INSURE method (INtubation-SURfactant-Extubation) in early and late premature neonates with respiratory distress: factors affecting the outcome and survival rate

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We studied the effects of administering exogenous surfactant for the treatment of respiratory distress in premature neonates (born before 37 weeks of gestational age [GA]) and compared the role of different risk factors on the outcome as well as survival rate.

All the neonates (242) suffered from moderate to severe respiratory distress, identified by clinical signs, chest X-ray, respiratory distress syndrome (RDS) score >6, and blood gas measurements. All the neonates included were treated by administering surfactant (Beractant or Poractant alfa, dosage 100 mg/kg).

The INSURE method was "successful" in 74% of patients, meaning there was no need for a second dose of surfactant or mechanical ventilation repetition. The factors that determined the "success" (Table II) were as follows: type of delivery, weight, GA, and number of fetuses. The factors affecting survival were: number of fetuses, mechanical ventilation dependency, pregnancy complications, and type of surfactant. The INSURE method reduced mortality (91.3% survived).

Key words: respiratory distress, respiratory distress syndrome (RDS), surfactant, INSURE method, mechanical ventilation.

Since alveolar surfactant is generally produced during weeks 30-33 of intrauterine life, premature neonates who are born before that period usually suffer from respiratory complications, and even neonates with gestational age (GA) of >32 weeks may show respiratory distress (RD), mainly due to surfactant deficiency[1]. A reduction in the mortality rate among neonates of 40% has been observed with the application of exogenous surfactant through the endotracheal tube[1].

Using nasal continuous positive airway pressure (NCPAP) and surfactant at an earlier point after birth has reduced the need for mechanical ventilation (MV) and has decreased some side effects[2]. The INSURE, or INtubation alongside the application of SURfactant and then Extubation, followed by CPAP applied to the nose is a very effective and useful method that reduces the need for MV, decreases side effects, shortens the hospitalization time, and eliminates extra hospital expenses[3-5].Verder and colleagues[6] showed that inducing one dose of surfactant through the nasal airway with CPAP reduces the later need for MV in neonates with respiratory distress syndrome (RDS). The sooner the surfactant treatment was started, the further the need for MV was reduced. Bohlin[7] showed that using the INSURE method reduces the need for MV and does not increase the side effects.

Andersen[8] reported a failure rate of 49%, which is different from that of our study since different criteria were used to perform the intubation. We did not intubate most of our patients in the delivery room as a prophylaxis since they were referred to us from other centers after birth. Hence, there were age differences for the INSURE application (on average, it was done 2-4 hours after birth). Furthermore, since we had a shortage of the surfactant drug at our hospital, we applied the INSURE method at the RDS score of ≥6. Ammari [9] concluded that need for alternative positive pressure

ventilation (PPV) during the delivery of the baby, oxygen gradient of >180 mm of mercury between the alveolar arteries and arterial blood, and severe primary RDS diagnosed by chest X-ray are the risk factors with poor prognosis that cause failure of the NCPAP method. Researchers have shown that using surfactant may decrease the cost and duration of the hospitalization in the neonatal intensive care unit (NICU)[10,11]. Administering corticosteroids before birth activates the surfactant system in the neonate's lungs and reduces the incidences of RDS, intraventricular hemorrhage, morbidity, and mortality by 50% in neonates[12]. Glucocorticoids change the gene expression responsible for controlling the protein synthesis for surfactant[13]. Administering surfactant at an earlier time (within 2 hours after birth) reduces the occurrence of pneumothorax and lung emphysema[14]. In addition, surfactant therapy can reduce the mortality rate and the incidence of bronchopulmonary dysplasia, intracranial bleeding, sepsis, and symptomatic patent ductus arteriosus[15]. However, in our study, we applied the surfactant therapy in a broader age range in neonates, meaning even in infants with a GA of ≥32 weeks, who required ventilation due to RD[16].

Material and Methods

We took a retrospective approach and included the neonates who suffered from RD confirmed by clinical signs and chest X-ray. Parental consents (ante-/post-natal) were acquired. The exclusion criteria were congenital heart disease and chromosomal anomalies.

The prenatal data collected included: weight at birth, GA, sex, race, singleton/multiple fetuses, mother's health during pregnancy, existence of PPROM (prolonged premature rupture of membrane), existence of chorioamnionitis, type of delivery, IUGR (intrauterine growth retardation), antenatal use of steroids, Apgar score (5th minute), whether mask and bag were used to apply PPV, and whether resuscitation was performed or oxygen was administered. The post-natal data collected included: frequency of surfactant administration, age of the newborn at the time surfactant was administered, number of days NCPAP was needed, oxygenation index and number of days MV was required, days of hospitalization, side effects, and number of patients who recovered/died since MV was required. For high-risk pregnancies, a neonatologist was present in the delivery room before the neonate's birth at Mahdie Hospital in Tehran, Iran. If intubation was needed, it was done by the physician, and the neonate was transferred to the NICU to receive MV treatment, and the surfactant was administered. In premature neonates with spontaneous breathing and no need for intubation, after transfer from the NICU, if clinical findings or radiological evaluations confirmed that RD existed, and if they met the study criteria, the INSURE method was applied. However, premature neonates with spontaneous breathing but who did not have clinical or radiological findings confirming the existence of RD were only monitored (no INSURE method was applied).

