# Comparison Between Less Invasive Surfactant Administration (LISA) and Intubation-Surfactant-Extubation (InSurE) in Preterm Infants with Respiratory Distress Syndrome: A Retrospective Study

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**Research article**

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# Abstract

**Background:** Bronchopulmonary dysplasia (BPD) is an important morbidity caused by neonatal lung injury due to mechanical ventilator use. Respiratory distress syndrome (RDS) is leading cause of mechanical ventilation in preterm infants. Surfactant was administrated through the endotracheal tube for management of RDS, which compels invasive mechanical ventilation. Recently, Intubation-SURfactant administration-Extubation (INSURE) and Less-invasive surfactant administration (LISA) have been introduced to avoid invasive mechanical ventilation. This study aimed to compare the effectiveness of LISA and INSURE.

**Methods:** This single-center, retrospective study enrolled 47 newborns admitted to the neonatal intensive care unit (NICU) of the Wonju Severance Christian's Hospital between January 1, 2017 and August 31, 2019, above a gestational age of 25 weeks, and required surfactant. The patient were divided into the LISA group and the INSURE group, and compared capillary gas analysis, oxygen saturation index (OSI), and morbidities.

**Results:** The LISA group and the INSURE group included 34 and 13 newborns respectively. Demographic feature and OSI showed no significant differences between two groups. In the LISA group, $pCO_2$ decreased over 1 hour(57.49±9.43mmHg), 2 hours(53.07±9.25mmHg, p=0.04) and 6 hours (46.50±8.53mmHg, p=0.01). $pCO_2$ of the INSURE group decreased steeper within 2 hours (49.55±8.96mmHg to 39.56±6.20mmHg) in the INSURE group, however, the trend was not significant (p = 0.06). There were no significant differences in morbidities.

**Discussion:** LISA and INSURE showed no significant differences in OSI and morbidities. Although LISA decreases $pCO_2$ more slowly than INSURE, the difference is not statistical significant. LISA and INSURE are equally effective modalities for surfactant administration.


# Background

Bronchopulmonary dysplasia (BPD) is one of the important diseases of premature infants as it affects them throughout their lifetime [1, 2]. It is caused by neonatal lung injury due to mechanical ventilation use or exposure to excessive oxygen concentration [3]. Accordingly, BPD is a risk factor for pulmonary hypertension and more frequent respiratory infections in infants admitted to the neonatal intensive care unit (NICU). Further, it is a cause of frequent re-admission (39.9% vs 24.8%) even after NICU discharge in Korea and causes limitations in exercise skills during school age and adolescence [1, 4, 5].

Respiratory distress syndrome (RDS) is a leading cause of invasive mechanical ventilation in premature infants [3]. To reduce the use of mechanical ventilation, premature infants with RDS are treated with nasal and mask continuous positive airway pressure (CPAP) instead of surfactant administration [6]. However, most neonatologists consider exogenous surfactant to be crucial for the treatment of RDS [7]. It is known that exogenous surfactants not only treat RDS, but also reduce BPD by improving oxygenation and lung compliance. Commonly, the surfactant is administered through the endotracheal tube, but this

may lead to mandatory mechanical ventilation, has a risk of ventilator-associated pneumonia, and tracheal damage from an invasive procedure [7, 8]. Therefore, less-invasive methods of surfactant administration have been developed. Among them, the effectiveness of Intubation, SURfactant, Extubation (INSURE) for RDS treatment has been reported in many studies [7, 9]. However, there is risk of lung injury induced by manual bagging during the INSURE, more non-invasive methods have been introduced recently including thin catheter administration, surfactant administration with nebulization and less-invasive surfactant administration (LISA), with LISA being the most frequently used [7, 10, 11]. Previous studies have reported that patients treated with LISA had better prognosis [12, 13]. However, despite several studies that have evaluated the effectiveness of non-invasive administration of surfactant, there is little research on the comparison between non-invasive methods, particularly between LISA and INSURE. To date, the superior modality between LISA and INSURE is controversial [9, 12, 14]. We undertook this study to identify which modality is more effective than the other and what is the differences between both modalities.

