IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Predicting Factors of INSURE Failure in Low Birth-Weight Neonates with Respiratory Distress Syndrome: A Logistic Regression Model

Bita Najafian[1], Amin Saburi[2]*, Seyyed Hassan Fakhraei[3], Abolfazl Afjeh[3], Fatemeh Eghbal[4], Reza Noroozian[2]

[1] Pediatrics Department, Faculty of Medicine, Baqiyat-o-Allah University of Medical Sciences, Tehran, Iran
[2] Baqiyat-o-Allah University of Medical Sciences, Tehran, Iran
[3] Pediatrics Department, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Pediatrics Department, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

ABSTRACT

Background: Respiratory Distress Syndrome (RDS) is the most common respiratory disorder in premature neonates and the leading cause of death among them. We have attempted to investigate factors to predict the success or failure of the INSURE Method as a therapeutic method for RDS.

Methods: In a cohort study, 45 neonates who had been diagnosed with RDS and had a birth weight of lower than 1500g were included and they underwent INSURE followed by Nasal Continuous Positive Airway Pressure (NCPAP). The patients were divided into the failure group and the successful group. The factors which can predict the success level of INSURE were investigated by logistic regression in SPSS, version 16.

Results: Twenty-nine and 16 neonates were observed in the successful and the failure group respectively. Birth weight was the only variable with a significant difference between the two groups (P=0.002). As a result, the logistic regression test indicated that birth weight can be the predicting factor only for the success group (P: 0.001, EXP[β]: 0.009, CI [95%]: 1.003-0.014) and the mortality (P: 0.029, EXP[β]: 0.993, CI [95%]: 0.987-0.999) of neonates who were treated with the INSURE method.

Conclusion: Predicting factors which affect the success level of INSURE can be useful for both treating and reducing the cost of treatment for the neonates diagnosed with RDS. Moreover, birth weight is one of the most effective factors in INSURE success in this study.

Keywords: Intubation-Surfactant-Extuberance (INSURE), Nasal Continuous Positive Airway Pressure (NCPAP), Surfactant, Respiratory Distress Syndrome (RDS)

Introduction

Respiratory Distress Syndrome (RDS) (1) or Hyaline Membrane Disease (HMD) (2) is the most common respiratory disorder in premature infants and the leading cause of their mortality. The disease, which is caused by the deficiency of alveolar surfactant, is also referred to as preterm neonatal respiratory distress (3). Thus, 60% of infants who are less than 30 weeks old, and 42% of infants with birth weights lower than 1500g are affected by the disease (1).

The syndrome appears immediately after birth or within a few hours later. It normally manifests with cyanosis, moaning and retraction of intercostals of muscles. Consequently, the patient might develop respiratory failure which is assessed with scoring of the respiratory distress severity (RDS score), lung radiography and blood gas analysis (Arterial Blood Gas: ABG) (2).

The diagnosis is confirmed by a combination of clinical signs of the disease, gestational age, ruling out other causes of respiratory distress and the chest x-ray view, including "Ground Glass" and "Air Bronchogram" (1). The risk factors of the disease include gestational age, birth weight, maternal diabetes and perinatal asphyxia; the gestational age and birth weight are two important factors with an adverse effect on the incidence and severity of the symptoms (1, 2).

The disorder is progressive and its severity increases during the first two days of the life. If it is not treated appropriately, mortality will occur due to progressive hypoxemia and breathing failure. Therefore, several different studies have been conducted on the pathophysiology of the disease. In

* *Corresponding author*: Amin Saburi, Baqiyat-o-Allah University of Medical Sciences, Tehran, Iran. Tel: 09127376851; Email: aminsaburi@yahoo.com

1929, the effect of surfactant on lung maturation was determined, and for the first time, the use of surfactant in infants with HMD was successfully reported in 1980 (3). The treatment of RDS is based on respiratory support and surfactant administration. Meanwhile, methods of respiratory support, mechanical ventilation and Nasal Continuous Positive Airway Pressure (NCPAP) are more widely known now due to their efficiency in the reduction of the disease mortality (4, 5).

