Surfactant Therapy in Neonates with Respiratory Distress Syndrome: Minimally Invasive Surfactant Therapy (MIST) or Intubation-Surfactant Adminstration-Extubation (INSURE) Technique

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Abstract

Objectives: Surfactant therapy is a widely accepted treatment, with different administration techniques such as INSURE (INtubation-SURfactant adminstration-Extubation) and MIST (Minimally Invasive Surfactant Therapy). This study aimed to compare the efficacy and side effects of INSURE and MIST for surfactant therapy in premature newborns with RDS.

Methods: This randomized clinical trial was conducted on 82 premature neonates with RDS admitted to the Namazee NICU in Shiraz, Iran from July to December 2020. Infants were randomly assigned to either the INSURE or MIST group for surfactant administration. Infants were randomly assigned to either the INSURE or MIST group for surfactant administration. In the MIST group, surfactant was administrated during spontaneous breathing utilized a thin vascular catheter inserted into the airway without intubation. In the INSURE group, the strategy involves intubation, administration of surfactant, and extubation. The various outcome data included the frequency of surfactant administration, duration of oxygen requirement; mechanical ventilation needs in the first 72 hours, and different complication were compared between the two groups.

Results: The most demographic characteristics were similar between the INSURE (n= 44) and MIST (n=38) groups. Timing of surfactant treatment was 10.5± 17.09 minutes in INSURE and 42± 42.5 minutes in MIST (< 0.001). All infants received the first dose of surfactant, requiring a second dose was 17 (38.6%) newborns in the INSURE group and 18 (47.3%) newborns in the MIST group (p= 0.4). There were no significant differences between the groups in the incidence of intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, or disseminated intravascular coagulation. The duration of NCPAP and the need for mechanical ventilation were also similar between the groups.

Conclusions: Use of the INSURE and MIST techniques in premature infants with RDS can be considered effective approaches for surfactant therapy.

Keywords: MIST; INSURE; Surfactant; Premature; Respiratory Distress Syndrome.

Introduction

Neonatal respiratory distress syndrome (RDS) is a significant contributor to morbidity and mortality in newborns. The infant's clinical presentation often manifests within minutes of birth, characterized by diminished breath sounds or increased respiratory effort, including tachypnea, expiratory grunting, nasal flaring, accessory muscle use, cyanosis, and poor peripheral perfusion. The incidence of RDS is inversely related to the gestational age of the infant, with more severe disease in smaller and more premature neonates.[1-3]

The fundamental etiology of neonatal RDS is a deficiency of surfactant, stemming from either inadequate surfactant production or surfactant inactivation in the context of immature lungs. Prematurity, a crucial risk factor, directly impacts both of these mechanisms, thereby contributing to the development of RDS. Surfactant plays a delicate role in maintaining the balance of pressures at the air-fluid interface, preventing the collapse or fluid filling of the alveoli. The deficiency of surfactant increases surface tension within the small airways and alveoli, thereby reducing the compliance of the immature lung.[4,5]

The management of neonatal RDS comprises antenatal corticosteroids, surfactant therapy, and advanced respiratory support of the neonate. Exogenous surfactant administration is indeed a widely accepted intervention for preterm infants diagnosed with RDS, particularly when their oxygen requirements exceed a FiO2 of 0.5. Surfactant replacement therapy is administered by trained personnel in a clinical setting with equipment for intubation and resuscitation readily available.[6,7] Different timing strategies for surfactant treatment in RDS are crucial for optimizing outcomes; prophylactic treatment administering surfactant very early < 30 min after birth, early < 2–3 h after birth and selective treatment refers to surfactant administration to preterm infants with appearance of clinical signs of RDS.[8]

