

# Comparison of Surfactant Administration Methods-Insure (Intubate Surfactant Administration Extubate) and Lisa (Least Invasive Surfactant Administration): A Randomized Controlled Study in Preterm Infants with Respiratory Distress Syndrome

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## Abstract

**Objective:** To compare the efficacy, need of mechanical ventilation within 72 hours of surfactant administration, and primary and secondary outcomes after LISA and INSURE methods.

**Methodology:** A randomized control study was conducted at NICUs at Medical college, Vadodara and GMERS, Gotri for period of 8 months. Total 40 preterm infants between 28 to 34 weeks of gestation with RDS who required surfactant administration were enrolled, and randomized in two groups of 20 patients each. Surfactant was administered by LISA and INSURE method according to randomization.

**Results:** There were 70% male infants in LISA group, and 55% in INSURE group. Mean GA in LISA group was 30.3±2.2 weeks, and 30.95±1.88 weeks in INSURE group, mean birth weight was 1.24±0.3 kg in LISA group and 1.25±0.3 kg in INSURE group. 40% patients in LISA and 55% in INSURE group had not received antenatal steroids. Basic characteristics and maternal risk factors were comparable in both groups. Mechanical ventilation was required within 72 hours of surfactant administration in 6 patients (30%) in LISA group and 14 patients (70%) in INSURE group (p value = 0.0238). 8 patients (40%) from LISA group and 16 patients (80%) from INSURE group required mechanical ventilation during their entire NICU stay (p=0.0268).

**Conclusion:** The requirement of mechanical ventilation within 72 hours of surfactant administration as well as during entire NICU stay was more in INSURE group than LISA group with statistically significant difference.

**Keywords:** Preterm; RDS; Surfactant; Mechanical ventilation; LISA; INSURE.

## Introduction

Lack of surfactant was described as the cause of respiratory distress syndrome (RDS) in preterm infants many years ago. Respiratory distress

syndrome (RDS) is a common neonatal condition in premature infants. Its treatment often requires the use of surfactants, which have been shown to reduce the risk of death and bronchopulmonary dysplasia (BPD) in this population.<sup>1,2</sup> In the last 30 years

surfactant replacement with exogenous surfactant preparations derived from animal sources became the most effective evidence-based therapy for RDS. The mode of administration has evolved especially in the last decade from endotracheal surfactant bolus administration during mechanical ventilation over Intubation-Surfactant-Extubation (INSURE) followed by continuous positive airway pressure (CPAP) towards less invasive techniques (less invasive surfactant administration (LISA) that aim to effectively provide an adequate dose of surfactant while the infant is breathing spontaneously.<sup>3</sup> Currently, the used strategy for management of RDS is nasal CPAP at onset with selective use of surfactant for those infants with increasing oxygen requirements.

Infants meeting the criteria for surfactant use are intubated and briefly ventilated for surfactant delivery by a protocol often referred to as INSURE (Intubation, Surfactant administration and Extubation).<sup>4,5</sup> To prevent intubation for surfactant delivery in preterm infants with RDS, less invasive surfactant administration (LISA) techniques have also been used and preferred.<sup>6</sup> Of these techniques, the use of a thin catheter for intratracheal surfactant delivery in spontaneously breathing preterm infants on nasal CPAP is the most studied<sup>7</sup>, which decreases the risk of BPD, need for mechanical ventilation and increases rate of survival.<sup>8</sup>

This study aimed at assessing the efficacy and safety of LISA method over INSURE method in preterm infants with respiratory distress syndrome requiring surfactant administration.

