

# Risk Factors Contributing to the Failure of Surfactant Administration with INSURE Method

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## ABSTRACT

**BACKGROUND:** The INSURE method (Intubation- Surfactant- Extubation) is effective in decreasing the need for mechanical ventilation and reducing ventilation-related adverse events. The aim of this study was to determine the risk factors for failure of the INSURE method.

**METHODS:** A prospective descriptive analytical study was conducted in a tertiary level neonatal intensive care unit (NICU) between March 2012 and December 2012. All preterm neonates who received intratracheal surfactant were enrolled in this study and allocated to INSURE failure and INSURE success groups depending on whether they needed intubation and mechanical ventilation or not.

**RESULTS:** Of the 147 neonates, 45 (30.6%) required intubation within the first 72 hours of intratracheal surfactant administration and, therefore, were included in the failure group. The mean birth weight and gestational age in the failure group were

1342±545 grams and 28.7±2.9 week, respectively, and were significantly lower than the success group (1688±472 grams and 31±2.2 week, respectively;  $p<0.001$ ). The Apgar scores at 1 and 5 minutes were significantly lower in the failure group than the success group (5.7±2.1 and 7.5±1.3 vs. 7.6±1.5 and 8.8±1, respectively;  $p<0.001$ ). Respiratory distress syndrome (RDS) score was 8.8±1 in the failure group and 7.1±1.3 in the success group ( $p<0.001$ ). The need for repeated doses of surfactant in the failure group was more than the success group (odds ratio (OR)=8.24, 95% confidence interval (CI): 3.10- 21.86). The patent ductus arteriosus (OR=3.42, 95% CI: 1.46-8.01;  $p=0.003$ ) and intra ventricular hemorrhage (OR=4.56, 95% CI: 1.90-10.93;  $p<0.001$ ) were significantly more common in the failure group.

**CONCLUSION:** Preterm infants with lower birth weight and gestational age and higher RDS score are at higher risk of INSURE method failure.

Keywords: Surfactant Administration; Preterm infants; INSURE method; Failure

## INTRODUCTION

Respiratory distress syndrome (RDS) is one of the most common causes of mortality and morbidity in preterm infants [1, 2]. The aim of respiratory management in RDS is the maintenance of adequate lung volume and gas exchange that can be achieved by prevention of alveolar collapse [3]. Surfactant replacement therapy improves clinical status and decreases mortality in neonates with RDS [4-7]. Prolonged intubation in preterm neonates is associated with increased morbidity, including bronchopulmonary dysplasia (BPD) [8-10]. In recent years, there is an increasing trend towards early extubation after surfactant administration or

complete avoidance of intubation and mechanical ventilation altogether. Early implementation of continuous distending pressure (CDP) can avoid mechanical ventilation and prolonged intubation [11-15]. Combination of continuous positive airway pressure (CPAP) and surfactant replacement therapy offers potential synergy in RDS treatment, mechanical ventilation avoidance and lung injury (e.g. BPD) prevention [16-22]. The INSURE (Intubation-SURfactant-Extubation) method involves the use of surfactant replacement therapy with transient intubation in spontaneously breathing infants. However, this method is not successful in all infants. This study was conducted to determine risk factors contributing to INSURE failure.

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## METHODS AND MATERIALS

This study was conducted at the neonatal intensive care unit (NICU) of a referral University Hospital in Tabriz, Iran, from March 2012 through to December 2012. The Ethics Committee of Tabriz University of Medical Sciences approved the study. All preterm infants who had spontaneous breathing and were given surfactant replacement therapy were enrolled in the study after obtaining parental consent. Newborn infants who were intubated after birth as part of their initial resuscitation and stabilization were excluded from study. Infants with major congenital malformations, chromosomal anomalies, severe birth asphyxia (Apgar score less than 4 at 5 minutes) were also excluded. Gestational age was determined by first trimester maternal ultrasound examination and physical examination of neonates and using Ballard scoring [23]. The diagnosis of RDS was based on clinical signs and symptoms, and confirmed by radiologic findings. RDS severity on chest X-ray was graded as mild, moderate or severe on the basis of standard classification [24]. RDS severity was determined by the RDS score.