Various techniques exist for the use of surfactant, each with its cost-benefit considerations. The standard method involves intratracheal surfactant replacement therapy via an endotracheal tube and mechanical ventilation by an experienced practitioner, which may result in transient airway obstruction, pulmonary injury, pulmonary air leak, and airway injury.[9] Another technique is the INSURE (INtubation-SURfactant administration-Extubation) method, which includes a certain sequence of intubation, surfactant administration, and extubation. This approach, approved by the FDA, facilitates complete and uniform distribution of surfactant in the lung and is considered the easiest way for prescription, but it requires proper endotracheal tube positioning to prevent airway injury and carries the possibility of hemodynamic instability.[10,11] The less invasive surfactant administration (LISA) technique utilizes a flexible thin catheter placed in the trachea with direct laryngoscopy during spontaneous breathing, with the newborn usually supported by nasal continuous positive airway pressure (NCPAP). This method, which does not require intubation, is associated with a lower rate of barotrauma and death and is currently adopted in Europe and Australia. However, it has disadvantages, such as the risk of accidental catheter removal during laryngoscopy, slow surfactant injection, increased risk of surfactant reflux, and the need for sufficient and spontaneous breathing by the baby.[12,13] The most commonly used term is LISA, followed by MIST (minimally invasive surfactant therapy). The MIST method involves the use of a feeding tube to instill surfactant in the airway, while the patient is connected to non-invasive respiratory support and the surfactant administration occurs during the work of spontaneous breathing through a respiratory device. This approach is increasingly used to reduce intubation rates and their associated complications.[14-16]

Further investigations are required to consider the invasiveness of older approaches and to establish the MIST technique as the standard method for surfactant administration in premature newborns with RDS, in place of endotracheal intubation. This study aims to compare the treatment results in the two groups of INSURE and MIST techniques for surfactant therapy in premature infants with RDS in terms of necessity for a second dose of surfactant, duration of mechanical ventilation, duration of nasal CPAP and requirement for oxygen. We also conducted to assess the side effects for two groups.

Methods

This randomized clinical trial was conducted on premature neonates with RDS admitted to the Namazee Neonatal Intensive Care Unit (NICU), the largest neonatal care center in Fars province, Southwestern Iran. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.509), and informed consent was written by the participants' parents before including neonates in this study. The study period

was from July to December 2020. Premature newborns were defined as those born before 37 weeks gestation, and the diagnosis of RDS was made by the neonatologist based on the color, breathing efforts of baby's need for supplemental oxygen by way of tachypnea and retraction. Chest X-rays, and arterial blood gas findings also show how well the lungs and heart are working. Premature newborns with pulmonary air leak syndromes, such as pneumothorax and pneumo-mediastinum, were excluded from the study. Infants with cyanotic congenital heart disease, thoracic dystrophy, suspected bacterial pneumonia, and early-onset sepsis were also excluded. All newborns' information, including gestational age, sex, birth weight, mode of delivery (vaginal or caesarian section), Apgar score at the fifth minute, and multiple pregnancies, were recorded.

Newborns with signs of RDS born in the delivery room or operation room underwent immediately treatment with NCPAP of 5–8 cmH2O pressure range, and an orogastric tube was inserted to prevent severe abdominal distension. Cardio-pulmonary monitoring and continuous monitoring of oxygen saturation were also carried out. If the need for FiO2 was greater than 40%, 200 mg/kg of surfactant (Curosurf, Chiesi Farmaceutici Group, Parma, Italy) was administered 30 minutes after NCPAP to maintain SpO2 in the range of 85% - 92%. In our center commonly surfactant therapy requires placement of an endotracheal tube according to standard method.

