

A study on the comparison of minimally invasive surfactant therapy with insure technique of surfactant therapy in preterm babies with respiratory distress in a tertiary care hospital – A prospective cohort study

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a common problem in preterm babies due to surfactant deficiency. Initially, babies were given surfactant therapy by intubation, surfactant administration, and extubation (INSURE) method. Minimally invasive surfactant therapy (MIST) is a novel method of surfactant administration without intubation to spontaneously breathing preterm babies with RDS without the removal of continuous positive airway pressure (CPAP). **Aim:** This study aims to compare the surfactant therapy in preterm babies with RDS through MIST and INSURE technique. **Methods:** This prospective, observational cohort study was conducted in the neonatology unit of Calcutta National Medical College and Hospital. A total of 212 preterm babies of <37 weeks of gestation with features of RDS, who require surfactant are taken and divided into two groups. Very sick babies with congenital anomalies are excluded from the study. In MIST group (n=102), 8 Fr feeding tube is used to deliver surfactant while the baby is on CPAP. In INSURE group (n=102), surfactant is given by intubation through endotracheal tube without CPAP and extubated. **Results:** Mean birth weight was 1.26 kg in MIST and 1.22 kg in INSURE. Mean gestational age was 31.33 weeks in MIST and 31.11 weeks in INSURE. It was observed that there is a significant difference in terms of duration of oxygen requirement, neonatal intensive care unit stay, and surfactant spillage during administration in MIST group compared to INSURE group. However, duration of mechanical ventilation, CPAP, number of doses of surfactant, sepsis, intraventricular hemorrhage, retinopathy of prematurity, pneumothorax, bronchopulmonary dysplasia, and mortality did not show significant difference in both the groups. **Conclusion:** MIST is safe, feasible, and more beneficial than INSURE technique.

Key words: Surfactant, Respiratory distress, Preterm, CPAP, MIST, INSURE

Preterm babies with respiratory distress syndrome (RDS) need exogenous surfactant as surfactant producing type 2 alveolar pneumocytes begin to develop after the third trimester. Surfactant replacement therapy has proven effective in reducing mortality and pulmonary morbidity [1,2] and has been a mainstay of therapy in preterm infants intubated soon after birth. Recent randomized multicenter trials have shown that the use of continuous positive airway pressure (CPAP) in the delivery room has been at least as effective as intubation and surfactant administration in the 1st minutes after birth with trends toward reduction of mechanical ventilation (MV) and the incidence of bronchopulmonary dysplasia (BPD) [3-5]. Techniques of minimally invasive surfactant therapy (MIST)

have recently been investigated, aiming to administer surfactant to spontaneously breathing infants, allowing them to remain on CPAP in the critical 1st days after birth and, hopefully, beyond without intubation. These techniques have included administration of exogenous surfactant by brief tracheal catheterization, pharyngeal instillation, nebulization, and laryngeal mask [6]. Of these, the methods involving brief tracheal catheterization have been most extensively studied, with surfactant administered using both a flexible feeding tube and a semi-rigid vascular catheter. INSURE technique needs intubation, bolus surfactant administration, temporary bag, and tube ventilation after surfactant administration. MIST is gentle, safe, feasible, and effective in preterm infants with non-invasive respiratory support by neonatologists [6]. In this study, we want to compare these two methods of surfactant administration in pre-term babies with RDS.

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METHODS

This is a prospective, observational cohort study carried out at the neonatology unit in Calcutta National Medical College and Hospital for a period of 1 year from June 2019 to June 2020 in preterm babies with RDS. Surfactant is given as per European Consensus Guidelines 2019 on RDS [7]. Extremely sick babies with congenital anomalies are excluded from the study. After obtaining ethical clearance, informed consent is taken from the parents in their own language. As the baby is received in sick newborn care unit, Silverman-Anderson scoring (SAS) [8] for RDS is done. If SAS >5, then the baby is put on nasal CPAP. Preterm neonates with RDS requiring surfactant therapy are divided into MIST group and INSURE group randomly. In preterm babies with RDS if $FiO_2 > 30\%$ on CPAP then according to European Consensus Guidelines 2019 on RDS [7], surfactant usually poractant alfa (200 mg/kg) of phospholipid given by either MIST or INSURE technique.