All neonates received CPAP after delivery by Neopuff infant resuscitators (Fisher & Paykel Healthcare Ltd, New Zealand). Nasal CPAP was continued at the NICU for respiratory support with initial pressure of 4-6 cm H<sub>2</sub>O. Surfactant was administered as rescue treatment to infants receiving CPAP at a pressure  $\geq$  5 cm H<sub>2</sub>O, and to those that needed a FiO<sub>2</sub> more than 30% to maintain oxygen saturation between 88% and 92%. Infants were extubated as soon as adequate heart rate and oxygen saturation were established. A second dose of surfactant was administered to infants with continued FiO<sub>2</sub> requirements more than 30% and persistent, increased work of breathing. Neonates were categorized into two groups: INSURE success and INSURE failure groups. Neonates in whom RDS improved after INSURE and were successfully weaned off CPAP without need for reintubation, were included in the INSURE success group. Neonates who need reintubation and mechanical ventilation during the first 72 hours after surfactant administration, or who could not be extubated after one hour of surfactant administration, were included in the INSURE failure group. Mechanical ventilation was started in neonates with acidosis, hypoxia and hypercarbia (pH < 7.20, PO<sub>2</sub> < 50 mmHg with FiO<sub>2</sub> more than 50 and PCO<sub>2</sub> > 65 mmHg),

or frequent apnea (defined as more than 4 episodes of apnea per hour). Neonates with increased respiratory distress or severe retractions on CPAP despite positive end expiratory pressure (PEEP) more than cmH<sub>2</sub>O were also considered for mechanical ventilation. Patent ductus arteriosus (PDA) was determined by a pediatric cardiologist using echocardiography in neonates with suspected clinical findings. Cranial ultrasound examinations were performed in all patients within the first 3 days of life, on day 7 and day 28 by the same radiologist. Bronchopulmonary dysplasia (BPD) was defined as supplemental oxygen requirement at or after 28 days of life and 36 weeks corrected gestational age. Patients' data were reported with mean and standard deviation, rates and percentages and were analyzed with SPSS software version 16.0. Statistical analyses were performed using Student's t-test for continuous variables and chi square test for qualitative variables.  $p < 0.05$  was considered statistically significant.

## RESULTS

During the study period 175 preterm neonates received surfactant. Of these, 28 neonates were excluded either because they needed intubation in the labor and delivery room, or because they had congenital abnormalities, leaving 147 eligible neonates. The mean gestational age was  $30.33 \pm 2.7$  weeks (range: 25-36 weeks) and the mean birth weight was  $1582 \pm 219$  grams (range: 580-2400g). Eighty five neonates (57%) were male. Forty five neonates (30.6%) needed intubation during the first 72 hours after INSURE surfactant replacement therapy and so were included in the INSURE failure group. The demographic characteristics of enrolled neonates in both groups are showed in (Table 1).

The severity of RDS was determined and compared among patients in the two groups (Table 2). Severe RDS chest X-ray findings were found in 20 neonates (19.6%) in the success group and in 29 neonates (64.4%) in failure group ( $p < 0.001$ ). Repeat surfactant replacement therapy was needed in 24 neonates (16.3%): 17 (37.8%) in the failure group and 7 (6.9%) in success group (OR=8.24, 95% CI: 3.10-21.86;  $p < 0.001$ ). Seven patients (15.5%) in the failure group and 10 patients (9.9%) in the success group were oxygen dependent beyond 28 days and were diagnosed with BPD ( $P=0.32$ ). Five neonates (4.9%) in the success group and 23 neonates (51.1%) in failure group needed respira-

**Table 1:** Demographic characteristics of studied patients in INSURE failure and success groups.

	INSURE failure group (n=45)	INSURE success group (n=102)	p value
Male Gender, n (%)	23 (51.1)	62 (60.8)	0.27
Route of delivery was Cesarean section, n (%)	27 (60)	65 (63.7)	0.66
Maternal preeclampsia, n (%)	11 (24.4)	33 (32.4)	0.33
Gestation age, weeks	28.7±2.9	31±2.2	<0.001
Birth weight, grams	1342±545	1688±472	<0.001
Antenatal corticosteroid therapy, n (%)	33 (73.3)	67 (65.7)	0.36
Apgar score			
1 minute	5.7±2.1	7.6±1.3	<0.001
5 minute	7.6±1.5	8.8±1	0.007