## Methodology

- This study was conducted in the neonatal intensive care units (NICUs) and postnatal wards of Pediatric Department, SSG hospital Medical college, Baroda and GMERS hospital, Gotri, Vadodara, from April 2020 to December 2020. Preterm infants having gestational age between 28 weeks to 34 weeks with respiratory distress syndrome requiring surfactant administration were considered for our study. Newborn infants with APGAR  $\leq 4$  at 5 minutes, those who required intubation and mechanical ventilation at birth and infants having any congenital malformation which could affect their respiratory function were excluded.
- RDS was diagnosed clinically in preterm infants by need of supplemental oxygen, clinical signs of tachypnea, retraction and grunting and the diagnosis was confirmed

radiologically by chest X-ray finding of reduced lung volume, reticulo-granular pattern of lung consolidation and air bronchograms.<sup>1</sup> In infants with respiratory distress syndrome since birth, nasal CPAP was started with PEEP of 5–6 cm of H<sub>2</sub>O, FiO<sub>2</sub> of 30% adjusted to achieve target saturation of 90 to 95%. Patients having RDS, who required FiO<sub>2</sub> more than 40% on nasal CPAP to maintain saturation (SpO<sub>2</sub>) between 90 and 95% in first 6 hours of life were randomized to receive surfactant either by LISA or INSURE technique.

In our study we had taken valid, informed and written consent in language legible to the parents prior to enrolling the neonate in the study. All infants who were satisfying our inclusion criteria were randomized in two groups by chit method with the help of on call doctor in charge.

One group received surfactant with Least Invasive Surfactant Administration (LISA) method and another one received surfactant with INSURE (Intubation-Surfactant-Extubation) method.

### *LISA (Least Invasive Surfactant Administration) Procedure*

In this method, a 5-F feeding tube was passed into the trachea through the vocal cords, using a standard laryngoscope with blade. If the catheter failed to pass through within 30 seconds, nasopharyngeal CPAP was used and another attempt was made later with the catheter. A 200 mg/kg dose of surfactant (Curosurf, ChiesiFarmaceutici group, Parma, Italy) was instilled into the infant's trachea over 1 to 3 minutes or in 3 to 4 stages lasting 15 to 30 seconds.

During the procedure, the infant's SpO<sub>2</sub> and heart rate was monitored using pulse-oximetry. If the SpO<sub>2</sub> dropped to less than 80% or the heart rate dropped to less than 100 beats/min, the procedure was stopped and FiO<sub>2</sub> increased, followed by PEEP increment. After completing the procedure, the infant's stomach was suctioned via an intra-gastric tube to ensure that surfactant had entered the lung. The catheter was then removed, CPAP resumed, and FiO<sub>2</sub> then gradually reduced. If apnoea persisted, PPV was administered with Ambu-bag and mask.

### *INSURE Procedure (Intubation - Surfactant Administration - Extubation)*

The infant was intubated through mouth with an endotracheal tube appropriate to his/her weight and gestational age. A 200 mg/kg dose of surfactant

(Curosurf, Chiesi Farmaceutici Group, Parma, Italy) was administered by a feeding tube passed through the tracheal tube over 1-3 minutes, during which positive pressure ventilation was applied by a self-inflating bag and the infant was then extubated and placed on nasal CPAP once again.

The vitals of all neonates were monitored post surfactant administration. SA score was done 6 hours and 12 hours after the procedure to look for clinical improvement. Radiological improvement was seen by repeating chest radiograph 12 hours after surfactant administration. Arterial blood gas analysis was done at 6 hours and 12 hours after surfactant administration, to look for acidosis or carbon-dioxide retention.

After 12 hours, if  $\text{FiO}_2 > 40\%$  was still required to maintain  $\text{O}_2$  saturation within the range of 85%-

95%, a second dose of surfactant was administered.<sup>2</sup> The treatment was considered to have failed if  $\text{pH} < 7.2$ ,  $\text{FiO}_2 > 60\%$ , and  $\text{PCO}_2 > 60$  mmHg persisted for longer than 2 hours or if prolonged apnoea occurred, upon which the infant was intubated.<sup>2</sup> The primary outcome of the study, including the need for intubation during the first 72 hours and afterwards, the incidence of surfactant reflux, pulmonary haemorrhage, pneumothorax, apnoea, bradycardia, coughing/gagging and late onset sepsis were observed and documented and compared between two groups.