The selected premature newborns with RDS were randomly assigned into two groups using block randomization to balance the number of infants in each study group. In the INSURE group; infants under NCPAP were intubated without the use of sedative, the position of endotracheal tube was confirmed by auscultation, each infant received a dose of 200 mg/kg of surfactant over 1- 2 minutes through the endotracheal tube. Then newborns underwent mechanical ventilation with a peak inspiratory pressure (PIP) of 20–22 cmH2O, a positive end- expiratory pressure (PEEP) of 5–6 cmH2O and a respiratory rate of 30–40 breaths/min to achieve a tidal volume of 4–6 ml/kg. After surfactant administration, endotracheal tube was withdrawn within ≥ 30 min if the infant exhibited a satisfactory respiratory drive. Following 12 to 24 hours, newborns of both groups can receive a subsequent dose of surfactant (100 mg/kg) if FiO2 > 40% was still required to maintain O2 saturation within the range of 85% - 95%. If the newborn persisted pH < 7.2, FiO2 > 60%, and PCO2 > 60 mmHg for longer than 2 hours or occurred apnea, the infant would be re- intubated and administrated surfactant.

In the MIST group, a dose of 200 mg/kg dose of surfactant was administered during spontaneous breathing via a number 5F feeding tube inserted into the trachea using laryngoscopy without sedative and took 1 to 3 minutes. The insertion depth of the feeding tube was determined using the formulas: weight in kg (weight + 6). The newborn’s SPO2 and heart rate were constantly monitored using pulse oximetry during the procedure. If the catheter failed to pass through within 30 seconds, a second attempt was made to insert the catheter. After completing the procedure, the infant’s stomach was suctioned to confirm that surfactant had entered the lung. The catheter was removed following the surfactant injection and the infant continued on NCPAP. If apnea persisted, intratracheal surfactant administration was performed via an endotracheal tube, followed by and mechanical ventilation if necessary.

Skilled neonatologists performed both the INSURE and MIST techniques for the newborns.

The outcomes data included the timing of surfactant treatment, the frequency of surfactant administration, duration of the need for oxygen, duration of the need for oxygen, the need for mechanical ventilation in the first 72 hours, the duration of treatment with NCPAP, the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, disseminated intravascular coagulation, NEC, sepsis and the duration of hospital stay. This study also evaluated death up to 28 days of age and compared it between the two groups.

A total of 98 premature newborns with RDS were needed for this study, considering an α of 0.05 and a $\beta 1$ of 0.80 (d=0.15, s1=0.26, s2=0.09) calculated using the PASS software. The data were analyzed using SPSS software (version 26). Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables were presented as frequencies and percentages. Differences between the two groups were analyzed using the t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

The study population comprised 98 premature neonates with RDS, of whom 16 were excluded due to asphyxia, early-onset sepsis, congenital pneumonia, and congenital heart disease. Ultimately, 82 preterm infants (34 females, 48 males) with a mean gestational age of 31 ± 2.3 weeks (range: 26-36 weeks) were enrolled (Figure 1). The demographic and clinical characteristics of the two study groups, INSURE and MIST, are presented in Table 1, and no statistically significant differences were observed between the groups.