In MIST, the baby will be on CPAP with initial settings started with 5 cm of H_2O and FiO_2 adjusted to achieve target saturation of 90–95% using a bubble CPAP or ventilator CPAP based on availability using nasal mask as interface. Heart rate and oxygen saturation (SpO_2) were monitored throughout the procedure. Required quantity of surfactant was taken into syringe and an additional 1 ml of air drawn into syringe taking account for the dead volume of the catheter used. Eight Fr feeding tube to be cut in sterile manner depending on length of endotracheal tube with nozzle end to be taken for surfactant administration and surfactant was given slowly over 2 min with syringe fitted with nozzle in a single bolus by direct laryngoscopy. After surfactant therapy, feeding tube was removed after pushing 1 ml of air for the surfactant to enter completely. The baby will be on nasal CPAP during the entire procedure. If the baby did not respond to the procedure or has $FiO_2 > 30\%$ even after 6 h of giving surfactant, then second dose of surfactant was considered. The maximum upper limit for CPAP was 7 cm of H_2O and FiO_2 of 70%. Infants not maintaining saturation on these settings were intubated.

In INSURE technique, the baby is removed from CPAP. Endotracheal tube was inserted using laryngoscope for surfactant therapy. Five Fr feeding tube was taken and cut according to the length of the endotracheal tube. Surfactant is instilled in 2–3 boluses through the feeding tube in the endotracheal tube into the trachea followed by continuation of the bag and tube ventilation for 2–3 min. The baby is then extubated and put on CPAP.

Main outcome parameters, compared between MIST and INSURE group of neonates, include number of doses of surfactant therapy, duration of CPAP, surfactant spillage during administration, duration of oxygen requirement, duration of MV, duration of neonatal intensive care unit (NICU) stay, and mortality. Statistical analysis was performed using IBM SPSS Statistics 22 software for Windows. Independent samples t-test was performed for continuous variables and they were expressed as means±standard deviation. Chi-square test (or Fisher's exact test)

was performed for categorical data. $p < 0.05$ was considered as statistically significant.

The sample size calculation was done by comparing the means of INSURE group and MIST group regarding primary outcome of our study. To have power of the study as 80% and significance level of 5% and using the standard deviation value of pilot study done before the main study and expecting an effect size of approximately 2 days difference in the duration of oxygen requirement, sample size calculated was 54 in each group. The current study, however, included 106 newborns in each group.

RESULTS

The baseline characteristics of the neonates included in our study are summarized in Table 1 which showed no significant difference in the MIST and INSURE groups.

The outcome variables are summarized in Table 2, showing significant difference between the MIST and INSURE groups in terms of surfactant spillage, duration of oxygen requirement, and NICU stay.

DISCUSSION

Several cases of RDS in preterm babies are now treated with nasal CPAP soon after birth. Surfactant replacement has become one of the common modalities which have improved the survival of preterm infant. MIST allows for surfactant administration while the baby is on CPAP, requiring no intubation and bagging. This can decrease lung injury and infection. In the neonatology unit of CNMCH, every year approximately 1900 (both inborn and outborn) admissions occur of which, nearly 41.3% are preterm admissions. As there is free supply of surfactant available, we wanted to compare MIST with INSURE technique of surfactant administration in preterm babies with RDS.

In our study, mean duration of oxygen requirement was significantly reduced in the MIST group compared to the INSURE group ($p < 0.002$) (Fig. 1). Similar observation was reported by Jena *et al.* [9] who reported that the duration of oxygen was 6 days in MIST and 12 days in INSURE, which was a significant reduction ($p < 0.01$). Significant difference was also reported in the study by Dargaville *et al.* [10]. In Accuitive Medical Ventures (AMV) [11], infants in the MIST group had lower need for oxygen therapy at 28 days compared to the INSURE group. This might be due to lung injury caused by few mechanical breaths in the INSURE group. End expiratory lung volume is improved after MIST and is associated with oxygenation improvement [12].

The mean duration of NICU stay was significantly less in the MIST group compared to the INSURE group ($p = 0.017$) in our study (Fig. 2). In a study by Jena *et al.* [9], NICU stay was 11 days in the MIST group and 28 days in the INSURE group showing significant reduction in the MIST group ($p < 0.01$) which corroborates with our study. This might be due to less oxygen requirement and less lung injury in the MIST group.

