] Using the LISA significantly lowered the demand for MV in newborns in the Boskabadi et al[15] trial ($p = 0.02$). Similar findings were noted in Kribs et al,[16] with the LISA group invasively ventilated for a shorter period ($p = 0.001$).

The difference between the two groups regarding MV is 75% in INSURE versus 33.3% in MIST. Such a relatively big difference between the two groups could be due to the optional use of sedatives with INSURE technique which could increase the incidence and duration of MV. Anand et al,[17] the largest study reporting on this outcome, the duration of MV (respiratory support with an ETT) in case of use of sedation versus placebo, found a significant difference in time spent on the ventilator between opioid and control groups ($p = 0.0338$). In the case of elective intubations in the NICU, sedation with an opioid and muscle relaxant results in greater intubation success on the first attempt.[18] However, the use of some analgesic premedications is associated with respiratory depression that can delay extubation and lead to prolongation of the period of MV.[19] Therefore, some clinicians prefer to avoid the use of analgesic premedication during the INSURE procedure to facilitate immediate extubation.[20,21] Further clinical trials are underway to assess the benefits and risks of sedation for LISA.

Animal studies have shown that a few mechanical breaths are enough to cause lung harm in the newborn period, which explains the pulmonary benefits of the MIST approach in lowering the need for MV and the duration of CPAP.[7] Moreover, it permits the maintenance of CPAP, preserving FRC and reducing atelectotrauma in the premature lung.[22] Furthermore, by allowing the infant to breathe on its own, the MIST technique distributes surfactant throughout the premature lung quickly and completely. Moreover, it is expected that PPV administered to a lung with nonhomogeneous time constants will cause nonuniform distension, raising the possibility of lung injury.[23] Thin catheter approach produced more consistent lung aeration than intubation in a small-scale study using electrical impedance tomography on preterm neonates delivered at a mean GA of 29 weeks.[24]

Yet there was no statistically significant difference between the LISA and INSURE groups in terms of needing MV during the first 72 hours of life, according to Gupta et al.[23] Nonetheless, the primary respiratory support in this trial was nasal intermittent positive pressure ventilation (NIPPV), which may have decreased the need for IMV in both research groups because there is evidence in the literature that using NIPPV as the primary respiratory support reduces the need for IMV.

Comparable rates of BPD were observed in both groups in this trial: 15.6% in the INSURE group and 13.3% in the LISA group. The difference was insignificant. Lau et al[25] conducted a meta-analysis comparing individuals in the thin catheter group and the INSURE group. They found that fewer infants developed BPD without statistical significance.[25] Kribs et al[16] and Han et al[26] conducted RCTs with BPD analysis as their primary objective. Han et al's[26] study showed a tendency toward a decline in the incidence of BPD, 19.2 versus 25.9% ($p = 0.17$), despite the lack of evidence of an apparent benefit with LISA on the incidence of BPD.

Kribs et al[16] randomized 211 newborns less than 27 weeks of gestation to the INSURE and LISA groups. The 36-week survival without BPD was the principal objective, and no statistically significant difference was observed. Isayama et al[27] randomized 298 neonates with RDS to the INSURE and LISA groups, and there was a trend toward a reduction in the incidence of BPD.

On the other hand, both Kanmaz et al[28] and Bao et al[29] demonstrated that the BPD rate was significantly reduced in the thin catheter group compared with INSURE group. The reason was that our study population had higher GA and birth weight, which resulted in a lower incidence of BPD compared with extremely preterm infants.

The current investigation demonstrated a statistically significant disparity in the occurrence of IVH between the two groups. Consistent with our result, Kribs et al's evaluation of PIVH grade 3 or 4, the LISA group also had noticeably less severe PIVH. It has been observed that LISA contributes to favorable secondary outcomes related to lifelong disabilities.[16]

Surfactant administration via a thin catheter was associated with a reduction in the risk of severe PIVH and mortality among survivors during their initial hospitalization, based on a Cochrane review of 10 RCTs comparing various methods of surfactant administration.[22]

A prospective cohort study was conducted to assess the occurrence of IVH in preterm children with a GA less than 34 weeks who had LISA versus a historical cohort who received surfactant via INSURE. The LISA group had a significant reduction in the incidence of severe IVH as compared with the historical group.[30]

Previous research by multiple authors, including Klebermass-Schrehof et al[31] and Härtel et al,[32] as well as multicentric clinical trials conducted by Kribs et al[16] and systematic reviews by Isayama et al[27] have demonstrated the favorable outcome of the LISA technique on severe IVH.

Nevertheless, many systematic reviews still exhibit inconsistency; Aldana-Aguirre et al[7] found no significant effect on severe IVH.

This effect could be attributed to a variety of factors; it is known that in small preterm infants, particularly in the first day of life, arterioles' autoregulatory response to the fluctuations in mean arterial blood pressure (MABP) and partial pressure of blood gases is weak.[28,33] Cerebral blood flow

(CBF) is highly reliant on MABP due to impaired autoregulation.[33] Furthermore, the immature blood vessels in the germinal matrix are very fragile, combined with a deficiency in cerebral autoregulation, which renders it more susceptible to changes in PCO_2 and CBF than the fully developed brain of a full-term infant.