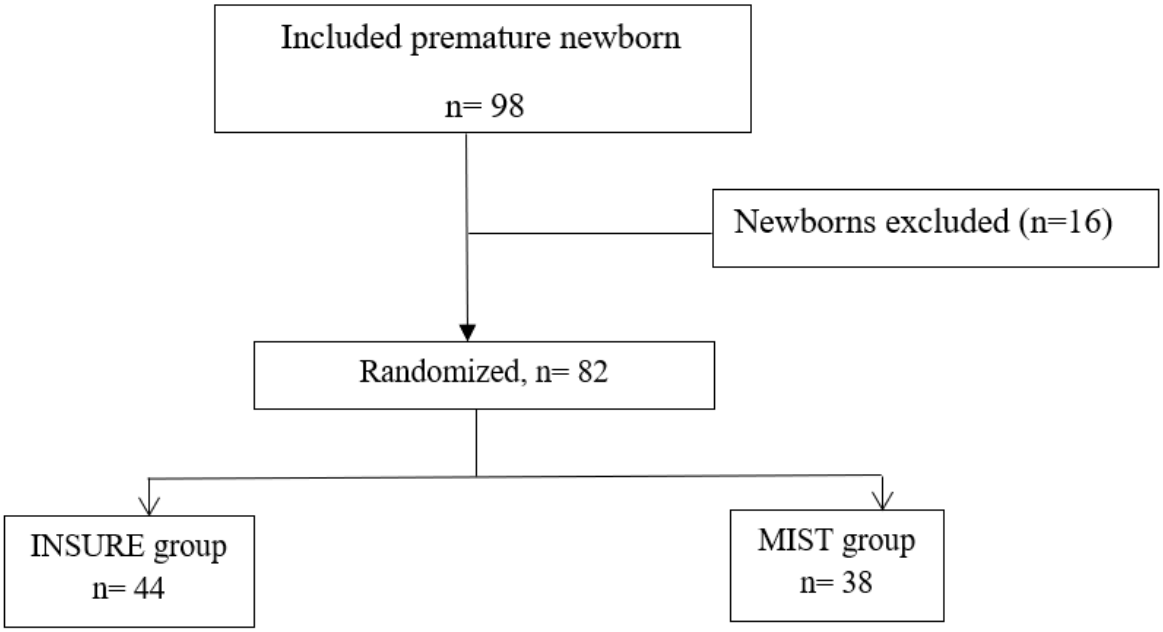

Figure 1: Flow diagram of participants in the study.

Table 1: Characteristics data of premature neonates with RDS in the two groups.

Characteristics	**INSURE**	**MIST**	***p*-value**
	n = 44	**n = 38**	
Boys, no. (%)	25(56.8)	23(60.5)	0.70
Girls, no. (%)	19(43.2)	15(39.5)	
Gestational weeks (mean± SD)	31.18± 2.24	30.86± 2.38	0.29
Birth weight (gram± SD)	1486± 515.82	1460± 444.2	0.71
Multiple pregnancies, no. (%)	22 (50)	18(47.4)	0.52
Cesarean section	35(79.6)	33(86.8)	0.38
Apgar score of min 5	7± 0.8	6.9±0.8	0.96
Timing of surfactant treatment, min(mean± SD)	10.5± 17.09	42± 42.5	<0.001

Based on our results, surfactant was administered in the range of 1 min to 180 min after birth in the premature newborns. All participants received an initial dose of surfactant replacement therapy, with 17 (38.6%) neonates in the INSURE group and 18 (47.3%) in the MIST group requiring a second dose (p = 0.4). The mean duration of NCPAP requirement was 3.3 ± 3.1 days in the INSURE group and 3.2 ± 3.08 days in the MIST group (p = 0.22). The proportion of neonates requiring mechanical ventilation was 18 (40.9%) in the INSURE group and 9 (23.7%) in the MIST group, but this difference was not statistically significant (p = 0.09). The incidence of intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, and disseminated intravascular coagulation did not differ significantly between the INSURE and MIST groups (Table 2). Similarly, no

statistically significant differences were found between the two groups regarding the duration of hospital stay and mortality rate. None of the newborn with RDS who administrated surfactant showed NEC and sepsis.

Table 2: Frequency of different variables categorized by INSURE or MIST technique in premature neonates.

Characteristics	INSURE	MIST	*p*-value
	n = 44	n = 38	
Intraventricular hemorrhage, no.	13	10	0.74
Bronchopulmonary dysplasia, no.	4	6	0.78
Pneumothorax, no.	4	2	0.80
Pulmonary hemorrhage, no.	1	4	0.11
*DIC, no.	2	2	0.88
**NEC, no.	0	0	Not report
Sepsis	0	0	Not report
Hospital stay duration (day), mean± SD	19.33± 13.42	21.23±16.32	0.65
Death	10	9	0.72

**DIC, Disseminated intravascular coagulation; **NEC, Necrotizing enterocolitis.*

Discussion

This study investigated the effects and outcomes of administering surfactant via the MIST technique compared to the INSURE method in premature neonates with RDS. The demographic and clinical characteristics, including sex, gestational age, birth weight, multiple pregnancies, mode of delivery, and Apgar scores between the MIST and INSURE groups indicated homogeneity between the two groups.

