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Original Article (Pages: 6069-6076)

# Effective Factors of INSURE Method Failure in Treatment of Respiratory Distress Syndrome in Preterm Infants

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***Abstract***

***Background***

INtubate-SURfactant-Extubate (INSURE) method is one of the effective methods in treatment of infants with respiratory distress syndrome (RDS). This study was performed to predict risk factors for the failure of INSURE method in treatment of RDS in preterm infants.

***Materials and Methods:*** In this cross-sectional study, 192 infants who born between July 2011 and April 2016 at women and children's hospital of Amiralmoemenin in Semnan, Iran, were included to the study. Inclusion criteria were infants with moderate to severe RDS, 26 to 38 gestational weeks and weighted 500 to 3,500 grams. All patients were treated with INSURE method, then were divided to success and failure INSURE. Severity of RDS was determined by RDS scoring system. The collected data including gender status, gestational age (GA), birth weight (BW), maternal diabetes mellitus, delivery type and neonatal morbidity (including intraventricular haemorrhage (IVH), Necrotizing enterocolitis (NEC) stage 1, sepsis, chronic lung disease (CLD), pneumothorax, and pulmonary bleeding. Statistical analysis was done using SPSS software, version 22.0.

***Results:*** Of the 192 patients, 82 (42.7%) infants were females. The mean GA and BW were 30.25 ± 1.85 weeks and 1950 ± 270 grams, respectively. Of all the patients, 156 infants (81.25%) were born via cesarean section. INSURE failure was observed in 79 infants (41.1 %) and INSURE success was observed in 113 (58.9%). Among the factors, INSURE method failure had a significant relationship with GA, BW, RDS severity and increased probability of IVH, CLD, pneumothorax and pulmonary bleeding ($p<0.05$). Based on logistic regression analysis, there was a significant relationship between the failure of INSURE method and RDS severity (odds ratio [OR]= 6.31, 95% 95%CI [CI]= 2.07-19.19, P=0.001), and GA OR=0.78, 95% CI= 0.67-0.91, P=0.001).

***Conclusion:*** According to the finding, among the risk factors, only higher severity of RDS and GA were able to predict INSURE method failure in treatment of RDS in preterm infants. Additional studies are recommended in this regard.

***Key Words:*** Infants, INSURE method, Gestational age, Respiratory distress syndrome.

*Please cite this article as: Danaei N, Seddigh M, Ghorbani R, Nooripour Sh. Effective Factors of INSURE Method Failure in Treatment of Respiratory Distress Syndrome in Preterm Infants. Int J Pediatr 2017; 5(11): 6069-76. DOI: **10.22038/ijp.2017.26022.2221**

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Received date: Jul.20, 2017; Accepted date: Aug. 22, 2017

## 1- INTRODUCTION

Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), is the most common respiratory disorder in preterm neonates, and the leading cause of their mortality, which is characterized by pulmonary immaturity and alveolar surfactant deficiency (1-4). RDS affected 60% of infants with gestational age (GA) of < 32 weeks, and 42% of infants with birth weight (BW) < 1,500g (3, 5). Hence, providing the best approach to RDS management is an interesting topic among the clinical researchers. Artificial respiratory support and exogenous surfactant replacement are the main strategy of the RDS management (1, 6-8). INtubate-SURfactant-Extubate (INSURE) to apply nasal continuous positive airway pressure (NCPAP), is an innovative method, which is associated with reduced the need for mechanical ventilation (MV), oxygen supplementation, and incidence of chronic lung disease (9), lower occurrence of sepsis and pneumothorax, and reduced the length of stay in the neonatal intensive care unit (NICU) (2, 6, 10, 11).

