

# Comparison of INSURE Method with Conventional Mechanical Ventilation after Surfactant Administration in Preterm Infants with Respiratory Distress Syndrome: Therapeutic Challenge

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**Abstract-** Administration of endotracheal surfactant is potentially the main treatment for neonates suffering from RDS (Respiratory Distress Syndrome), which is followed by mechanical ventilation. Late and severe complications may develop as a consequence of using mechanical ventilation. In this study, conventional methods for treatment of RDS are compared with surfactant administration, use of mechanical ventilation for a brief period and NCPAP (Nasal Continuous Positive Airway Pressure), (INSURE method ((Intubation, Surfactant administration and extubation)). A randomized clinical trial study was performed, including all newborn infants with diagnosed RDS and a gestational age of 35 weeks or less, who were admitted in NICU of Valiasr hospital. The patients were then divided randomly into two CMV (Conventional Mechanical Ventilation) and INSURE groups. Surfactant administration and consequent long-term mechanical ventilation were done in the first group (CMV group). In the second group (INSURE group), surfactant was administered followed by a short-term period of mechanical ventilation. The infants were then extubated, and NCPAP was embedded. The comparison included crucial duration of mechanical ventilation and oxygen therapy, IVH (Intraventricular Hemorrhage), PDA (Patent Ductus Arteriosus), air-leak syndromes, BPD (Broncho-Pulmonary Dysplasia) and mortality rate. The need for mechanical ventilation in 5th day of admission was 43% decreased ( $P=0.005$ ) in INSURE group in comparison to CMV group. A decline ( $P=0.01$ ) in the incidence of IVH and PDA was also achieved. Pneumothorax, chronic pulmonary disease and mortality rates, were not significantly different among two groups. ( $P=0.25$ ,  $P=0.14$ ,  $P=0.25$ , respectively). This study indicated that INSURE method in the treatment of RDS decreases the need for mechanical ventilation and oxygen-therapy in preterm neonates. Moreover, relevant complications as IVH and PDA were observed to be reduced. Thus, it seems rationale to perform this method as the initial treatment for neonates with mild to moderate RDS.

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**Keywords:** RDS; Conventional Mechanical Ventilation; INSURE; NCPAP; IVH; PDA; Surfactant

## Introduction

Respiratory distress syndrome (RDS) is the most common respiratory disorder in preterm neonates, resulted from surfactant deficiency. Consequently, lung collapse or the compliance decreases. The foremost treatment of RDS is administration of exogenous surfactant along with mechanical ventilation (1,2).

Administration of surfactant in early two hours of the birth is indicated to be beneficial compared to surfactant therapy in well-established RDS. Furthermore, bronchopulmonary dysplasia (BPD), pneumothorax and mortality rates are reported to be reduced (3).

Two strategies have been defined for surfactant therapy. Endotracheal administration of surfactant is the customary method, followed by prolonged

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mechanical ventilation. It eventually results in pulmonary barotrauma, pneumothorax, long-term hospitalization and hypoxia subsequent to tracheal suctioning. Thus, educated staff and specialized equipments are vital.

On the other hand, INSURE (Intubation, surfactant administration, rapid extubation to NCPAP) is an innovative method, emerged for RDS treatment (4-7). In this method, intubation along with surfactant administration is performed.

In the case of spontaneous breathing of the infant, mechanical ventilation is discontinued gradually during an hour. Ultimately, the neonate will be extubated, and NCPAP is applied. If no clinical or preclinical improvement achieved, conventional mechanical ventilation is employed once more, which is known as INSURE failure (8).

It is reported that the early use of mechanical ventilation is the main risk factor for chronic lung diseases in preterm neonates with low-birth weights (9). On the other hand, surfactant and CPAP co-administration has synergistic effects on treatment of RDS, as well as reducing the BPD incidence (3).

In this study, efficacy of two mentioned strategies (INSURE vs. CMV) are assessed. Oxygen requirement, complications, chronic lung diseases, INSURE failure, and mortality rates are compared among two groups.

## Materials and Methods

A randomized clinical trial (RCT) was performed, involving 42 preterm newborn infants with diagnosed RDS, admitted in NICU of Valiasr hospital, Tehran University of Medical Science. We included:

- All preterm neonates with gestational age of 28 weeks or less, who had minimal respiratory distress symptoms such as tachypnea

Or

- Preterm infants with a gestational age 28 to 35 weeks gestational age possessing one of the following conditions:
  - 1) Respiratory distress with Downes score of 7 or more (Table 1)
  - 2) Requiring fraction of inspired oxygen (Fio<sub>2</sub>) 45% or more
  - 3) Radiographic evidences, accordant to RDS

A similar method of inclusion is performed by Reininge *et al.*, studying preterm infants with less than 35 weeks gestation (1).