**Table 2:** Clinical and laboratory findings of patients in the two INSURE groups

	INSURE failure group (n=45)	INSURE success group (n=102)	p value
RDS score	8.8±1	7.1±1.3	<0.001
First ABG:			
pH	7.27±0.09	7.28±0.07	0.25
PCO <sub>2</sub>	46.64±17.4	41.89±10.4	0.001
HCO <sub>3</sub>	20.49±4.1	7	0.26
PO <sub>2</sub>	48.86±13.2	19.7±3.7	0.14
		52.64±14.9	
FiO <sub>2</sub> before surfactant	53±19	40±11	<0.001
Age at surfactant administration, hours	5.9±11.2	5.2±5.4	0.04
Duration of oxygen therapy, days	17.4±2.2	9.3±1.1	0.001
Duration of hospital stay, days	23.6±18	20.2±14.7	0.22

tory support with CPAP (OR=20.28, 95% CI: 6.9-59.25, p<0.001).

Trans-fontanel ultrasound showed intra ventricular hemorrhage (IVH) in 11 neonates (10.8%) in the success group and 16 neonates

(35.6%) in the failure group (OR=4.58, 95% CI: 2.6-12.44, p=0.001). PDA was diagnosed by echocardiography in 13 neonates (12.7%) in the success group and 15 neonates (33.3%) in the failure group (OR=3.42, 95% CI: 1.46-8.01, p=0.003). Eleven neonates died during follow-up, all were from the failure group.

## DISCUSSION

Our study showed that gestational age, birth weight and Apgar score were significantly lower in the INSURE failure group. The radiologic severity of RDS, PCO<sub>2</sub> and repeat surfactant replacement therapy were higher in this group. The likely reason for failure appears to be the immaturity of lungs in neonates with lower birth weight and gestational age, as was identified with higher RDS scores and severe radiologic patterns of RDS. Infants in the INSURE failure group had higher rates of IVH, PDA and mortality. These associations identified in our study signify the need for early diagnosis and management of the complications of prematurity to facilitate early extubation. The best respiratory management for preterm infants remains a controversial issue. Due to adverse effects of mechanical ventilation [9, 25], there is an increasing trend of avoiding the use of mechanical ventilation. Early use of continuous positive end expiratory pressure is thought to be a valuable initial ventilator strategy in preterm infants. Preterm infants treated with nasal continuous positive airway pressure (NCPAP) and early surfactant (at the mean of 5.2 hours) exhibit reduced needs for subsequent mechanical ventilation [14, 15]. Dani reported 2 of 13 neonates (15%) required mechanical ventilation after surfactant treatment with CPAP [12]. Consistent with our findings, Cherif showed a 32.1% INSURE failure among 109 neonates and reported significant association of failure with arterial partial pressure of carbon dioxide, mean arterial to alveolar oxygen tension ratio and severe radiological grade [26]. In another study, Dani and coworkers demonstrated that a birth weight less than 750 g, PO<sub>2</sub>/FiO<sub>2</sub> less than 218 without units and arterial/alveolar gradient PO<sub>2</sub> less than 0.44 mmHg at the first blood gas analysis were independent risk factors for INSURE failure in preterm infants less than 30 weeks of gestational age. They postulated that instituting INSURE multiple times may decrease the failure rate and prevent need for mechanical ventilation [27]. In our study, the need for subsequent surfactant doses was common in neonates with INSURE failure. This may be

related to different study populations, study design, strategies for mechanical ventilation or different criteria for intubation. It is believed that premature newborn infants with lower birth weight and lower gestational age have more severe RDS and are more susceptible to complications of prematurity and hence INSURE failure. As intubation and mechanical ventilation are associated with pulmonary injury, the INSURE failure group had longer oxygen dependency. The incidence of BPD in our patients varied from 9.9% to 15.5% in the INSURE success and failure groups, respectively. However, because of lower incidence of BPD with NCPAP use, we attribute the present difference between the two groups to the use of NCPAP. The transfusion rate was higher in the INSURE failure group and so it is hypothesized that anemia causes decrease in oxygen delivery, and an increase in cardiac load and work of breathing. We recommended that future studies are undertaken with larger numbers of patients, and in neonates with gestational age less than 32 weeks to clarify risk factors for INSURE failure.

## CONCLUSION

Our study showed that preterm infants with lower birth weight and gestational age, severe RDS and severe radiologic findings are at more risk for INSURE failure. On the other hand, need for repeated doses of surfactant, packed cell transfusion, PDA and IVH are more common in INSURE failure group patients.