# Methods

### *Study design and patients*

This retrospective study aimed to analyze the difference in disease prognosis and effectiveness between LISA and INSURE. The subjects were RDS patients who admitted to the NICU of WSCH, Gangwon-do, South Korea between January 1, 2017 and August 31, 2019. The inclusion criteria were as follows: (1) preterm infants with spontaneous breathing with gestational age 25 weeks or more, (2) respiratory distress requiring FiO2 0.4 or higher for support, and (3) administered surfactant within 48 hours of birth. Patients in whom tracheal intubation was performed at the delivery site for resuscitation and congenital malformation were excluded from the study. The patients who received surfactant through the gastric tube and endotracheal tube were assigned to the LISA and INSURE groups, respectively.

### *Ethics statements*

The study was approved by the Ethics Committee of Yonsei University Wonju College of Medicine (approval number CR320011). The need for informed consent was waived owning to the retrospective nature of the study.

### *Diagnosis of diseases*

In this study, RDS was diagnosed as clinical respiratory distress with chest wall retraction or nasal flaring requiring 0.4 or more $FiO_2$ and radiologic finding such as reticular, ground-glass opacity or air bronchogram. Pulmonary hemorrhage was defined as endotracheal tube bleeding and increased oxygen requirements or ventilator setting. The criteria of the National Institutes of Health consensus were used to define BPD in this study [15]. Retinopathy of prematurity (ROP) was classified according to the International Classification of Retinopathy of Prematurity criteria, while intraventricular hemorrhage (IVH) was graded following the Papile grading system[16, 17].

### *Surfactant administration*

Poractant alfa(Curosurf®, Chiesi Pharmaceuticals, Parma, Italy) 200mg/kg was used as the surfactant. The surfactant delivery method was selected alternately every day by one of the LISA and the INSURE. In both the LISA and the INSURE method, surfactant was instilled with syringe for one minute. There was no need for changing the position of infants after surfactant administration because we adopted Poractant alfa.

The authors uses the TAKE CARE method with modification, which is one of the methods for LISA surfactant administration using a thin catheter. Briefly, a 4-5 Fr gastric tube is used. The vocal cord was assessed through a laryngoscope, then the catheter was inserted using curved tissue forceps. Subsequently, the surfactant was administered through a gastric tube, and 5-8 cm $H_2O$ CPAP or 3-8L/min heated flow nasal cannula was provided after surfactant administration. In INSURE, the surfactant was administered through an endotracheal tube and manual bagging was applied for a minute to distribute the surfactant. Likewise, 5-8 cm $H_2O$ CPAP or 3-8L/min heated flow nasal cannula was provided after surfactant administration through INSURE method.

### *Outcome assessment*

Maternal factors (e.g., maternal age, delivery type, maternal pre-eclampsia, diabetes mellitus, prenatal steroid administration, PPROM, and histologic chorioamnionitis) and neonatal factors (e.g., gestational age, birth weight, sex, and Apgar score) were analyzed as perinatal factors. Progress of treatment was investigated according to the need for mechanical ventilation within 72 hours after birth. Results were divided into primary and secondary outcomes based on 72 hours after surfactant administration. The primary outcome measures were oxygen saturation index (OSI) and artery or capillary gas analysis. Authors conducted gas analysis and recorded method of respiratory support before surfactant administration, after 1 hour, 2 hours, 6 hours, 12 hours, 24 hours, 48 hours and 72 hours. Additional gas analysis and changing modality of respiratory support between the time interval mentioned before were performed if there were clinical deterioration of individual infants. OSI was calculated as , where $SpO_2$ represents percutaneous oxygen saturation, and $FiO_2$ means a fraction of inspired oxygen. Mean airway pressure (MAP) was calculated as , where PIP stands for peak inspiratory pressure, and Ti and Te indicate inspiration time and expiration time, respectively. The secondary outcome measures were BPD, pulmonary hemorrhage, air leak syndrome, patent ductus arteriosus (PDA) requiring intervention, necrotizing enterocolitis (NEC) with modified Bell's criteria stage 2 or higher, ROP requiring photocoagulation, IVH stage 2 or higher, number of days needing respiratory assistance, and duration of NICU admission.