Table 1: Baseline characteristics of MIST and INSURE technique for surfactant administration

Baseline characteristics	MIST	INSURE	p-value
Mean gestational age (weeks) (Mean±SD)	31.33±2.899	31.11±2.87	0.203
LSCS	38 (37.3%)	41 (40.2%)	0.47
Mean birth weight (kg) (Mean±SD)	1.26±0.31	1.22±0.30	0.236
Boy	53 (52%)	54 (52.9%)	0.07
Multiple births	12 (11.7%)	20 (19.6%)	0.18
SGA babies	31 (30.3%)	32 (31.3%)	0.19
1 st dose surfactant within 2 h of birth	58 (56.8%)	56 (54.9%)	0.24
Complete dose of antenatal steroids	45 (44.1%)	47 (46%)	0.28

MIST: Minimally invasive surfactant therapy, INSURE: Intubation, surfactant administration, and extubation, SD: Standard deviation, LSCS: Lower segment cesarean section, SGA: Small for gestational age

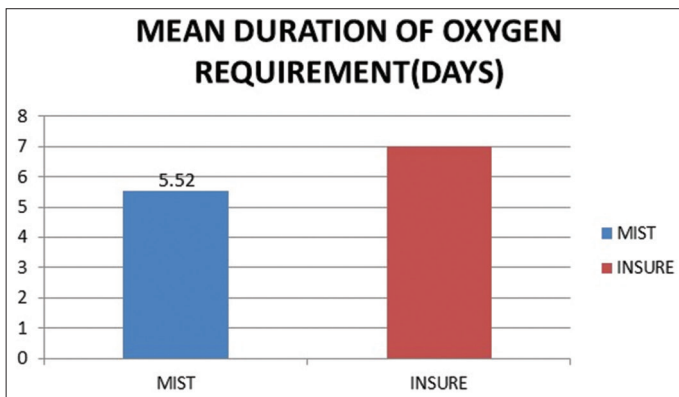


Figure 1: Mean duration of oxygen requirement in minimally invasive surfactant therapy and intubation, surfactant administration, and extubation technique of surfactant administration

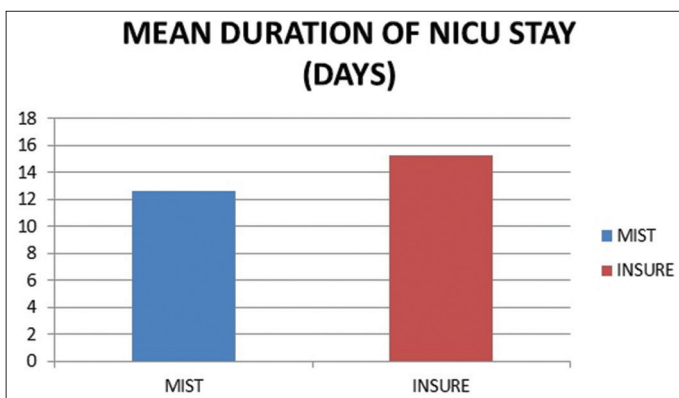


Figure 2: Mean duration of neonatal intensive care unit stay in minimally invasive surfactant therapy and intubation, surfactant administration, and extubation technique of surfactant administration

Spillage during surfactant therapy was also significantly reduced in the MIST group compared to the INSURE group in the current study. Dargaville *et al.* reported that one-third of preterm infants (25–28 weeks of gestation) developed this complication on using the MIST technique [10]. Cologne method involves, closing the mouth during surfactant administration which has helped to reduce the surfactant spillage [13]. Furthermore, using a lower volume surfactant formula, Curosurf would be another option to decrease surfactant spillage.

Mortality showed no significant difference in both the groups as was also in evidence in AMV [11] trial. Aldana-Aguirre *et al.* [14] in another recent meta-analysis with a total of 895 infant observed reduction in mortality ($p=0.01$) in the MIST group. Jena *et al.* [9] reported that there was no difference in mortality between the two groups. In a recent study done in Taiwan, the MIST group was found to have significantly lower rate ($p<0.05$) of mortality [15].

It was also observed that there were no differences seen in both the groups in terms of sepsis, ROP, BPD, pneumothorax, and IVH in our study. Although the risk of BPD appears to be lower in infants over 28 weeks of gestation, it should be noted that, in more-preterm infants, the need for intubation and even brief positive pressure ventilation by bagging for surfactant administration could be more damaging when using the INSURE method than with the MIST method. On the other hand, spontaneous breathing during the MIST technique is believed to spread surfactant more uniformly causing less lung injury [9]. The incidence of BPD could thus be reduced. In a study by Jena *et al.* [9], significant reduction in BPD was observed in the MIST group with no significant difference in terms of sepsis and IVH. In a recent Taiwan-based study, the MIST group had significantly lower rate ($p<0.05$) of composite outcome of BPD [15].

