Factors associated with INSURE method failure in preterm infants with respiratory distress syndrome

A Cherif, C Hachani, N Khrouf

Citation

Abstract

Objective : To identify which factors can predict INSURE failure in preterm infants with respiratory distress syndrome.

Study design : A retropective analysis of the prenatal histories, clinical courses and paraclinical data of all inborn infants (birth weight < 2000g) with respiratory distress syndrome treated with INSURE method. Infants were categorized into 2 groups : "INSURE failure group" and " INSURE success group".

Results : Seventy infants were eligible to the study. INSURE failure was registered in 26 infants (37.1 %). After control for confounding variables, INSURE failure was significantly associated with CRIB score > 4 with a positive predictive value equals to 80 % (adjusted odds ratio [95 % CI] = 14,81 [1.96-111.56]). Complication rates in INSURE failure group were worse than those in INSURE success group.

Conclusion : CRIB score > 4 was the main factor of failure of INSURE method in preterm infants with RDS. However, a prospective randomised controlled trial is needed to determine whether or not infants at risk for INSURE failure are better off being treated with mechanical ventilation.

Abbreviations : RDS : Respiratory distress syndrome, SUR : surfactant, INSURE : INtubation - SURfactant - Extubation, MV : mechanical ventilation, N-CPAP : Nasal continuous positive airway pressure, FiO2 : fraction of inspired oxygen

BACKGROUND

Respiratory distress syndrome (RDS) in preterm infants is characterised by pulmonary immaturity and surfactant (SUR) deficiency, which lead to alveolar collapse, intrapulmonary shunting and poor lung compliance. Goals of the respiratory management of this disease are the maintenance of adequate lung volume, minute ventilation and gas exchange. Assisted ventilation and SUR replacement therapy are the main tools of this management. There are several respiratory strategies which varied according to mode of ventilation (tracheal, nasal), time of intubation (elective, selective), time of extubation (early, late) and modalities of administration of SUR (prophylactic, early, late). INSURE method (INtubation - SURfactant - Extubation) is one wide used of these strategies and is associated with reduced need for mechanical ventilation

(MV) and reduced incidence of chronic lung disease ([1,2,3]). Nevertheless, this method may fails and then infant clinical condition may worsen with subsequent respiratory and neurological consequences. Although, various rates of failure of this method have been reported ([4,5,6]), variables associated with this failure have been studied by any author. Thus, we conducted this study to identify which factors can predict INSURE failure ?

MATERIAL AND METHODS

Nasal continuous positive airway pressure (N-CPAP, Infant Flow System, Eme Ltd, Brighton, United Kingdom) is routinely used at the neonatal intensive care unit of Tunis, as an initial respiratory support modality in spontaneously breathing preterm infants with RDS. The initial respiratory support modality for infants without spontaneous respiratory efforts is MV via an endotracheal tube. SUR (Curosurf, chiesi, Italy, a vial of 1.5 ml containing 120 mg) is administered intratracheally within 2 hours after birth when fraction of inspired oxygen (FiO2) > 30 % or in presence of chest radiological signs of hyaline membrane disease, to

maintain arterial oxygen pressure between 50 and 70 mmHg and oxygen saturation between 88 and 92 %. When indicated, SUR is delivered with MV (intermittent positive pressure ventilation : Babylog 8000 ; Drager, Lübeck, Germany or high-frequency oscillatory ventilation : Sensormedics 3100 A, Sensormedics corp, Yorba Linda, CA) or with INSURE method : intubation, manual ventilation until adequate heart rate and oxygen saturation, 30 ° proclive position, instillation of the first bolus of surfactant for the right lung, manual ventilation until adequate heart rate and oxygen saturation, instillation of the second bolus of surfactant for the left lung, manual ventilation until adequate heart rate and oxygen saturation, extubation and N-CPAP restoration.

We performed a retrospective analysis of the prenatal histories, clinical courses and paraclinical data of all inborn admissions to the neonatal intensive care unit between may 2004 and may 2007, to determine which variables might be associated with failure of INSURE method in preterm infants < 2000g at birth. Infants with congenital cardiopathies or malformations were excluded. Infants were categorized into 2 groups : "INSURE failure group" and " INSURE success group". INSURE method was considered as failed when the infant was intubated within 24 hours for one of these conditions : FiO2 > 45 %, PCO2 > 60 mm Hg, recurrent apnea. Infants received, then, MV with or without a second dose of SUR. High-frequency oscillatory ventilation was indicated as an ultimate resort when FiO2 > 70 % or when alveolar pathology required more pressure. Inhaled nitric oxide was used, always connected to high-frequency oscillatory ventilation, to treat persistent pulmonary hypertension.