### *Statistical analysis*

The method of surfactant delivery was defined as an independent variable. Continuous variables were analyzed using Student t-test, while nominal variables were analyzed using the Chi-square test and

Fisher's exact test, respectively. Authors also analyzed $pCO_2$ using repeated measure analysis of variance (ANOVA). Since there were only two levels for comparison, post hoc tests were not conducted. Instead, mean of $pCO_2$ and OSI of the two groups compared according to the time after surfactant administration using independent t test. All statistical analyses were performed using SPSS (version 25.0 ; SPSS inc, Chicago, IL, USA), and $p < 0.05$ was considered significant.

# Results

### *Clinicodemographic features*

Sixty-nine preterm infants met the inclusion criteria. Of them, 22 were excluded due to transfer to another health care center for PDA ligation (n=2), diagnosis of congenital anomaly (n=3), and surfactant treatment via the conventional method (n=17). In total, 47 patients were included in the final analysis. Of them, 13 infants were categorized to the INSURE group, while 34 infants were categorized to the LISA group (Figure 1).

**Table 1. Clinicodemographic Patient Characteristics by Group**

| | LISA group (n=34) | INSURE group (n=13) | *p value* |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Maternal age (y) | 31.21±5.41 | 36.31±4.939 | 0.005 |
| GDM, n (%) | 3 (8.82%) | 2 (11.18) | 0.607 |
| Preeclampsia, n (%) | 8 (23.52%) | 5 (38.46%) | 0.251 |
| Gestational age (weeks) | 29±2.198 | 30.23±3.00 | 0.260 |
| Antenatal steroid, n (%) | 32 (94.12%) | 11 (84.62%) | 0.881 |
| PPROM, n (%) | 14 (41.18%) | 3 (23.08%) | 0.209 |
| Preterm labor, n (%) | 16 (47.06%) | 4 (30.77%) | 0.323 |
| Pathologic chorioamnionitis, n (%) | 8 (23.53%) | 4 (30.77%) | 0.335 |
| Birth weight (g) | 1452±537 | 1523±589 | 0.694 |
| Male sex, n (%) | 19 (55.88%) | 4 (30.77%) | 0.112 |
| C sec, n (%) | 27 (79.41%) | 11(84.62%) | 0.52 |
| 1 min Apgar score | 4.97±1.80 | 5.08±1.891 | 0.863 |
| 5 min Apgar score | 7.56±1.236 | 7.31±1.251 | 0.955 |
| Number of surfactant administration | 1.15±0.359 | 1.15±0.376 | 0.956 |

Abbreviations: GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membrane, ±SD, Standard deviation

There were no significant differences in gestational age, birth weight, sex, Apgar score, delivery type, maternal diabetes, gestational hypertension, administration of prenatal steroid, preterm premature rupture of membrane, preterm labor, and histologic chorioamnionitis between the two groups. The number of surfactant administration was also not significantly different between the two groups. Only maternal age was different, with the LISA group younger than the INSURE group (average maternal age 31.21±5.41 years vs 36.31±4.939 old) (Table 1).

### *Primary outcome*

Both the LISA and the INSURE groups showed improvement in respiratory acidosis. However, the $pCO_2$ of the LISA group decreased slower within 2 hours after surfactant administration than that of the INSURE group (57.88 ± 10.16 mmHg to 53.07 ± 9.25 mmHg vs 49.56 ± 8.96 mmHg to 34.76 ± 6.78 mmHg). In the LISA group, there was a significant difference in $pCO_2$ between 1 hour and 2 hours after surfactant administration (p=0.04) and between 2 hours and 6 hours after surfactant administration (p=0.01) (Figure 2). In contrast, there was a steeper decreasing trend of $pCO_2$ within 2 hours in the INSURE groups, but there were no significance within 6 hours after surfactant administration (p = 0.15 for 1 hour, p = 0.66 for 2 hours, p = 0.65 for 6 hours). There were no significant differences between pCO2 of two groups after 6 hours of surfactant administration.