Although beneficial in clinical practice, the INSURE method is unsuccessful in a significantly of preterm infant that may be resulted in respiratory and neurological dysfunction (1, 10). The INSURE failure rate reported from 9% to 50% depending to different inclusion criteria, and the different definition treatment failure (12-14). INSURE failure was defined as the need for MV within 72 hours from the treatment (pH < 7.20, partial pressure arterial oxygen ($PaO_2$) < 50 mmHg with fraction of inspired oxygen ($FiO_2$) > 0.50, partial pressure arterial carbon dioxide ($PaCO_2$) > 65 mmHg or repeated apneas requiring bag and mask ventilation) (1, 12). Dani et al. showed that BW < 750 gr, $pO_2/FiO_2$ < 218, and alveolar–arterial gradient ($a/ApO_2$) < 0.44 at the first blood gas analysis were independent risk factors for INSURE failure, while in Cherif et al. study, BW < 1,000 g, severity of RDS and severe radiological grade were the main risk factors of INSURE failure (1, 12). In another study, preterm infants with low Apgar score at 1 and 5 minute, higher Fio2 requirement, and higher RDS score had more risk for INSURE failure (15). In addition to the disagreement on the risk factors of INSURE failure, a few studies have been conducted in this area. Hence, this study aimed to predict risk factors for the failure of INSURE method in treatment of Respiratory Distress Syndrome in preterm infants.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This cross-sectional study was conducted on the preterm infants born between July 2011 and April 2016 at women and children's hospital of Amiralmoemenin in Semnan city, Semnan province, Iran.

### 2-2. Methods

After INSURE, the patients were divided into two groups (success and failure), based on their response to the treatment. The preterm infants without RDS symptoms, normal Arterial Blood Gas (ABG), and Chest X-ray interpretation were considered as success group. If they had no signs of respiratory distress, Fio2 < 0-40, Paco2 < 60mmHg and Pao2 > 50mmHg and PH > 7.25 in arterial blood gas and Positive End Expiratory Pressure (PEEP) < 5 cmH2O, were separated from NCPAP and placed under Oxygen-Hoods with the flow of 5-7 Lit/min (3).

In contrast, infants were considered as the failure group, If they were intubated within 24 hours after treatment due to oxygen saturation of less than 85% with PaCO2 > 60mmHg, PaO2 < 50 mmHg and PH < 7.2 in ABG report and recurrent apnea. They connected to mechanical ventilation with FiO2 higher than 40% and the additional

dose of surfactant to maintain the oxygen saturation level > 85% (3).

### 2-3. Measuring tools

Severity of RDS was determined by RDS scoring system, which is an index designed to objectively assess the clinical severity of hyaline membrane disease, in which intensity of 5 symptoms including cyanosis, retraction, grunting, air entry-make baby cry and listen to breath sounds while baby cries and respiratory rate were scored at 0, 1 and 2. The score was measured after allowing the infant to stabilize for at least 5 minutes at a constant F1O2 (suitable for patient). An RDS score more than 8 is defined as moderate to severe dyspnea (9, 16, 17).

### 2-4. Intervention

All infants received INSURE treatment protocol with surfactant administration (Intratracheal Suspension of Survanta, Beractant, and Columbus, Ohio, USA) with a dosage of 100mg/kg, which had been heated to the temperature of 37 °C. Then, they received NCPAP using MV (Babylog 8000s; Drager, Lübeck, Germany), with the pressure of 4-8 cm of water (1, 3, 9).

INSURE method was as follows: intubation, manual ventilation until acceptable heart rate ( > 100 beats/min), and oxygen saturation ( > 80%), instillation of the first bolus of surfactant for the right lung within 1-3 min, manual ventilation until acceptable heart rate and oxygen, instillation of the second bolus of surfactant for the left lung, manual ventilation until acceptable heart rate and oxygen; then extubation and connection to the NCPAP (1).

### 2-5. Data measurements

The collected data were gestational hypertension (HTN), maternal diabetes mellitus, delivery type, parity, GA, BW, gender status, time of surfactant therapy, duration of NCPAP, severity of RDS and neonatal morbidity (including intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC) stage 1, sepsis, chronic lung disease (CLD), pneumothorax, pulmonary bleeding.

### 2.6-Ethical consideration

Ethical approval was obtained for this study from the Ethics Commitee of the Semnan University of Medical Sciences. All recruited parents' infants provided informed and written consent to the study.