Regarding requirement of the second dose of surfactant, we found no difference between the two groups. In a study by Kanmaz *et al.* [16], an almost equal percentage of both groups (about 20%) required the second dose of surfactant which is in accord to our observation. Studies by Jena *et al.* [9] and Aldana-Aguirre *et al.* [14] also reported no difference in the 2nd dose of surfactant in both the groups. In the study by Aguar *et al.* [17], the infants in the MIST group received a 100 mg/kg dose of Curosurf and those in the INSURE group received a 200 mg/kg dose, and about 36% of the MIST group and only 6.5% of the INSURE group needed the second dose of surfactant. From these, it was observed that initial dose of surfactant appears to dictate the need for a second administration of surfactant regardless of the technique used.

The mean duration of CPAP showed no statistically significant difference in both the groups in the current study. Jena *et al.* [9], however, showed that the mean duration of CPAP was 4 in MIST and 8 in the INSURE group, having significant reduction in the

Table 2: Outcome variables comparing MIST with INSURE technique of surfactant administration

Outcome variables	MIST	INSURE	p-value
2 nd dose of surfactant	10 (9.8%)	10 (9.8%)	0.258
Mean duration of CPAP (days) (Mean±SD)	2.27±1.415	2.5±1.510	0.924
Surfactant spillage	13 (12.7%)	21 (20.5%)	<0.01
Mean duration of oxygen requirement (days) (Mean±SD)	5.52±3.665	7.06±4.82	0.002
Mean duration of MV (days) (Mean±SD)	0.46±0.972	0.81±1.494	0.746
Mean duration of NICU stay (days) (Mean±SD)	12.59±7.801	15.25±9.613	0.017
Mortality	19.6%	20.5%	0.64
Sepsis	17 (16.7%)	17 (16.7%)	0.55
ROP	1 (0.98%)	1 (0.98%)	1
IVH	2 (2%)	2 (2%)	0.806
BPD	0	1 (1%)	0.32
Pneumothorax	1 (1%)	0	0.32

MIST: Minimally invasive surfactant therapy, INSURE: Intubation, surfactant administration, and extubation, SD: Standard deviation, CPAP: Continuous positive airway pressure, NICU: Neonatal intensive care unit, ROP: Retinopathy of prematurity, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia

MIST group compared to the INSURE. In the take care trial [18], a significantly shorter duration of CPAP was observed in the MIST group compared to the INSURE group.

Required ventilation in the two groups showed no statistically significant difference in our study, whereas Jena *et al.* [9] observed a significant reduction in the need for MV in the MIST group (MIST: 19%, INSURE: 40%, $p < 0.01$, risk ratio=0.49). In Hobart method [19], there was a significant reduction in the need for intubation at <72 h for infants between 25 and 28 weeks' gestation (32% vs. 68%; $p = 0.0011$), with a similar trend in those at 29–32 weeks' gestation (22% vs. 45%; $p = 0.057$) in the MIST group. Duration of ventilation was similar in both cohorts. Studies by Kanmaz *et al.* [16] and Aldana-Aguirre *et al.* [14] observed decrease in MV in the MIST group. In AMV trial [11], a significant reduction in duration of ventilation after birth in the intervention (MIST) group compared to the standard group (INSURE) (28% vs. 46%; $p = 0.008$) was observed. Moreover, fewer infants in the intervention group needed MV at any time compared to infants in the standard group (33% vs. 73%; $p < 0.0001$). In a Taiwan-based recent study [15], the duration of intubation and MV was significantly shorter ($p < 0.001$) in the MIST group than in the intubated group. The study by Seo *et al.* in Korea showed that the need for MV was reduced in MIST [20] whereas the study by De Luca and de Winter [21] demonstrates that there was no significant difference in duration of MV in both the groups.

CONCLUSION

Taken together, significant difference in terms of duration of oxygen requirement, NICU stay, and surfactant spillage was observed in the MIST group compared to the INSURE group. Hence, MIST can be a safe and preferable method of surfactant administration in neonates.

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