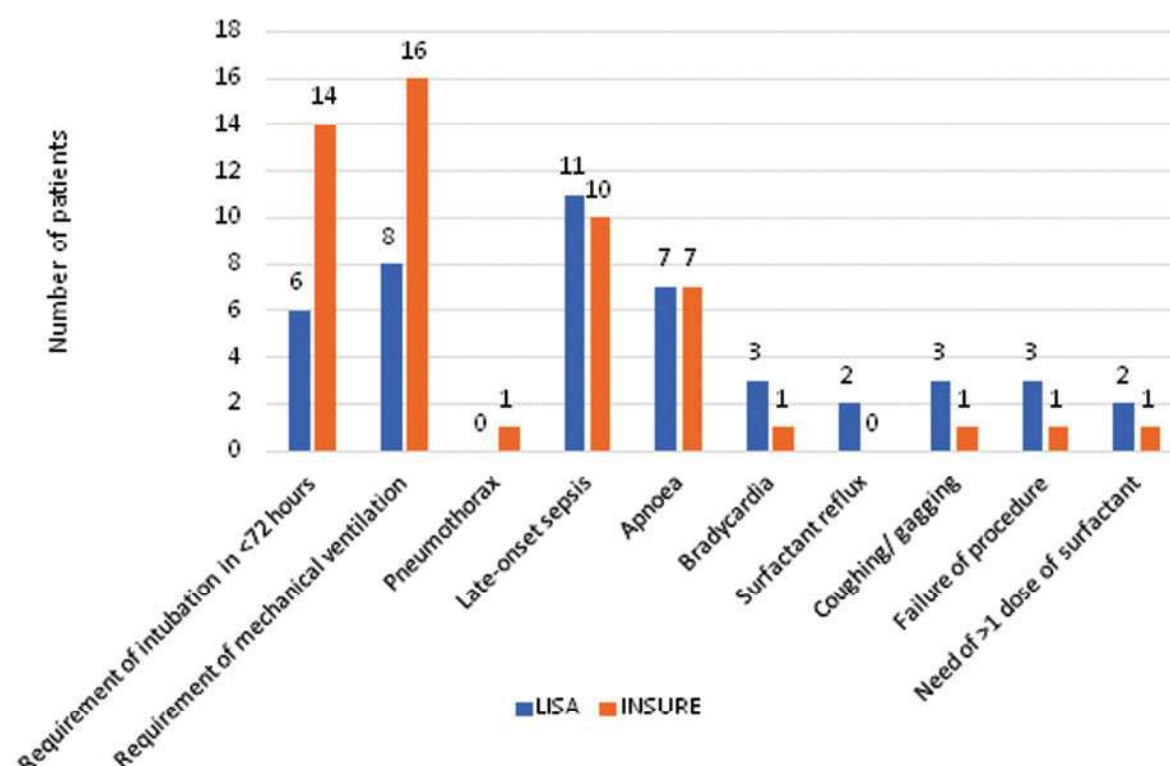
The secondary outcomes including pulmonary haemorrhage, Patent ductus arteriosus (PDA) requiring treatment, intraventricular haemorrhage (IVH) stage  $\geq 2$  (USG head on day 3 and 7 of life), Broncho-pulmonary dysplasia (BPD) (oxygen