The maternal variables examined included : pregnancy-induced hypertension, diabetes mellitus, premature rupture of membranes > 12 hours, chorioamnionitis, corticotherapy, fetal distress and cesarian section.

The infants variables before INSURE method included : birth weight, gestational age, postnatal age, small for gestational age, sex, Apgar score, severity of RDS, CRIB (clinical risk index for babies, 7) score, perinatal asphyxia, early onset neonatal infection, systemic arterial pressure, serum hemoglobin level and maximal FiO2 . The severity of RDS on the initial chest x-ray was graded as mild, moderate or severe according to standard classification[8]. The infants variables after INSURE method included : intubation delay, duration of intubation, duration of ventilation, neonatal morbidities : pneumothorax, patent ductus arteriosus,

persistent pulmonary hypertension, intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia, chronic lung disease, death and duration of hospital stay. Intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis were graded respectively according to Papille's, Bell's, and de Vries's classifications ([9,10,11]). Chronic lung disease was defined according to the new Bancalari's classification ([12]).

Data were analysed using the statistical package for social science software version 11.0. Variables were expressed in percentages and means standard deviation. Qualitative variables were compared with chi 2 test and Fischer test. Quantitative variables were compared with Student t test and Mann Whitnney test. The differences were considered as significant for p value < 0.05. There were three statistical analysis : An univariante analysis was done first, to compare the groups for maternal and infant variables. Second, all variables with a p value < 0.05 were included in a model of logistic regression to control for the effect of potential confounding variables with calculation of adjusted odds ratios and 95% confidence intervals. Finally, a prediction analysis was done for variables which were strongly associated with INSURE failure. These variables were dichotomized at the intersection point between the sensitivity and the specificity of the test yielding cut-points and their positive predictive values were assessed.

RESULTS

During the study period, 1721 preterm infants < 2000g were admitted in the neonatal intensive care unit of Tunis. Seventy infants were eligible to the study. INSURE failure was registered in 26 infants (37.1 %) and INSURE success in 44 infants (62.9 %). Their baseline characteristics are presented in table 1.

Figure 1

Table 1 : baseline characteristics of the study infants

Characteristic		N (%)
sex	male	40 (57.1)
	female	30 (42.9)
gestational age (weeks)	mean	29,5±1.6 (range:24-33)
	< 28	13 (18.6)
	28,1-30	23 (32.8)
	30,1-32	23 (32.8)
	> 32	11 (15.7)
Birth weight (g) mean		1239±112 (range:650-1750)
	< 1000	16 (22.8)
	1001-1500	40 (57.1)
	> 1500	14 (20)
small for gestational age		7 (10)
fetal distress		4 (5.7)
pregnancy induced hypertension		43 (61.4)
maternal diabetes		3 (4.3)
antenatal corticosteroids		36 (51.4)
caesarean section		51 (72.8)
perinatal asphyxia		3 (4.3)
early onset neonatal infection		12 (17.1)

SUR was administered at 50 8.9 min of life (range : 20-70 min) and extubation occurred 5.5 1.2 min (range : 3-7 min) after SUR administration. Univariate comparative analysis between the groups (table 2) showed significant differences concerning 4 variables : small for gestational age, birth weight < 1000 g, serum hemoglobin level < 14 g/dl and CRIB score > 4.

Figure 2

Table 2 : Univariate comparative analysis

variable		INSURE failure group(n = 26)	INSURE success group(n = 44)	P
pregnancy induced hypertension (%)		14 (53.8)	29 (65.9)	NS
maternal diabetes (%)		1 (3.8)	2 (4.5)	NS
antenatal corticosteroids (%)		14 (53.8)	22 (50)	NS
caesarean section (%)		16 (61.5)	35 (79.5)	NS
perinatal asphyxia (%)		1 (3.8)	2 (4.5)	NS
male sex (%)		14 (53.8)	26 (59.1)	NS
gestational age (weeks)	mean	29.7±1.2	29.4±1.1	NS
	< 29 (%)	10 (38.5)	8 (18.2)	0.06
Birth weight (g)	mean	1238±123	1239±106	NS
	< 1000 (%)	10 (38.5)	6 (13.6)	0.03
small for gestational age (%)		6 (23)	1(2.7)	<0.01
mean arterial pressure (mm Hg)		39.9±2.5	41.1±1.9	NS
serum hemoglobin level (g/dl)	mean	15.9±1.9	16.4±2.1	NS
	< 14 (%)	8 (30.7)	4 (9.1)	0.02
CRIB score	mean	4.3±0.9	2.7±0.6	<0.01
	> 4 (%)	11 (42.3)	2 (4.5)	<0.01
FiO2 (%)	mean	48.8±9.8	42.5±8.5	NS
	> 60 (%)	10 (38.4)	11 (25)	NS
severe RDS (%)		9 (34.6)	26 (59.1)	NS
early onset neonatal infection (%)		6 (23)	6 (13.6)	NS