### 2-7. Inclusion and exclusion criteria

During the study, all preterm infants who had our inclusion criteria including confirmed diagnosis of RDS, GA of 26-36 weeks, BW between 500- 3,500 gr and those hospitalized for up to 48 hours after their birth were included in this study (9, 16, 17). RDS was confirmed by preterm infants' medical history, clinical findings and chest radiograph. Furthermore, infants with any congenital malformations (such as diaphragmatic hernia, esophageal atresia), anomaly in the lung structure, or any evidence of sepsis and congenital heart disease, and receiving the first dose of surfactant in other centers were excluded from the study.

### 2-8. Data Analyses

Statistical analysis was done using SPSS software, version 22. Chi-squared test, independent test, ANOVA, Mann-Whitney and the regression model were applied. The level of statistical significance was set at $P < 0.05$. In the logistic regression test, all variables with a $P < 0.05$ in the above tests were entered into the logistic regression model to assess the effective factors of INSURE method failure

## 3- RESULTS

In the duration of the study, 239 preterm infants developed RDS that among them, 47 patients were excluded

due to congenital malformations and anomaly in the lung structure (10 patients), sepsis (10 patients), and receiving the first dose of surfactant in other centers (27 patients). Finally, based on the inclusion criteria, 192 patients included to the study. Of the 192 patients, 82 (42.7%) infants were females, and rest (n=110, 57.3%) were males.

The mean GA was 30.25 ± 1.85 weeks. The majority of infants had GA of 30-31 weeks (17.7%). The mean BW of infants was 1950 ± 270 gr. Fifty-six of them (29.2%) received INSURE method within the first 2 hr after birth. Other infants received INSURE during 2.1- 6 hr (n= 86, 44.8%), 6.1-24 hr (n= 34, 17%), and 24.1-72 hr (n=16, 9%) after birth. Of all the patients, 156 infants (81.25%) were born via cesarean section and rest through normal vaginal (n=36, 18.75%). INSURE failure was observed in 79 infants (41.1 %), and INSURE success among 113 infants (58.9 %). Their demographic and clinical characteristics are presented in **Tables 1, 2**.

Among the demographic and clinical characteristics between the INSURE failure and success groups, GA, BW, severity of RDS, and having IVH, CLD, pneumothorax and pulmonary bleeding were effective factors of INSURE method failure. Logistic regression analysis revealed that only GA and severity of RDS were associated with a significant increased risk of failure of INSURE method (**Table.3**).

**Table-1**: Demographic characteristics of infants and mothers in the INSURE failure and success groups

| Variables | Sub-group | INSURE failure n= 79 (%) | INSURE success n=113 (%) | P-value |
|---|---|---|---|---|
| GA (week) | < 30 | 46 (58) | 34 (30) | 0.001 |
| | > 30 | 33 (42) | 79 (70) | |
| BW (grams) | < 1,500 | 48 (61) | 28 (25) | 0.001 |
| | < 1,500 | 31 (39) | 85 (75) | |
| Gender | Male | 49 (63) | 61 (54) | 0.268 |
| | Female | 30 (38) | 52 (46) | |
| Delivery type | C-section | 66 (83.5) | 90 (79.6) | 0.496 |
| | Vaginal | 13 (16.5) | 23 (20.4) | |
| Gestational HTN | Yes | 17 (21.5) | 37 (32.7) | 0.657 |
| | No | 62 (78.5) | 76 (67.3) | |
| Parity | Primiparous | 39 (49.5) | 50 (44.5) | 0.221 |
| | Multiparous | 40 (50.5) | 63(55.5) | |
| Maternal diabetes | Yes | 1 (1.2) | 2 (1.7) | 0.478 |
| | No | 78 (98.8) | 111 (98.3) | |

INSURE: INtubate-SURfactant-Extubate; GA: gestational age; BW: birth weight; HTN: gestational hypertension.