OSI decreased in both groups (Figure 2). The decrease in OSI was more evident in the LISA group than in the INSURE group. However, there were no significant differences between the two groups with respect to the 95% confidential interval (Table 2).

In repeated measure ANOVA, both two groups showed decreased $pCO_2$ through time. Interaction between time and method of surfactant administration showed statistical significance.

**Table 2 $pCO_2$ and OSI of the LISA and INSURE Group**

| | | LISA group | | INSURE group | | Significance (*p value*) |
|---|---|---|---|---|---|---|
| Time(hours) | | Mean | SD | Mean | SD | |
| 0 | $pCO_2$(mmHg) | 57.88 | 10.16 | 49.56 | 8.96 | 0.012 |
| | OSI | 2.74 | 0.92 | 2.69 | 1.07 | 0.885 |
| 1 | $pCO_2$(mmHg) | 57.49 | 9.43 | 39.56 | 6.20 | 0.009 |
| | OSI | 1.60 | 0.67 | 1.82 | 1.02 | 0.397 |
| 2 | $pCO_2$(mmHg) | 53.07 | 9.25 | 34.76 | 6.78 | 0.004 |
| | OSI | 1.41 | 0.41 | 1.67 | 0.93 | 0.184 |
| 6 | $pCO_2$(mmHg) | 46.50 | 8.53 | 37.97 | 9.35 | 0.066 |
| | OSI | 1.48 | 0.51 | 1.52 | 0.57 | 0.786 |
| 12 | $pCO_2$(mmHg) | 45.21 | 9.71 | 37.17 | 11.33 | 0.194 |
| | OSI | 1.43 | 0.52 | 1.48 | 0.45 | 0.726 |
| 24 | $pCO_2$(mmHg) | 40.02 | 9.09 | 38.69 | 6.29 | 0.526 |
| | OSI | 1.53 | 1.08 | 1.40 | 0.55 | 0.588 |
| 48 | $pCO_2$(mmHg) | 40.55 | 5.99 | 39.33 | 6.97 | 0.738 |
| | OSI | 1.37 | 1.68 | 0.97 | 0.71 | 0.408 |
| 72 | $pCO_2$(mmHg) | 39.47 | 8.43 | 39.60 | 6.94 | 0.465 |
| | OSI | 1.14 | 1.16 | 0.86 | 0.65 | 0.413 |
| | | | | | | |
| | | | | | | |

Abbreviations: SD, standard deviation

***Secondary outcome***

**Table 3. Comparison of Morbidities**

| | LISA group (n=34) | INSURE group (n=13) | *p value* |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Death, n (%) | 1 | 0 | 0.525 |
| Hospital stay (d) | 55.94±27 | 46.08±24 | 0.994 |
| Need for mechanical ventilation within 72 hours of SRT, n (%) | 4 (11.76%) | 2 (15.38%) | 0.415 |
| Non-invasive respiratory supports (d) | 14.79±13.9 | 10.00±11.0 | 0.166 |
| Duration of mechanical ventilator (d) | 2.91±6.1 | 1.69±3.7 | 0.114 |
| Total duration of respiratory support (d) | 17.71±16.1 | 11.69±13.0 | 0.242 |
| Moderate or severe BPD, n (%) | 3 (6.40%) | 0 | 0.536 |
| Pulmonary hemorrhage, n (%) | 1 (3.1) | 0 | 0.806 |
| Air leaks, n (%) | 0 | 1 (8.30%) | 0.252 |
| PVL, n (%) | 1 (2.94%) | 0 | 0.519 |
| IVH, n (%) | 0 | 0 | 0.631 |
| ROP requiring photocoagulation, n (%) | 3 (8.82%) | 0 | 0.385 |
| PDA requiring ibuprofen, n (%) | 7 (20.59%) | 0 | 0.182 |
| Duration of full feeding (120 cc/kg/day) (d) | 13.03±10.7 | 10.08±7.3 | 0.366 |
| NEC, n (%) | 4 (11.76%) | 1 (8.30%) | 0.905 |
| SIP, n (%) | 0 | 0 | 0.631 |