The symptoms caused by using the invasive mechanical ventilation resulted in the designing of a variety of strategies in order to reduce the need for Mechanical Ventilation (MV) (5). The early use of NCPAP and surfactant has proven to be effective in reducing the need for mechanical ventilation and diminishing the side effects (6). Early use of NCPAP, even without the use of surfactants, has also contributed to improving the prognosis of infants with RDS (7, 8). Several studies have been done and different therapeutic strategies were introduced for surfactant administration and the use of CPAP. Among those strategies, the INSURE method is a very useful and effective approach which results in reducing the need for mechanical ventilation, diminishing side effects and hospital stay duration and its costs (9-11).

The present study was designed to investigate the effective factors in predicting the success or failure of INSURE method in infants with respiratory distress syndrome in the group with the body weight of less than 1,500 grams, via the MV method in the Neonatal Intensive Care Units (NICU) of Mofid Hospital and Mahdieh Hospital from 2009 to 2010.

Material and Method

This was a cohort study in which the infants born in 2009 and 2010 in Mofid Hospital and Mahdieh Hospital in Tehran, Iran were enrolled upon parental consent. The infants with RDS weighing less than 1500 grams whose disease was confirmed by their medical history, clinical findings and chest radiograph, and had also been hospitalized for up to 48 hours after their birth, were enrolled in this study. Furthermore, infants with any congenital malformations, anomaly in the lung structure, chromosomal abnormality or any evidence of sepsis and congenital heart disease were excluded from the study.

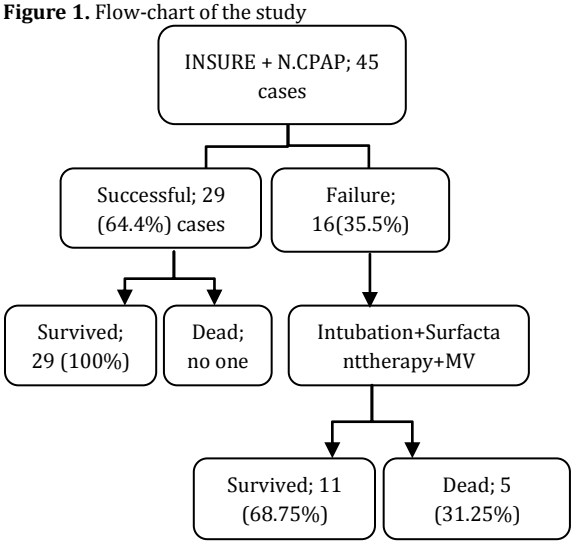
Finally, 45 patients were enrolled and received INSURE treatment protocol with surfactant administration (Intratracheal Suspension of Survanta, Beractant, Columbus, Ohio, US) with a dosage of 100mg/kg, which had been heated to the temperature of 37 °C. Afterwards, they received NCPAP with the pressure of 4 cm of water.

Based on their response to the treatment, the patients were divided into two groups: success and failure. The infants with no RDS symptoms, normal ABG and Chest X-Ray examination interpretation were placed in the success group. If they showed no signs of respiratory distress, with Fio2 <0-40, Positive End Expiratory Pressure (PEEP) <5 cmH2O, having Paco2 <60mmHg and Pao2> 50mmHg and PH> 7.25 in their arterial blood gas, they would be separated from NCPAP and placed under Oxygen-Hoods.

In contrast, in infants who had oxygen saturation of less than 85% with PaCO2> 60mmHg, PaO2 <50 mmHg and PH <7.2 in ABG assessment, when the PEEP reached to 6 cm of water, they were first placed under intubation and then mechanical ventilation. Thus, they were considered as the failure group. In cases of FiO2 higher than 40%, the additional dose of surfactant was given to maintain the oxygen saturation level above 85% (Figure 1).