**Table-2**: Clinical characteristics of infants between the INSURE failure and success groups

| Variables | Sub-group | INSURE failure n= 79 | INSURE success n=113 | P-value |
|---|---|---|---|---|
| Time of surfactant therapy (hours) | ≤ 2 | 28 (35) | 28 (25) | 0.290 |
| | 2.1-6 | 34 (43.5) | 52 (46) | |
| | 6.1- 24 | 13 (16.5) | 21 (18.5) | |
| | 24.1-72 | 4 (5) | 12 (10.5) | |
| Duration of NCPAP (hours) | ≤ 6 | 8 (10) | 17 (15) | 0.354 |
| | 6.1-12 | 15 (19) | 39 (34.5) | |
| | 12-24 | 26 (33) | 34 (30) | |
| | > 24 | 30 (38) | 23 (20.5) | |
| Severity of RDS | Mild | 8 (10) | 30 (26.5) | 0.011 |
| | Moderate | 67 (85) | 81(71.5) | |
| | Severe | 4 (5) | 2 (2) | |
| Neonate morbidity | IVH | 30 (38) | 19 (17) | 0.001 |
| | NEC (stage 1) | 6 (8) | 7 (6.2) | 0.704 |
| | Sepsis | 20 (25) | 18 (16) | 0.108 |
| | CLD | 7 (8.85) | - | 0.002 |
| | Pneumothorax | 25 (31.5) | 3 (2.5) | < 0.001 |
| | Pulmonary bleeding | 23 (29) | - | < 0.001 |

INSURE: INtubate-SURfactant-Extubate; NCPAP: Nasal Continuous Positive Airway Pressure; RDS: espiratory distress syndrome; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; CLD: Chronic lung disease.

**Table-3**: Logistic regression for INSURE failure by risk factors

| Variables | P- value | OR | 95% CI |
|---|---|---|---|
| GA (week) | 0.001 | 0.78 | 0.67-0.91 |
| BW (grams) | 0.27 | 0.39 | 0.04-3.9 |
| Severity of RDS | 0.001 | 6.31 | 2.07-19.9 |
| IVH | 0.351 | 1.25 | 0.79-1.95 |
| CLD | 0.512 | 0.61 | 0.25-2.49 |
| Pneumothorax | 0.783 | 1.32 | 0.5-4.6 |
| Pulmonary bleeding | 0.235 | 2.34 | 1.12-5.1 |

INSURE: INtubate-SURfactant-Extubate; GA: gestational age; BW: birth weight; IVH: Intraventricular hemorrhage; CLD: Chronic lung disease; CI: confidence interval; OR: odds ratio.

## 4- DISCUSSION

The aim of present study was to determine the effective factors of INSURE method failure in preterm infants with RDS and GA of 26-36 weeks or BW between 500- 3500 grams. The logistic regression analysis indicated that among the infants, maternal and INSURE method variables, only GA < 30, and severity of RDS were associated with INSURE failure. Cherif et al., in a retrospective study reported a INSURE failure rate of 37.1 % among preterm infants. They indicated that GA < 29, BW < 1,000 gr, serum hemoglobin level < 14 g/dl and clinical risk index for baby (CRIB) score > 4 were the predictors of INSURE method failure; however, in their study, logistic regression revealed that only CRIB score > 4 [95 % CI] = 14,81, [1.96-111.56]) was associated with a significant increased risk of failure of INSURE method (1). Our findings are not in agreement with this study, which GA and severity of RDS