Abbreviations: SRT, surfactant replacement therapy; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; SD, standard deviation; SIP, spontaneous intestinal perforation

During hospitalization in the NICU, there were no significant differences in mortality, admission duration, number of days needed respiratory support, occurrence of moderate to severe BPD between the LISA group and the INSURE groups. Also, there were no significant differences of incidence of pulmonary hemorrhage, air leak syndrome, periventricular leukomalacia, intraventricular hemorrhage, ROP treated with photocoagulation, PDA requiring intervention and NEC (Table 3)

# Discussion

In this study, authors compared the effectiveness between the LISA and the INSURE method for surfactant administration for RDS in preterm infants. The LISA and the INSURE were equally efficacious methods to improve respiratory acidosis and OSI, and there were no significant differences in morbidity and mortality. As an indicator of the effect of exogenous surfactant administration, $pCO_2$ was decreased quickly in the INSURE group within 1 hour after surfactant administration, although there was no significance. In contrast, the LISA group showed no significant decrease in $pCO_2$ within 1 hour after surfactant administration, but it fell rapidly after 2 hours. The results of repeated measure ANOVA showed that there was interaction between the surfactant administration methods and the time. These results imply that onset time of surfactant depends on the method of administration, and further investigation is needed.

The authors presumed that the distribution of the surfactant caused these differences. Using animal experiments, Niemarkt reported decreased surfactant distribution to the right upper lobe in the LISA method compared with the intubation method [18]. Surfactant distribution, which is affected by the volume of the administered surfactant, rate of installation, the position of the infant, and underline the status of the lung of the patient, is an essential factor of surfactant administration [19].

Efforts to reduce BPD have continued for many years. Various methods, such as prenatal or postnatal steroid, have been attempted, but the most effective method to reduce BPD is avoiding invasive mechanical ventilation. Caffeine is administered to decrease respiratory support [4, 7, 20]. Application of non-invasive mechanical ventilation and aggressive weaning of invasive mechanical ventilation are recommended to shorten the duration of invasive mechanical ventilation. However, despite these efforts, many premature infants still require invasive mechanical ventilation to achieve sufficient lung capacity for oxygenation, ventilation, and prevention of atelectasis.

RDS is one of the leading causes of invasive mechanical ventilation. RDS is a common respiratory disease for premature infants caused by an insufficient amount of surfactant and immaturity of the peripheral airway. Perinatal hypoxic insults, Cesarean section, and acidosis affect decreased production of surfactant, and the immature lung itself is unable to produce a sufficient amount of surfactant. RDS causes a vicious cycle of interrupted oxygenation and ventilation, respiratory acidosis and hypoxic insults, and reduced surfactant production. Therefore, surfactant replacement is crucial in the management of RDS

In Korea, an animal-derived surfactant, such as Surfactant-TA (Surfacten®), Korean bovine surfactant (Newfactan®), poractant alfa (Curosurf®), and calfactant (Infasurf®), is used. Surfactant-TA and Korean bovine surfactant are extracted from minced bovine lung and administered after diluting with normal saline. The disadvantage of these two surfactants is that the patients' position should be changed during administration. Meanwhile, poractant alfa and calfactant have advantages in that there is no need to dilute the medication, and less position changes are needed.

Our center uses poractant alfa (Curosurf®) only due to higher efficacy and advantage of the reduced number of positioning changes, and there were no differences in instillation rate and position changes found in our study [21]. The authors presumed that the diameter of the catheter used for surfactant delivery and the method of respiratory support after surfactant administration affected the results. Hugo et al. [19] reported that the catheter diameter affected administration of surfactant in an animal experiment. Further investigation about the effect of administration methods in surfactant distribution is required to improve the efficacy of surfactant treatment.

Traditionally, the surfactant is administered through an endotracheal tube, and invasive mechanical ventilation is performed thereafter. However, to avoid ventilator-induced lung injury, various methods of non-invasive surfactant administration were studied since the 1990s. Currently, the surfactant can be delivered without mechanical ventilation through various non-invasive method such as INSURE and LISA method, thus decreasing the occurrence of BPD. Nebulized preparation and pharyngeal preparation have also been studied as feasible delivery method [22].