Statistical analysis was done using SPSS software, version 16. In addition, independent and paired t-Student test, ANOVA, Wilcoxon, Mann-Whitney and the regression model were applied for this experiment which were considered statistically significant with $P < 0.05$. In the logistic regression test, it should be noted that the variables with results of $P < 0.2$ in the above tests were entered into the logistic regression model to assess the predictive power of INSURE method in case of both failure or success. Due to the limited sample size and in order to increase the

Figure 1. Flow-chart of the study



regression model power, a variable per 15 subjects was added to the model. In other words, having the sample size of 45 subjects, three variables were evaluated for each time of the model testing. In total, the most influential variables were added to the final model and their impact on the success rate of INSURE method was specified.

This study was done upon the approval of the Scientific and Ethical Committee of Beheshti University of Medical Sciences, Tehran, Iran. The reports on various stages of the project were presented to the concerned authority. Moreover, all interventions were done after obtaining informed consent from the the infants' parents imposing no additional costs on the patients.

Results

Forty-five patients were included in the study. twenty-five of them (55.5%) were male. A total of 6 patients (13.3%) were born through Normal Vaginal Delivery (NVD). Of all the patients, 31 neonates (68.8%) were born from nulliparous women. The average birth weight of the patients was equal to 1171 ± 218 g and their average age at birth was equivalent to 29.60 ± 2.28 weeks.

The demographic, para-clinical and clinical values are shown in Table 1. According to Table 1, there was no significant difference between the male and female cases in either the success or the failure group. Also, no significant difference was observed between the two groups regarding the method of delivery and age at birth. However, a significant difference was noted on the birth weight between the two groups (P = 0.002). Thus, from the patients with weighing less than 1000 g, one was placed in the success group and 8 were placed in the failure group. Among the patients with a birth weight between 1000-1250 grams, 12 and 5 patients were placed in the success and failure group respectively. Of the patients with a birth weight between 1250-1500 g, 16 patients were placed in the success group and 3 in the failure group. Moreover, no significant differences were observed regarding the age at birth between different categories (P = 0.465) (<28 weeks, between 28-32 weeks and 33-37 weeks). However, the duration of hospital stay and the age at birth showed significant differences (P = 0.001). This means in 15 infants aged less than 28 weeks, the length of stay was on average 51.5 days; in 26 infants with 32-28 weeks of age, the duration of hospitalization was on average 31.9 days, and in 4 infants aged 33-37 weeks, the length of stay, on average, was 20.7 days, which indicates that with the age of infants increasing, their duration of hospitalization will reduce.

No significant difference was seen among other demographic, clinical and para-clinical values between the two groups (Table 1). The variables with P <0.2 were entered the logistic regression model and it was concluded that only the birth weight (P: 0.001, EXP [β]: 0.009, CI [95%]: 1.003-0.014) was significantly associated with the success rate in the INSURE group. Furthermore, only the birth weight of (P: 0.029, EXP [β]: 0.993 and CI [95%]: 0.987-0.999) had a significant effect on the mortality in the INSURE group.

Discussion

The results of our study indicate that multiple factors can be involved in the success or failure of INSURE method in treating infants with RDS. In the current study, a total of 45 children were examined, of which 29 patients (64.4%) were placed in the success group and the rest were placed in the failure group. The birth weight was one of the factors influencing the success level of the method.

Most of the previous studies had focused on comparing the effectiveness of INSURE method with other methods of treatment, and only a small number of studies have examined the predictors of success in using INSURE method (12-14). For instance, in Cherif et al. study conducted on 70 infants, it was concluded that the arterial partial pressure of CO2, a/A pO2 and extreme degree of radiology are among the factors affecting the success rate of this method (15). Our findings are consistent with the aforementioned study. Thus, significant changes can be observed between the success and the failure group. However, by univariate analysis in the study mentioned, it was found that in addition to the birth weight, other factors such as small size, serum hemoglobin level < 14 g/dL as well as Clinical Risk Index for Babies (CRIB) score> 4 are also involved in success rate. Following Logistic Regression Analysis, it was found that out of the four factors, only the CRIB score> 4 factor is effective on the success rate, which was not mentioned in our study; probably due to the differences in the number of patients. The point lacking in the above-mentioned study and our study is that the gestational age (GA) is not raised as a predictor of success, which is consistent with previous studies suggesting that the low birth weight is a factor for the incidence of respiratory distresses (16, 17).