**Table 1:** Baseline Characteristics.

| Birth History                                                         | LISA(n=20) |                 | INSURE(n=20) |                  | p-value |
|-----------------------------------------------------------------------|------------|-----------------|--------------|------------------|---------|
|                                                                       | No.        | Percentage      | No.          | Percentage       |         |
| Mean Gestational age (weeks)                                          |            | 30.30 $\pm$ 2.2 |              | 30.95 $\pm$ 1.88 | 0.9258  |
| <b>Gestational age category</b>                                       |            |                 |              |                  | 0.6376  |
| 28-30 weeks                                                           | 11         | 55%             | 11           | 55%              |         |
| 31-32 weeks                                                           | 5          | 25%             | 3            | 15%              |         |
| 33-34 weeks                                                           | 4          | 20%             | 6            | 30%              |         |
| Mean Birth Weight (kg)                                                |            | 1.24 $\pm$ 0.30 |              | 1.25 $\pm$ 0.29  | 0.9152  |
| <b>Birth weight Category</b>                                          |            |                 |              |                  | 0.9140  |
| < 1 kg                                                                | 4          | 20%             | 3            | 15%              |         |
| 1-1.5 kg                                                              | 13         | 65%             | 14           | 70%              |         |
| >1.5 kg                                                               | 3          | 15%             | 3            | 15%              |         |
| <b>Gender Distribution</b>                                            |            |                 |              |                  |         |
| Male                                                                  | 14         | 70%             | 11           | 55%              | 0.7229  |
| Female                                                                | 6          | 30%             | 9            | 45%              | 0.9650  |
| Type of delivery                                                      |            |                 |              |                  |         |
| Vaginal                                                               | 17         | 85%             | 14           | 70%              | 0.3218  |
| LSCS                                                                  | 3          | 15%             | 6            | 30%              | 0.6442  |
| APGAR                                                                 |            |                 |              |                  |         |
| At 1 minutes                                                          |            | 6.25 $\pm$ 1.91 |              | 6.79 $\pm$ 1.85  | 0.3695  |
| At 5 minutes                                                          |            | 8.58 $\pm$ 0.51 |              | 8.71 $\pm$ 0.83  | 0.5542  |
| <b>Resuscitation Required at birth</b>                                |            |                 |              |                  |         |
| Routine care                                                          | 12         | 60%             | 15           | 75%              | 0.4139  |
| Initial steps including Tactile stimulation                           | 3          | 15%             | 1            | 5%               | 0.8842  |
| Free flow oxygen                                                      | 3          | 15%             | 2            | 10%              | 0.8842  |
| Bag and Mask                                                          | 2          | 10%             | 2            | 10%              | 1.000   |
| Intubation                                                            | 0          | 0%              | 0            | 0%               | NA      |
| <b>Corticosteroid Coverage</b>                                        |            |                 |              |                  |         |
| Full Coverage                                                         | 2          | 10%             | 2            | 10%              | 1.00    |
| Partial Coverage                                                      | 10         | 50%             | 7            | 35%              | 0.55    |
| Steroid not Covered                                                   | 8          | 40%             | 11           | 55%              | 0.52    |
| Mean duration of surfactant administration since birth(hours)         |            | 3.45 $\pm$ 2.11 |              | 3.7 $\pm$ 2.7    | 0.746   |
| Mean $\text{FiO}_2$ and PEEP value prior to surfactant administration |            | 42/5.7          |              | 42/5.8           | NA      |

**Table 2(A):** Primary outcome parameters.

| Primary Outcome                                                        | LISA          |            | INSURE        |            | P value |
|------------------------------------------------------------------------|---------------|------------|---------------|------------|---------|
|                                                                        | No.<br>(n=20) | Percentage | No.<br>(n=20) | Percentage |         |
| Req. of Intubation< 72 hours of surfactant administration              | 6             | 30%        | 14            | 70%        | 0.0238  |
| Req. of Mechanical Ventilation during Stay (within and after 72 hours) | 8             | 40%        | 16            | 80%        | 0.0268  |
| Pneumothorax                                                           | 0             | 0%         | 1             | 5%         | NA      |
| Late onset sepsis                                                      | 11            | 55%        | 10            | 50%        | 1.000   |
| Apnea                                                                  | 7             | 35%        | 7             | 35%        | 0.7403  |
| Bradycardia (HR<100/min)                                               | 3             | 15%        | 1             | 5%         | 0.5984  |
| Surfactant Reflux                                                      | 2             | 10%        | 0             | 0%         | 0.4682  |
| Coughing/Gagging                                                       | 3             | 15%        | 1             | 5%         | 0.5982  |
| Failure of procedure on 1st attempt                                    | 3             | 15%        | 1             | 5%         | 0.820   |

**Fig. 1:** Primary outcome parameters.

dependence at 36 weeks of postmenstrual age), retinopathy of prematurity (ROP)  $\geq$  stage 2 and final outcome including discharge/DAMA/expiry was documented along with total duration of stay at our hospital and the data was evaluated and compared between the two groups.

The data was entered in Microsoft Excel worksheet in a password protected file. This data was analysed using MedCalc version 12.5 and

statistical tests applied were unpaired t-test and Chi-square tests.