Some studies reported lower mortality in patients treated with the LISA than in patients treated with the INSURE method.[12,13] More than half of the centers in Europe use the LISA method for the management of RDS, but there is a difference in the actual use by country. For example, less than 1% of centers in Poland manage RDS patients using the LISA method [23]. This difference may be caused by the difference in human and material resources and experiences. In our center, the surfactant is administered through the LISA method in more than half of the preterm RDS cases. With respect to staff resource, the LISA method is more convenient in that although it requires proper equipment, an experienced medical staff can perform the procedure. Meanwhile, the INSURE method should be performed by doctors experienced in endotracheal intubation.

However, because of the difficulty in the maneuver of a thin catheter, the LISA method needs more experience and skills. There are several methods of tracheal catheterization according to catheter type and guidance through vocal cord. In Cologne method, flexible nasogastric tube is used, and Magill's forceps are used for guidance of the catheter to vocal cord. Semi-rigid vascular catheter is used in Hobart method, and flexible nasogastric tube is guided without forceps in the TAKE CARE method [7, 24]. The authors adopt the TAKE CARE method and modified it to introduce catheters using fine tip curved forceps.

In the case of the Cologne method, Magill forceps are used for inserting a catheter, which has an advantage in less probability of airway injury due to the blunt edge of the forceps. However, Magill forceps have disadvantages in difficulty in handling and preference of small-sized forceps suitable for extremely premature infants. Thus, fine-tip curved forceps are used instead of Magill forceps in our center.

A 4–5 Fr feeding tube is used for surfactant instillation. Although an angiocatheter is easier to operate due to its stiffness, there is also a higher risk of vocal cord injury. The difficulty in maneuverability of the

feeding tube is compensated with the use of fine-tip curved forceps. In our center, these modifications have made it easier to perform LISA.

There are several limitations to this study. First, the number of cases was limited. Second, OSI was used to measure the severity of respiratory difficulty. The OSI of patients in whom surfactant administration was followed with heated high-flow nasal cannula may be less accurate than that of patients in whom mechanical ventilation was performed [25, 26]. Finally, although the number of days needed for respiratory support was evaluated, it was difficult to determine the cause of respiratory distress. There may have been undetected nosocomial respiratory infection. More frequent evaluation may be required for clinical deteriorations or difficulties in weaning of mechanical ventilation.

# Conclusion

In this study, while improvement of respiratory acidosis within the first 2 hours was slower in the LISA method, there were no significant differences in respiratory acidosis after 24 hours of surfactant administration. Further, there were no significant differences in morbidities and mortality in preterm infants. Thus, LISA and INSURE are equally effective methods for surfactant administration.

# Abbreviations

*ANOVA* analysis of variance

*BPD* Bronchopulmonary dysplasia

*CPAP* continuous positive airway pressure

*IVH* intraventricular hemorrhage

*INSURE* Intubation, SURfactant administration, Extubation

*LISA* less-invasive surfactant administration

*MAP* mean airway pressure

*NEC* necrotizing enterocolitis

*NICU* neonatal intensive care unit

*OSI* oxygen saturation index

*PDA* patent ductus arteriosus

*PIP* peak inspiratory pressure

*RDS* respiratory distress syndrome

*ROP* retinopathy of prematurity

*WSCH* Wonju Severance Christian Hospital

# Declarations

### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yonsei University Wonju College of Medicine (approval number CR320011). The need for informed consent was waived owning to the retrospective nature of the study.

### Consent to publish

Not applicable.

### Availability of data and materials

All authors declare that data and any supporting material regarding this manuscript are available and can be requested at any time.

### Competing interest

The authors declare that there is no competing interest.

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The authors received no specific funding for this work.