were an independent risk factors for INSURE failure. In our study, the cut off point for GA and BW was considered at 30 weeks and 1,500 gr, respectively. While Cherif et al. these points were 29 and 1,000 gr (1). Further studies are required to determine the border line of GA and BW, which could predict the INSURE method failure in preterm infants. Also, they used a different surfactant type in comparison with surfactant type that we used (Curosurf vs. Survanta). In another study by Dani et al., BW < 750 gr, indices of severity of RDS including PO2/FiO2 < 218, and a/ApO(2) < 0.44 at the first blood gas analysis were independent risk factors for INSURE failure in infants with gestational age < 30 weeks (12). In their study, INSURE method success was observed among the 91% of the preterm infants (12). These differences are likely due to the lower sample size, GA and severity of RDS compared to our study. Their population had mean GA of 27 weeks, while our subjects had GA of 30.25 weeks and the majority of infants had GA of 30-31 weeks (17.7%). However, Najafian et al., in a cohort study conducted on 45 infants with RDS who had a BW < 1,500gr, exanimated INSURE followed by NCPAP. Twenty-nine and 16 infants had successful and the failure INSURE, respectively. BW was the predicting factors only for INSURE success (3).

Also, in Gutbrod et al. and Torrance et al. studies GA was not as a factor of success, which is not consistent with our study (18, 19). In Dani et al. study, 70% of the patients received one unit of surfactant. In our study instillation of surfactant for all infants was performed twice (12). This may be showed that GA, BW and severity of RDS, which in both studies, were a risk factors for INSURE method failures, are more effective than surfactant dose in INSURE failures. However, we recommend a clinical trial aimed with different surfactant dose and type. Tagare et al., in own study, assessed outcome of INSURE in managing preterm neonates with RDS. They investigated 28 infants underwent INSURE that 12 infants had INSURE failure. BW was significantly higher in INSURE success group than failure group and in contrast, start of NCPAP was significantly less in success group than failure group (0.5 h vs 3 of life) (20). Targare et al. study is a small size observational trial and the findings of these trials need to be confirmed with large randomized controlled trials. However, their study is agreement with results of Kandraju et al., study who conducted a clinical trial aimed to compare the efficacy of early routine versus late selective surfactant treatment in reducing the need for mechanical ventilation (MV) among preterm infants with RDS. In this study, infants were divided to early surfactant group (within the first 2 hr of life) or to late surfactant group. Their study showed that need for MV was significantly lower in the early surfactant group (16.2 vs. 31.6%; relative risk 0.41, 95% confidence interval 0.19–0.91) (21).

Both studies indicated that early surfactant administration compared to late administration reduce the INSURE failure, and need for MV especially in the first week of life. We did not observe any significant relation between these variables. Differences in severity of RDS could be responsible for disagreement in suitable time of surfactant therapy. In previous studies, INSURE followed by CPAP applied to the nose was defined as a very effective and useful method that may reduce the need for MV, and shorten the hospitalization stay (22, 23). Also, Garib et al. undertook a clinical trial study of 90 patients with RDS who were treated by surfactant replacement therapy to compare outcomes between early surfactant administration (within 6 h after birth) followed by prompt estuation, and later use of surfactants followed by continued

mechanical ventilation. In their study, early administration of surfactants was associated with lower re-intubation, less duration of total oxygen administration and less hospital stay (6). In our study, morbidity rates in infants who failed on INSURE method were more than those who succeeded on INSURE method. IVH, pneumothorax and lung bleeding were the main complications that were significantly more present in INSURE failure group than success group. In similar study, Cherif et al. reported a higher complication rates INSURE failure group compared to success group (1). In Ammari et al. study IVH, chronic lung disease, pneumothorax, and death were significantly more occurred in CPAP failure group (24). In Garib study, transient bradycardia, pneumothorax, and lung bleeding were the main complications following application of INSURE method (6).

### 4-1. Limitations of the study

The most important limitation of this study was the lack of similarity in personnel involved in the study in terms of work experience, performance and skill. Since, intubation procedure requires especial skills. Other limitations were lake of examine the different surfactant doses and types and NCPAP pressure, which we did not consider them due to homogenize the subjects.

## 5- CONCLUSION

Among risk factors considered in this study, only GA and severity of RDS were associated with a significant increased risk of failure of INSURE method. Further studies are required to determine potential effective factors of INSURE method failure in preterm infants with RDS.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENTS

We would like to thank the Clinical Research Development Unit of Kowsar Educational and Research and Therapeutic Center of Semnan University of Medical Sciences for providing facilities to this work.

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