## Result

A total of 40 patients were enrolled and randomized in two groups of LISA and INSURE (Fig.1). Both groups were comparable with the baseline characteristics (Table 1). The average gestational

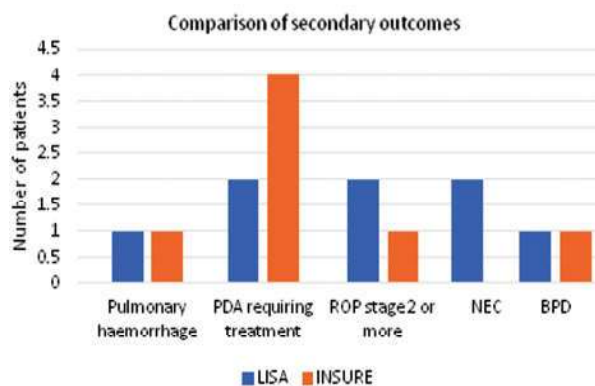
**Table 2(B):** Secondary outcome parameters.

| Secondary Outcome                                  | LISA       |            | INSURE     |            | P value |
|----------------------------------------------------|------------|------------|------------|------------|---------|
|                                                    | No. (n=20) | Percentage | No. (n=20) | Percentage |         |
| Pulmonary Hemorrhage                               | 1          | 5%         | 1          | 5%         | 0.4682  |
| Intra ventricular hemorrhage (IVH) $\geq$ stage II | 0          | 0%         | 0          | 0%         | 0.1000  |
| Patent ductus arteriosus (PDA) requiring treatment | 2          | 10%        | 4          | 20%        | 0.6589  |
| Retinopathy of prematurity $\geq$ stage II         | 2          | 10%        | 1          | 5%         | 0.8744  |
| Necrotizing enterocolitis (NEC)                    | 2          | 10%        | 0          | 0%         | 0.4682  |
| Bronchopulmonary dysplasia (BPD)                   | 1          | 5%         | 1          | 5%         | 0.4682  |

age of the infants was 30.3 weeks in LISA group and 30.95 weeks in INSURE group whereas the average birth weight of the population was 1.25 kg. Mean duration of surfactant administration since birth in LISA group was 3.4 hours and 3.7 hours in INSURE group.

The results of primary and secondary outcomes are depicted in table 2(A), (B). There was a statistically significant difference in need on MV within 72 hours after surfactant administration between the LISA group (30%) and the INSURE group (70%) (p value 0.0238).

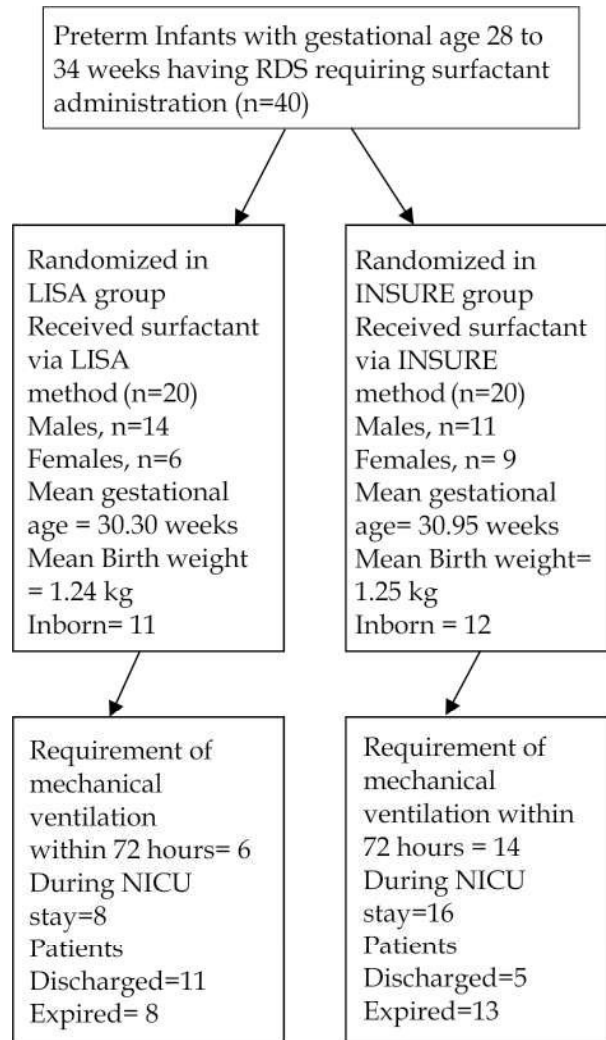
Need of MV during NICU stay was also statistically significant between two groups. We did not observe any statistically significant difference in requirement of 2nd dose of surfactant between two groups.