### Authors' contributions

Yang SM collected data and drafted the initial manuscript. Kim YH reviewed and analyzed data and reviewed the manuscript. Lee BK conceptualized the study design, reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable

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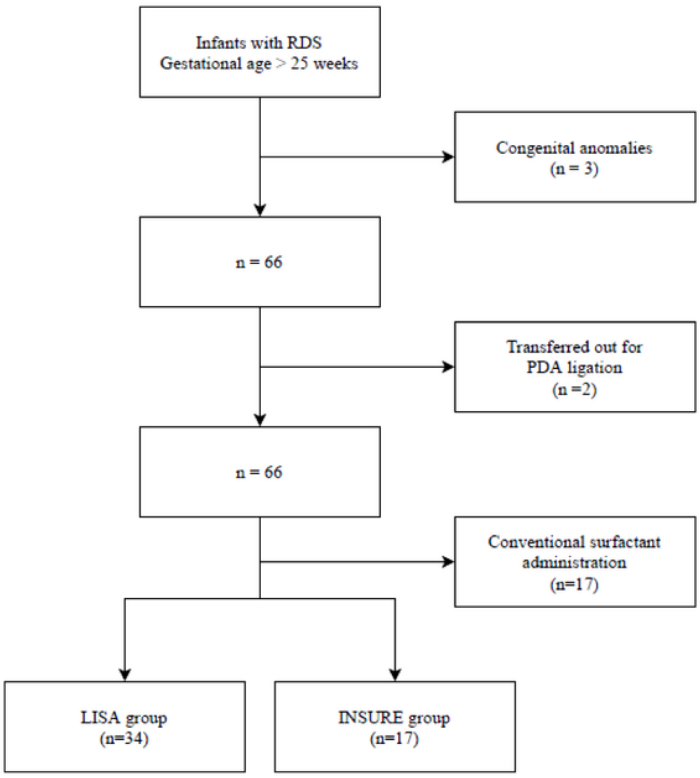
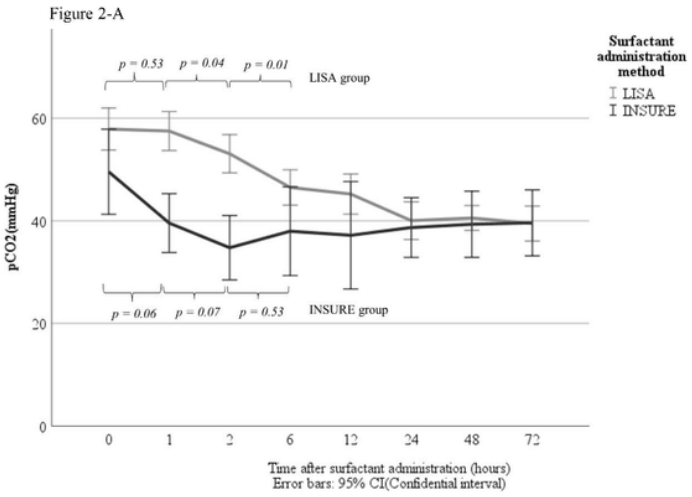
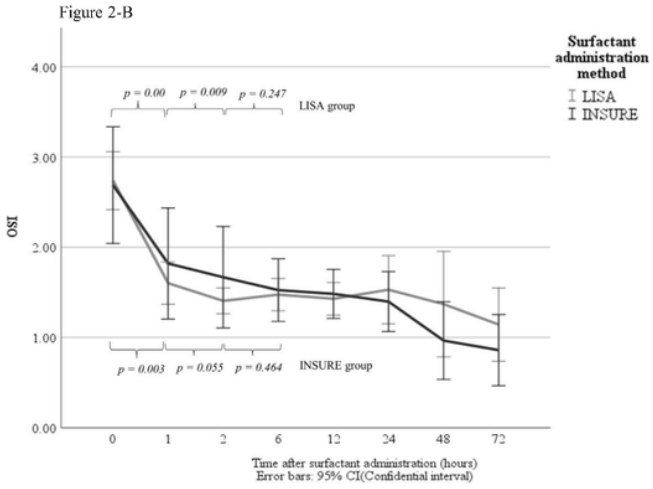
# Figures




## Figure 1

Study population



## Figure 2

A pCO2 of LISA and INSURE group. Figure 2-B OSI of LISA and INSURE group