Although the MIST approach demonstrated a lower requirement for mechanical ventilation in the first 72 hours after birth compared to INSURE, this difference did not reach statistical significance ($p = 0.09$), which may be attributed to the relatively small number of neonates requiring mechanical ventilation in each group. Previous studies by Boskabadi et al. and Kribs et al. have reported a significant reduction in the need for mechanical ventilation with surfactant administration via a thin endotracheal catheter compared to the INSURE method.[17,18] Similarly, Kanmaz et al. found a significantly lower requirement and duration of mechanical ventilation in preterm infants treated with the thin catheter technique during spontaneous breathing.[16] Similar to us, Choopani et al. found the need for mechanical ventilation 72 hours after birth was not significantly different within the two groups, although it was lower in catheter insertion versus the INSURE group.[19]

Our data showed the need for the second dose of surfactant in INSURE and MIST groups was 38.6% and 47.3%, ($p= 0.4$)..Kanmaz et al. reported in line with our findings; that about 20% using the second dose of surfactant among the infants treated with both techniques.[16] Mosayebi et al. showed about 15% in the INSURE group and 7.5% in the MIST group required a second dose of surfactant.[20] Furthermore, Another study conducted by Aguar et al. assessed the infants and about 36% of the MIST group and only 6.5% of the INSURE group needed the second administration of surfactant.[21] While we did not evaluate the severity of RDS in our study, it appears that newborns exhibiting more severe RDS required a second dose of surfactant more frequently. .In the current study, the average duration of need for NCPAP in newborns in the both groups was about 3 day with no significant difference. Mirina et al. reported CPAP duration decreased significantly in two NICU and increased in the other with no overall difference between tracheal catheterization and INSURE groups.[22]

The incidence of intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, and disseminated intravascular coagulation did not differ significantly between the INSURE and MIST groups ($p > 0.05$). These findings are consistent with those reported by Gupta et al., who observed no significant differences in patent ductus arteriosus, intraventricular hemorrhage, and bronchopulmonary dysplasia between the two surfactant administration techniques.[23] A recent systematic review and meta-analysis of 17 randomized controlled trials involving 2,408 preterm infants also showed that surfactant administration via a thin catheter decreased the risk of bronchopulmonary dysplasia in survivors compared to

controls.[24] Similarly, Mosayebi et al. found no differences in early and delayed complications between the MIST and INSURE groups.[20]

The duration of hospital stay and mortality rates were not significantly different between the MIST and INSURE groups in the present study. In contrast, Mirnia et al. reported a significantly lower mortality rate in the tracheal catheterization group compared to the INSURE group in a multicenter study.[22] Mohammadizadeh et al. also found no statistically significant differences in mortality and the combined outcome of chronic lung disease between the two surfactant administration methods.[25]

All patients were recruited from one referral center in Shiraz and therefore the sample size of our patients was limited. Multicenter research is still needed to fully elucidate any potential advantages or disadvantages between these two surfactant administration methods. In this study, data on the administration of antenatal steroids to pregnant women was not available for comparison between two groups

Conclusion

Our results showed no significant differences between the two groups in terms of key outcomes such as the need for additional surfactant doses, duration of NCPAP and mechanical ventilation, incidence of complications like intraventricular hemorrhage and bronchopulmonary dysplasia, hospital length of stay, and mortality. Both the INSURE and MIST methods appeared to be effective approaches for surfactant delivery in preterm infants with RDS. Similar outcomes suggest that either technique can be utilized successfully, allowing clinicians to choose the approach that best fits their NICU's practices and resources. Overall, this study provides valuable evidence to guide surfactant therapy in the care of premature neonates with RDS.

Disclosure

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