NS : non significant

For gestational age, when we considered the border line at 29 weeks, the difference was almost statistically significant (p = 0.06). When logistic regression analysis was performed, only CRIB score > 4 was associated with a significant increased risk of failure of INSURE method (table 3).

Figure 3

Table 3 : adjusted odds ratios for INSURE failure by risk variable

Variable	p	Adjusted OR	95 % CI for adjusted OR
CRIB score > 4	0.009	14.81	1.96-111.56
small for gestational age	0.13	6.94	0.56-85.34
serum hemoglobin level < 14 g/dl	0.49	1.82	0.32-10.16
birth weight < 1000g	0.62	0.63	0.09-4.02

OR : odds ratio, CI : confidential interval

When prediction analysis was performed, the dichotomous variable CRIB score > 4 maximized the specificity and sensitivity of CRIB score to predict INSURE failure. INSURE failure rate for this variable was 80 %. This failure rate is equivalent to the positive predictive value of the test.

In the INSURE failure group, intubation delay was 9 0.9 h (range :6-18 h). In the INSURE success group, 3 patients were secondary intubated because nosocomial septic shock. Duration of ventilation and intubation were significantly more long in the INSURE failure group(table 4).

Figure 4

Table 4 : outcome of the study infants

	INSURE failure group (n = 26)	INSURE success group (n = 44)	p
mean duration of ventilation (d)	15.5±2.3	9.4±1.9	<0.01
mean duration of intubation (d)	8.5±1.2	3.1±0.9	<0.01
patent ductus arteriosus (%)	15(57.7)	10(22.7)	<0.01
nosocomial sepsis (%)	10(38.4)	10(22.7)	NS
pneumothorax (%)	1(3.8)	0(0)	NS
persistent pulmonary hypertension (%)	3(11.5)	0(0)	NS
chronic lung disease (%)	3(11.5)	1(2.2)	NS
necrotizing enterocolitis n (%)	2(7.7)	3(6.8)	NS
grade 1	1	1	
grade 2	1	1	
grade 3	0	0	
intraventricular hemorrhage n (%)	11(42.3)	14(31.8)	NS
grade 1-2	8	12	
grade 3-4	3	2	
periventricular leukomalacia n (%)	2(7.7)	2(4.5)	NS
grade 1	1	1	
grade 2	1	1	
grade 3	0	0	
mean time to full entering feeding (d)	13.1 ± 3.5	11.7 ± 2.9	NS
mean time to regain birth weight (d)	16.1 ± 4.1	18.1 ± 3.1	NS
mean duration of hospital stay (d)	27.5 ± 6.3	26.5 ± 6.2	NS
death within 28 days (%)	9(34.6)	15(34)	NS

Patent ductus arteriosus was significantly more present in the INSURE failure group. There were more persistent pulmonary hypertension, chronic lung disease, intraventricular hemorrhage and periventricular leukomalacia in the INSURE failure group, but differences were not statistically significant. Death occurred in 24 infants (34.2 %) with any difference between the groups. Mean age at death was 12.3 1.1 d (range : 10-19 d). Nosocomial sepsis with shock and intravascular coagulopathy was the first cause of death (12 infants). Multiorgan failure was incriminated in the death of 5 infants, extreme immaturity (25 weeks' gestation) in 5 infants, pneumothorax in 1 infant and hypoxemia in another. Proven nosocomial sepsis occurred in 20 infants (28.5 %) at an age ranging from 9 to 24 days with a mean age of 8.5 days. Isolated microorganisms were : negative coagulase staphyloccocus in 9 infants, klebsiella pneumoniae in 7 infants, acinetobacter baumani in 3 infants and candida albicans in 1 infant.