**Fig. 2:** Secondary outcome parameters.

No statistical difference was observed in Pneumothorax, incidence of LOS, apnoea, pulmonary haemorrhage, IVH grade or more, PDA requiring treatment, ROP stage or more, NEC grade or more and BPD.

The following flowchart shows the summary of our results:



## Discussion

In this randomized control study, we compared efficacy of LISA over INSURE method of

surfactant administration in preterm infants of 28 to 24 weeks in RDS. We had use CPAP as primary support of ventilation. We found that the need for mechanical ventilation within 72 hours of surfactant administration as well as during whole NICU stay was higher in INSURE group than LISA group (p value= 0.0238, 0.0268) which shows statistical significance. Decreased need of MV in the LISA group compared to the INSURE group was reported in few other studies.<sup>9</sup> There was no statistically significant difference in incidence of BPD and mortality between two groups. The use of LISA was found to reduce the death or BPD along with need for MV within 72 hours after surfactant administration in various recent meta-analysis.<sup>10</sup>

Failure to insert the catheter/tube through vocal cords at first attempt, significant surfactant reflux, coughing/gagging, bradycardia and need of manual ventilation during surfactant administration during LISA method were reported in <10% to >30% in different studies. There was a smaller proportion of patients developing pneumothorax in LISA group compared to INSURE group which is though statistically not significant but this result is consistent with similar study by Halim et al.<sup>11</sup>

In our study, the requirement of second dose of surfactant was low.<sup>2</sup> patients in LISA group and 1 patient in INSURE group needed 2nd dose of surfactant. There was no significant statistical difference between both groups. In some studies 2nd dose of surfactant was required more in LISA group compared to INSURE group possibly due to use of lower dose of surfactant in the LISA method than INSURE method.<sup>12</sup>

Requirement of more than 1 dose of surfactant in LISA group may also be due to the fact that LISA method does not provide any positive pressure to help the surfactant to spread while INSURE does.<sup>12</sup> There was no statistically significant difference in other outcomes like incidence of Pulmonary haemorrhage, NEC grade or more, ROP grade or more, PDA requiring treatment and IVH grade or more. In present study discharged rate is higher in LISA group compared to INSURE group. But it is not statistically significant. But this outcome is significantly influenced by various factors like complications during NICU stay, social factors and public health factors.

Until those factors are not in well powered trials, these outcomes should not be taken seriously for implementation of LISA as a standard therapy. Infants with gestational age less than 28 weeks were not included. Sample size was low and it was calculated with the use of previous NICU data. All

these can produce bias in the results. It is also found that our study population had fast worsening RDS and also had a very high occurrence of combined outcome of mortality/BPD in contrast with the reports from other centres in developed countries. This can be related with very poor coverage of complete course of antenatal steroid coverage in our population.

## Conclusion

This study compared primary and secondary outcome/complications between two of the surfactant administrations: LISA and INSURE. Requirement of mechanical ventilation within 72 hours of surfactant administration in INSURE group is significantly higher than LISA group. There was a statistically significant difference in requirement of mechanical ventilation during NICU stay between both the groups and LISA is better than INSURE in this parameter. We had noted higher incidence of procedure related complications in LISA group but it is not statistically significant and required further evaluation. More studies and larger population are required.

*Contributor:* 1st author Dr. Omprakash Shital Shukla, 2nd author Dr. Akshit Ganasva.

*Completing interest:* None stated.

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