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## REFERENCES

1. Angus DC, Linde-Zwirble WT, Clermont G, Griffin MF, Clark RH. Epidemiology of neonatal respiratory failure in the United States: projections from California and New York. *Am J Respir Crit Care Med* 2001;164(7): 1154-1160.
2. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birth weight infants. *Am J Obstet Gynecol* 2007;196(2): 149.e1
3. Geoggy GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N Eng J Med* 1971;284:1333-1340.
4. Cheng-Hwa C, Ma S. The role of surfactant in respiratory distress syndrome. *The Open Respir Med J* 2012;6: 44-53.
5. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet* 1980;12: 55-59.
6. Jobe AH, Ikegami M. Biology of surfactant. *Clin Perinatol* 2001; 28(3): 655-69.
7. Suresh GK, Soll RF. Exogenous surfactant therapy in newborn infants. *Ann Acad Med Singapore* 2003;32 (3): 335-345.
8. Burri PH. Fetal and postnatal development of lung. *Ann Rev Physiol* 1984;46(1): 617-628.
9. Miller JD, Carlo WA. Pulmonary complications of mechanical ventilation in neonates. *Clin Perinatol* 2008;35(1): 273-81.
10. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infant preventable? A survey of eight centers. *Pediatrics* 1987 ;79(1): 26-30.
11. Rojas MA, Lozano JM, Rojas MX, Laughon M, Bose CL, Rondon MA, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized controlled trial. *Pediatrics* 2009;123(1): 137-142.
12. Dani C, Bertini G, Pezzati M, Cecchi A, Caiglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants < 30 weeks' gestation. *Pediatrics* 2004;113(6): e560-e563.
13. Gitterman MK, Fusch C, Gittermann AR, Regazzoni BM, Moesinger AC. Early nasal CPAP treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr* 1996;156(5): 384-388.
14. Ramanathan R. Optimal ventilatory strategies and surfactant to protect the preterm lungs. *Neonatology* 2008;93(4): 302-308.
15. Pas AB, Lopriore E, Engbers MJ, Walther FJ. Early respiratory management of respiratory distress syndrome in very preterm infants and bronchopulmonary dysplasia. *PLoS One* 2007;2(2): e192.
16. Hutchison AA, Bignall S. Non-Invasive pressure ventilation in the preterm neonate: reducing endotrauma and the incidence of bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 2008;93(1): F64-F68
17. de Winter JP, de Vries MA, Zimmermann LJ. Clinical practice: Noninvasive respiratory support in newborns. *Eur J Pediatr* 2010;169(7): 777-782.
18. Millar D, Kirpalani H. Benefits of non invasive ventilation. *Indian Pediatr* 2004;41(10): 1008-1017.
19. Stevens TP, Blennow M, Myers EH, Soll R. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007; 4:CD003063.
20. Verder H, Bohlin K, Kamper J, Lindwall R, Jonsson B. Nasal continuous positive airway pressure and surfactant for treatment of respiratory distress syndrome and prevention of bronchopulmonary Dysplasia. *Acta Pediatr* 2009;98(9): 1400-1408.

21. Bohlin K, Jonsson B, Gustafsson AS, Blennow M. Continuous positive airway pressure and surfactant. *Neonatology* 2008;93(4): 309–315.
22. Andersen T, Holm HS, Kamper J. Surfactant treatment of newborn infants receiving continuous positive airway pressure treatment. *Ugeskr Laeger* 2006;168: 3723–3727.
23. Ballard JL, Khory JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. *J Pediatr* 1991;119: 417–423.
24. Kero PO, Makinen EO. Comparison between clinical and radiological classification of infants with the respiratory distress syndrome. *Eur J Pediatr* 1979;130: 271–278.
25. Biarent D. New Tools in ventilatory support: high frequency ventilation, nitric oxide, tracheal gas insufflation, non-invasive ventilation. *Pediatr Pulmonol Suppl* 1999; 18: 178–181.
26. Cherif A, Hachani C, Khrouf N. Risk factors of the failure of surfactant treatment by transient intubation during nasal continuous positive airway pressure in preterm infants. *Am J Peinatol* 2008;25(10): 647–652.
27. Dani C, Berti E, Barp J. Risk factors for INSURE failure in preterm infants. *Minerva Pediatr* 2010;62(3 Suppl 1): 19–20.