Preterm infants with gestational age less than 35 weeks, who suffered from respiratory distress due to pulmonary hemorrhage or meconium aspiration, were excluded. Patients with moderate to severe hypoxic-ischemic encephalopathy (HIE) (defined with Apgar score of 0-3 in the fifth minute of birth or a pH<7 of umbilical cord) and severe anomalies did not enter the study, as well.

**Table 1. Downes score system (10)**

Score	0	1	2
Cyanosis	room air (21%) in	FIO <sub>2</sub> <40%	FIO <sub>2</sub> >40%
Retraction	No	Mild	Moderate to severe
Grunting	No	Audible with Stethoscope	Audible without Stethoscope
Air Entry (crying)	Clear	Delayed or decreased	Barely audible
Respiratory Rate (breaths/min)	<60	60-80	>80
Gestational age (weeks)	>34	30-34	<30

On the basis of Dani *et al.*, study in which the need for mechanical ventilation was 43% in NCPAP group versus 0% in INSURE group(15); we estimated that 42 infants were needed to demonstrate this magnitude of difference with a power of 80% and significance level of 95%.

The selected infants were divided into two groups via double-blind method; each group contained 21 patients. The first group was served as control, receiving CMV while interventions with INSURE method was performed in the other group. All 42 neonates were intubated and received Survanta® (4 cc/kg) in the first two hours of life.

The patients in the control group were assisted with mechanical ventilation for several days and were observed for clinical improvement. The neonates were then extubated, when the ventilator (BEAR CUB 750®) settings reached following parameters: PIP=12-15cmH<sub>2</sub>O, Rate=10-15/min, Fio<sub>2</sub><0.4.

In the other group (INSURE), following surfactant administration, the infants were weaned from the ventilator during an hour and NCPAP was applied. However, in case of clinical deterioration, mechanical ventilation was replaced; which is known as INSURE

failure. This failure has been defined in more details:

- 1) Oxygen saturation of less than 85% despite FiO<sub>2</sub> ≥ 0.7 and PEEP>7 cmH<sub>2</sub>O
- 2) Prolonged (>15 seconds) or recurrent (>2 episodes within 24h) apnea with bradycardia, requiring bag and mask ventilation
- 3) Respiratory acidosis defined as PCO<sub>2</sub>>60 mmHg and PH<7.2 in arterial blood gas (ABG)

All patients were studied for the requirement of mechanical ventilation in the fifth day of life. Followings were compared among two groups, as well: mean FiO<sub>2</sub> requirement and its duration, pneumothorax, patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and mortality rate.

The collected data was saved in the data bank software SPSS v. 16 and analyzed, using Pearson chi-square, Fisher's exact test and student's t - tests. Descriptive statistics as absolute and relative frequency, standard deviation (both for quantitative variances) and the mean were calculated.

**Ethics approval**

Medical ethics was seriously considered in this

study. Consent informs were willingly completed and signed by parents. Parents were aware of possible side effects and participated in the study on a voluntary basis. This study was the subject of the thesis of neonatal subspecialty and was approved by Research Deputy of TUMS ref. no 758-8/9/1388.

**Results**

Forty-two neonates were involved in this study, divided equally into CMV and INSURE groups. Twenty-five neonates were male (60%), while 17 were female (40%).

Both groups were similar in demographic characteristics, and no significant differences were observed (Table 2).

The need for mechanical ventilation was significantly reduced to one-third in INSURE group, compared to CMV group. PDA and IVH have also occurred less frequent in INSURE group. However, no significant reduction was observed in pneumothorax, BPD and mortality rate, between two groups (Table 3).