In another study conducted by Dani et al., it was claimed that such factors as birth weight <

750 g, PO2/FiO2 <218, and a/ApO2 <0.44 can affect the success rate of INSURE method (18).

Furthermore, in a related study by Afjeh et al. in 2010, it was reported that several factors are associated with the complications and success rate of INSURE method in low birth weight infants. However, the study mentioned above was a cross-sectional study, while the present study was performed in order to predict the success factors or eliminate the underlying confounding factors using regression models, which were not mentioned in the other study (19). Given the efficacy of INSURE method, which will make it the method of choice for the treatment of neonatal RDS in the near future, it will be able to predict the success and failure factors of the procedure and as well as attempt to remove the causes of failure which can significantly influence the effectiveness of treatments associated with reduced costs.

Acknowledgement

We would like to humbly thank all the nurses and staff of Mofid Hospital and Mahdieh Hospital.

References

1. Fanaroff AA, Martom RH. Neonatal Perinatal medicine: diseases of the fetus and infant. 7th ed. St Louis, USA: Mosby company; 2002; pp: 1097-8.
2. Sweet D, Bevilacqua J, Carnielli V, Greisen G, Plavka R, Saugstad OD, et al. European Vonsensus guidelines on the management meonatal respiratory distress syndrome. J Perinat Med. 2007; 35:175-86.
3. Jobe AH, Ikegmi M. Biology of surfavtant. Clin Perinatol. 2001; 28:655-69.
4. Henderson-Smart DJ, Wilkinson A, Raynes-Greenow CH. Mechanical ventilation for newborn infants with respiratory failure due to pulmonary disease. Cochrane Database Syst Rev. 2002; 4:CD002770.
5. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS. Cochrane Database Syst Rev. 2002; 2:CD003063.
6. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al. Nasal continuous positive airway pressure and earlysurfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics. 1999; 103:E24.
7. Alba J, Agarwal R, Hegyi T, Hiatt IM. Efficacy of surfactant therapy in infants managed with CPAP. Pediatr Pulmonol. 1995; 20:172-6.
8. Mandy GT, Moise AA, Smith EO, Hansen TN. Endotracheal continuous positive airway pressure after rescue surfactant therapy. J Perinatol. 1998; 18:444-8.
9. Habeman B, Shankaram S, Sterenson DK. Dose surfactant (S) and immediate extubtion to nasl continuos positive airway pressure (sp ap) reduce use of Mechanical ventilation. Pediatr Res. 2002;.51:349
10. Soll RF, Conner JM, Howard D. Early surfactant replacement in spontaneously breathing premature infant with RDS. Pediatr Res. 2003;.53:312
11. Cherif A, Hachani C, Khrouf N. F Factors associated with INSURE method failure in preterm infants with respiratory distress syndrome. Internet J Pediatr Neonatol. 2008; 8(1).
12. Andersen T, Holm HS, Kamper J. Surfactant treatment of newborn infants receiving continuous positive airway pressure treatment. Ugeskr Laeger. 2006;168:3723-7.
13. Reininger A, Khalak R, Kendig JW, Ryan RM, Stevens TP, Reubens L, et al. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: arandomized controlled trial. J Perinatol. 2005; 25:703-8.
14. 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; 123:137-42.
15. 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 Perinatol. 2008; 25:647-52.
16. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed. 2000; 82:F208-14.
17. Torrance HL, Mulder EJ, Brouwers HA, van Bel F, Visser GH. Respiratory outcome in preterm small for gestational age fetuses with or without abnormal umbilical artery Doppler and/or maternal hypertension. J Matern Fetal Neonatal Med. 2007; 20:613-21.
18. Dani C, Corsini I, Poggi C. Risk factors for intubation-surfactant-extubation (INSURE) failure and multiple INSURE strategy inpreterm infants. Early Hum Dev. 2012; 88:S3-4.
19. Afjeh SA, Sabzehei MK. The INSURE method in VLBW preterm infant with RDS. Pajoohandeh Journal. 2010; 15:199-203.