DISCUSSION

There are several methods and strategies in the initial respiratory management of RDS in preterm infants. Which is the most appropriate strategy to use is a hot controversial debated issue in neonatology. The recently updated international guidelines on neonatal resuscitation do not provide specific recommendations on how to provide initial respiratory management in very preterm infants due to lack of data [13]. The best supported approach includes elective intubation and early SUR replacement. An alternative approach which includes early application of nasal CPAP with selective SUR replacement may prove to confer greater protection to the preterm lung. For infants initially treated by nasal CPAP, when decision to administer SUR is taken, it is so important to have clinical and paraclinical criteria, on which kind of ventilatory support, either nasal or tracheal, is determined. Several studies have reported improved respiratory outcomes with INSURE method [14,15,16,17], however, there is evidence, that if INSURE method fails, many adverse consequences can occur. Our study showed that : 1.failure of INSURE method, for infants initially treated by nasal CPAP, occurred in 37.1 %, 2. CRIB score > 4 is the main factor of this failure with a positive predictive value equals to 80 %, 3.complication rates in infants who failed on INSURE method were worse than those who succeeded on INSURE method.

Few studies have reported failure of INSURE method and no study has studied factors of failure [4,5,6]. Andersen [4], in a retrospective study of 11[5] premature infants, reported a rate of failure of 49 %. Reininger [5], in a randomised controlled study comparing INSURE method to nasal CPAP alone in infants 29 to 35 weeks' gestation, reported a rate of failure of 50 %. Variability of these rates is due to a variability in criteria for intubation and an hetergeneity of the studied populations. In the study of Andersson[4], failure of INSURE method was GA depending with a rate of failure ranging from 14 % in week 29 to 78 % in week 24. In our study, failure was GA depending, too, with a rate of failure ranging from 20 % in week 29 to 50 % in week 27. Dani [6], in a small randomised trial comparing INSURE method to MV/SUR in preterm infants < 30 weeks gestation, reported a rate of failure of 15 %. In this study, which was conducted with the aim to determine whether INSURE method can reduce the need for MV, infants were randomised relatively late (6 hours of life), the enrolment criteria were selective and the outcome during the first week of life has not been reported. It is, then, so difficult to extrapolate these results.

Ammari ([18]), undertook a retrospective analysis of a cohort of 261 preterm infants (BW < 1250g) of variables associated with early failure of N- CPAP. He found that need for intermittent positive pressure ventilation at delivery, alveolar-arterial oxygen tension gradient > 180 mm Hg on the first arterial blood gas and severe RDS on the initial x-rays were risk variables but with weak predictions. In this study, intraventricular hemorrhage, chronic lung disease, pneumothorax and death were significantly more present in CPAP failure group. Although, the results of this study can not be extrapolated, they support that, when failure of N-CPAP occurs, outcome is worsen. A prospective, randomised controlled trial to determine whether or not infants at risk for INSURE failure are better off being treated with MV / SUR is warranted.

Finally, our study showed a high mortality rate (34.2 %). Most deaths occurred in a context of septic multiorgan failure with multiple abcesses on postmortem examination. Some factors which are specific to our recently established neonatal intensive care unit may account for this rate : inadequate nurse / patient ratio and inadequate intensive neonatal care beds / stillbirths ratio, nosocomial microorganisms from the delivery room and from the other maternity clinics. These factors select multiresistant microorganisms and lead to a rapid spread of infection ([19]). Strategies to fight nosocomial sepsis and to reduce its medical, social and economic costs have been undertaken and have decreased this mortality rate.

CONCLUSION

It is so important to have criteria on which one of the many modalities of initial respiratory management of RDS in preterm infants is determined. Our study is retrospective and includes a relatively small number of infants, but it can serve as an initial check-up to conduct a larger randomised studies. It showed that a CRIB score > 4 is the main factor of failure of INSURE method with a positive predictive value equals to 80 %.

CORRESPONDENCE TO

Ahmed cherif, Neonatal intensive care unit, neonatology and maternity center, 1007, Jebari, Tunis, Tunisia, phone : + 216 71 56 56 55, fax : + 216 71 57 27 11, e-mail : ahmedcherif@voila.fr

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Author Information

Ahmed Cherif

Neonatal intensive care unit, Neonatology and maternity center, faculty of medicine, Department of neonatology, University of Tunis

Chadlia Hachani

Neonatal intensive care unit, Neonatology and maternity center, faculty of medicine, Department of neonatology, University of Tunis

Naima Khrouf

Neonatal intensive care unit, Neonatology and maternity center, faculty of medicine, Department of neonatology, University of Tunis