**Table 2. Demographic characteristics of cases**

Variable	M.V group (Control), n=21	INSURE group (Intervention), n=21	Significance
Weight(g)	1484.7(SD ± 572)	1532.4(SD ± 539)	0.783
Gestational age(week)	30.3(SD ± 2.87)	31(SD ± 2.6)	0.404
Sex			
Male	13	12	0.75
Female	8	9	

**Table 3. Frequency of outcomes**

Variable	M.V group (Control), n=21	INSURE group (Intervention), n=21	p-value
Need for mechanical ventilation on the 5 <sup>th</sup> day	(14)66.7%	(5)23.8%	0.005
Pneumothorax	(6)28.6%	(3)14.3%	0.259
PDA	(12)57.1%	(1)4.8%	0.001
IVH	(9)42.9%	(2)9.5%	0.014
BPD	(2)9.5%	(0)0%	0.147
Mortality rate	(6)28.6%	(3)14.3%	0.259

**Discussion**

Preterm infants usually require respiratory support to some extent in the first days of life. Thus, proper usage of mechanical ventilation is fundamental in reduction of morbidity and mortality in preterm neonates. Herein, the efficacy of CMV and INSURE groups are compared.

Our study indicated that the need for mechanical ventilation in the 5th day of life in INSURE group was

43% less than CMV group (P=0.005). Similarly, other studies reported a 10-50% decrease in mechanical ventilation requirement, using INSURE method (1,6,11-13). Stevens *et al.*, demonstrated that using CPAP, followed by surfactant administration reduced the need for mechanical ventilation and thus, reduced pneumothorax and chronic pulmonary disease (3). These beneficial effects can be explained as CPAP keeps the alveoli open and prevents the lungs to be collapsed, as

well as preventing apnea due to prematurity.

In this study, PDA and IVH occurred less frequent in INSURE group ( $P=0.001$  and  $P=0.014$ , respectively). Nevertheless, no significant difference in pneumothorax was observed among two groups ( $P=0.25$ ). Although BPD occurred exclusively in CMV group, the difference was not meaningful, due to few numbers of BPD cases ( $P=0.14$ ).

Some studies revealed a decline in mentioned complications (2,5,11,12,14,15), while others reported no significant differences in pneumothorax and BPD incidences between two groups (1,6).

It is believed that surfactant administration in RDS treatment does not prevent BPD (16). New BPD cases may not essentially correlate with severe RDS. However, it may be accompanied with or without mild respiratory distress (17,18). Furthermore, some other factors as alveolar structural imperfections may play a role in BPD development (19).

In our study, five patients (23.8%) needed re-intubation and mechanical ventilation, referred to as INSURE failure. Other studies reported a variation of 15-50% for INSURE failure. It is noteworthy that PDA, IVH, pneumothorax and mortality rates were higher in these patients, in comparison to those, who were recovered and did not require re-intubation. The reasons are not fully understood. High PaCO<sub>2</sub>, a/A PO<sub>2</sub><0.22 and severe radiographic illustrations of RDS are among the probable reasons (1,4,5,8,11,14,20,21). Dani *et al.*, reported birth weight <750 g, PO<sub>2</sub>/FiO<sub>2</sub> <218, and a/A PO<sub>2</sub> <0.44 at the first-blood gas analysis as the independent factors of INSURE failure (15). Moreover, Low gestational age is likely to be an influencing factor (5,7,14). Multiple INSURE strategy is probably accounted for less failure and increased efficacy in extremely preterm infants (8,15,22,23).

In this study, no gender preference in need for mechanical ventilation was demonstrated. Nonetheless, female gender has been assumed to be an influencing factor in other studies. It is reported that mechanical ventilation requirement is higher in female neonates. However, further investigations did not confirm the idea. Male neonates seemed to have a gestational age more than 29 weeks or less severe disease because of maternal corticosteroid administration (2,11). Consequently, surfactant administration through INSURE method is effective in both genders.

Mortality rates were not significantly different among two groups in our study; 28.6% in CMV group compared to 14.3% in INSURE group ( $P=0.226$ ). A total mortality rate of 17-30% for both groups with a

gestational age lower than 30 weeks was reported in the literature (2,5,24). Nonetheless, Kribs *et al.*, indicated a mortality rate of 7% in the INSURE group vs. 35% in CMV group (7). Higher mortality rates among CMV group is reported in another study, as well (13). These discrepancies in reports seem reasonable. Although respiratory failure is the leading cause of death in preterm neonates, other complications such as IVH, necrotizing enterocolitis (NEC), nutritional defects, low-calorie intake and sepsis contribute to mortality rate.

Most preterm neonates with a gestational age less than 35 weeks are at high risk of RDS. Surfactant administration through INSURE method decreases the requirement to ventilator and trained staff. Thus, it can be used in less equipped medical centers.

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