The fluctuations in blood pressure observed in the INSURE group during the procedure have an impact on cerebral perfusion, ultimately leading to an increased risk of intracranial hemorrhage. Throughout the administration process, the INSURE group consistently maintained elevated levels of SpO_2, which were directly correlated with the pressure of the operator's resuscitating airbag. The LISA approach effectively sustains nCPAP while administering surfactant, resulting in stabilized SpO_2 levels and eliminating the operator's need for manual pressure on the lungs. This led to a notable decrease in pulmonary barotrauma and severe IVH, improving treatment outcomes.[34]

Thus, by maintaining a preterm newborn in spontaneous breathing with a recruited lung by noninvasive ventilation, the cardiopulmonary interactions are reduced and a more stable circulation is maintained. This helps minimize fluctuations in systemic blood pressure and, consequently, CBF. This beneficial impact would also be amplified by a more balanced and steadier CO_2 level and by decreased use of atropine, sedatives, and inotropic medications, which might contribute to keeping the CBF steadier.[35,36]

Within the scope of this study, there was a single occurrence of NEC stage 2 in the MIST group, while the INSURE group had two instances. The prevalence of PDA was lower in the MIST group, with an overall prevalence of 6.7%, compared with an overall prevalence of 15.6% in the INSURE group. The disparity was negligible.

The duration of hospitalization was similarly reduced in the MIST group. Despite the lack of statistical significance, the decrease in the duration of hospitalization has had a considerable social and economic effect. Several variables influence early discharge, including NICU-related challenges (sepsis and feeding issues), social elements, and public health issues.[37]

Between the two groups, there was no statistically significant difference in the need for a second dosage of surfactant. According to Aguar et al,[37] the MIST group required a significantly higher amount of surfactant for the second treatment as compared with the INSURE group. The fact that the surfactant dose in MIST was 100 mg/kg as opposed to 200 mg/kg in the INSURE group may have contributed to this result. We used the same dose of surfactant in both groups in this trial, and the results were consistent with previous studies showing that a dose of 100 mg/kg produced satisfactory outcomes.[25,28]

Failure to require intubation and ventilation in preterm infants within 72 hours after MIST is regarded as MIST success. The reported incidence of MIST failure, defined as the necessity for intubation and mechanical breathing within 72 hours after the procedure, is 24% in newborns. This rate is significantly lower compared with the 67% recorded with the INSURE approach.

Univariate logistic regression analysis for prediction of MIST failure among the studied preterm neonates showed that lower GA, lower birth weight, history of PROM, not receiving antenatal steroids, and IVH are significant predictors of MIST failure. The results of the multivariate logistic regression analysis demonstrated that lower GA and a lack of antenatal steroids remain important predictors of MIST failure. Thus, the use of prenatal corticosteroids and postnatal surfactants in the prevention and treatment of RDS has considerably improved neonatal outcomes by lowering respiratory morbidity and mortality (►**Table 3**).

The current study's key advantages are its acceptable sample size and resilient design. However, our research had a significant constraint that should be noted in future

Table 3 Univariate and multivariate logistic regression models of risk factors for MIST failure ($n = 45$)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Gestational age	0.213	0.068–0.672	0.008[a]	0.149	0.034–0.657	0.012[a]
Birth weight	0.986	0.977–0.996	0.007[a]			
APGAR score at 1 min	0.431	0.200–0.929	0.032[a]			
Multiple births	2.175	0.426–11.116	0.351			
Cesarean section	0.302	0.064–1.425	0.130			
PROM (yes vs. no)	8.167	1.800–37.048	0.006[a]			
Antenatal steroid (yes vs. no)	11.250	1.293–97.856	0.028[a]	19.743	1.428–272.968	0.026[a]
Downes score before surfactant	1.538	0.733–3.231	0.255			
Age of first-dose surfactant therapy	0.529	0.245–0.141	0.104			
No. of surfactant (twice vs. once)	2.786	0.519–14.963	0.232			
IVH > grade II (yes vs. no)	12.375	1.132–135.236	0.039[a]			

Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; MIST, minimally invasive surfactant therapy; OR, odds ratio; PROM, premature rupture of membranes.
[a]*p*-Value is significant.

studies: it was a single-center study, and infants with gestations less than 28 weeks were excluded. Furthermore, the types of surfactants used varied between the study arms and were not standardized. Furthermore, we have no data on the research population's long-term neurodevelopment outcomes.

Conclusion

The MIST technique is an applicable, trustworthy, and efficient method for delivering surfactant via a thin vascular catheter or a feeding tube to preterm neonates with RDS with spontaneous breathing. It reduces the need for MV and may also lower the rate of PIVH in certain susceptible subgroups. MIST can be easily mastered and adapted in our neonatal units. MIST failure rates can be reduced by recommending antenatal steroids in cases of suspected preterm labor, using a higher recommended dose of surfactant, and performing MIST at lower FiO_2 thresholds for more immature infants.

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Conflict of Interest
None declared.

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