Table1. The factors in successful and unsuccessful INSURE

P Value	DH	P Value	Death No. %		Failure No.%		Success No.%		Number	Sub-group	Item
0.960	31.8	1	12.8	5	33.3	2	66.7	4	6	Vaginal	Delivery
	38.3				35.9	14	64.1	25	39	C/S	
0.227	35	0.639	9.7	3	29	9	71	22	31	Primiparous	Parity
	42		14.3	2	50	7	50	7	14	Multiparous	
0.166	33.8	0.362	16	4	32	8	68	17	25	male	gender
			5	1	40	8	60	12	20	Female	
0.867	33.8	1	13	3	47.8	11	52.3	12	23	No	Twins
	37		9.1	2	22.7	5	77.3	87	22	Yes	
0.829	37	0.423	14.3	1	42.9	3	57.1	4	7	yes	Gestational HTN
	39		10.5	4	34.2	13	65.5	25	38	no	
0.164	46.6	0.002	44.4	4	88.9	8	11.1	1	9	<1000	Birth weight (gr)
	39		5.9	1	29.4	5	70.6	12	17	1001 - 1250	
	31.7		0	0	15.8	3	84.2	16	19	1251-1500	
0.001	51.5	0.465	20	3	66.7	10	33.3	5	15	<W28	Gestational age
	31.9		7.7	2	23.1	6	76.9	20	26	28 -32 W	
	20.7		0	0	0	0	100	4	4	33-W37	
0.756	37	1	12.2	5	31.7	13	68.3	28	41	One unite	Surfactant dose
	34		0	0	75	3	25	1	4	More	
0.256	29	0.586	18.2	2	27.3	3	72.7	8	11	<2h	Time of surfactant therapy
	41		5.6	1	33.3	6	66.7	12	18	2-4 h	
	46		22.2	2	55.6	5	44.4	14	19	h4-6	
	25		0	0	50.6	1	49.4	1	2	h7-12	
	30		0	0	20	1	80	4	5	h13-24	
0.195	26	0.586	0	0	0	0	100	8	8	<6 h	Duration of N.CPAP
	38		0	0	25	1	75	3	4	7-12 h	
	35		0	0	11.1	1	88.9	8	9	13-24 h	
	34		18.2	2	36.4	4	63.6	7	11	1-2 day	
	47		23.1	3	76.9	1	23.1	4	13	>2day	
0.999	37	0.212	50	1	100	2	0	0	2	yes	pneumothorax
	37		9.3	4	32.6	14	67.4	29	43	no	
0.641	37	1	11.4	4	40	4	60	6	10	yes	Sepsis
	33		10	1	34.3	12	65.7	23	35	no	
0.734	37	0.550	50	2	100	4	0	0	4	yes	NEC (Stage1)
	33		12	3	29.3	12	70.7	29	41	no	
0.735	37	0.210	11.4	4	40	4	60	6	10	yes	Lung bleeding
	39		10	1	34.3	12	65.7	23	35	no	
0.734	37	0.304	33.3	1	33.3	14	66.7	2	3	yes	ROP
	33		9.5	4	66.7	2	33.3	8	42	no	

DH: Duration of hospitalization, NCPAP: Nasal Continuous Positive Airway Pressure, NEC: Necrotizing Enterocolitis, ROP: Retinopathy of Prematurity, C/S: cesarean section, W: Week, h: hour, gr: gram.