For the hospitalized neonates, the clinical findings for RD were compared to the RDS scoring system (Table I), and if the score was >6, the RD was classified as moderate to severe dyspnea, and as long as this was confirmed by clinical findings and chest X-ray, the neonate was entered into the study.

If the neonates needed FiO2 >40% (fraction of inspired oxygen) in order to reach oxygen saturation (SpaO2) of 85-92%, or if they showed signs of moderate to severe RD (RDS score >6), or the presence of RD was confirmed by their radiologic findings at 30 minutes (min) of age or later, they were intubated and the surfactant was administered (either Beractant or Poractant alfa, at a dosage of 100 mg/kg).

To administer surfactant, the neonate's head was placed in the tracheal intubation position. Then, under direct laryngoscopy, the neonate was intubated by a tracheal tube suitable for the baby's weight.

The surfactant syringe was at body temperature. Using a feeding tube or a side-hole connection tube attached to the tracheal tube, the surfactant was administered during 2-3 min using a bag. If, during the administration of surfactant, the heart rate decreased to <100 beats/min or the oxygen saturation (SpaO2) reached <80%, or if coughing and choking occurred, the administration of surfactant was stopped and was resumed only after those problems were resolved. We used a bag for ventilation during the administration.

Following the administration of surfactant, the neonate was extubated and received nasopharyngeal continuous positive airway pressure (NPCPAP) at 4 cm of pressure.

If no RD signs appeared, and the blood gas analysis and follow-up chest X-ray were normal with FiO2 <60% and positive end-expiratory pressure (PEEP) of 4-6 cm H2O, the neonate was considered as being successfully recovered by the INSURE method.

If the neonates did not have RD signs, mean airway pressure (MAP) was <6 cm of water, FiO2 was <40%, PaCO2 was <60 mmHg, and PaO2 was >50 mmHg, the neonate was separated from NPCPAP and received oxygen (5-7 L/min) under the Oxyhood.

If the neonate showed signs of RD under NPCPAP, the oxygen saturation was <85%, and the blood gas analysis revealed RD (PaCO2 >60 mmHg, PaO2 <50 mmHg, pH <7.2), we first increased the amount of PEEP from 4 to 6 cm of water. If no improvement was seen, the neonate was treated under the nasopharyngeal rate of 20/min and peak inspiratory pressure (PIP) of 14 cm H2O.

If there was still no improvement, the neonate was intubated again and the MV was re-started. This was counted as failure in the evaluation of the INSURE (no success). After 12-24 hours, if FiO2 >40% was needed to reach SpaO2 of ≥85%, the second dose of surfactant was administered.

We strictly observed that the moral code regarding patient treatment conformed to the provisions of the Declaration of Helsinki, and considered findings from other studies to minimize jeopardizing the neonates' lives.

To choose the participating neonates for the study, a neonatologist followed the aforementioned guidelines to eliminate the selective bias effect and other interfering outliers to minimize misleading results.

The difference in the number of times one type of surfactant versus the other was used was due *only* to the availability of that type at the time.

Statistical Method

For data collection and statistical method, the Statistical Package for the Social Sciences (SPSS) software (IBM Company) was used. For comparing averages, for quantitative variables, T-test, and for qualitative variables, chi-squared distribution, were used. For obtaining the descriptive results, in case of quantitative variables, the following data were exploited: average, mean and standard deviation. In the case of qualitative variables, ratio was used. P-values less than 0.05 were considered significant.

Results

In total, 242 neonates were studied, of which 64% (155) were boys and 36% (87) were girls. Minimum weight at birth was 600 g and maximum weight was 3800 g (average: 2026 g with the standard deviation of 751 g). The complications in the mothers resulting from the pregnancy included: gestational diabetes in 3.7% (9), high blood pressure in 13.6% (33), PPROM >18 hours in 4.1% (10), presence of thick meconium in amniotic fluid in 0.8% (2), and addiction to narcotics in 0.4% (1). However, 77.3% (187) of the pregnancies did not show any side effects.

INSURE was successful in 74% (179), and the need for MV following the administration of surfactant was eliminated. However, in 26% (63) of the neonates, after administration of surfactant through the INSURE method, there was no success, and the neonate was reintubated and connected to the mechanical

Table I. RDS Scoring System

Score	0	1	2
Respiratory Rate (breaths/minute)	60	60-80	>80 or apneic episode
Cyanosis	None	In room air	In 40% oxygen
Inter-costal	None	Mild	Moderate to severe
Retractions			
Sub-costal	None	Mild	Moderate to severe
Grunting	None	Audible with a stethoscope	Audible without a stethoscope

Table II. Individualized Analysis of the Outcomes of Our Study for Applying the INSURE Method (p values <0.05 are significant)

Variables	INSURE Success Rate				P Value
Type of delivery	Normal delivery	C-section			
	59.5% (25)	77% (154)			0.032
Gravida	Multipara	Primipara			
	73.6% (89)	74.4% (90)			1.000
Pregnancy complications	Present	Absent			
	75.9% (41)	73.4% (138)			0.860
Steroids before birth	Used	Not Used			
	73.4% (163)	80% (16)			0.606
Sex	Boy	Girl			
	74.2% (115)	73.6% (64)			1.000
Number of fetuses	Singleton	Multiple			
	75.3% (131)	70.6% (48)			0.051
Weight at birth (gram)	<1500	1500 – 2500	>2500		
	59.1% (39)	75.5% (80)	85.7% (60)		0.002
Gestational age (week)	<28	28-32	33-37	>37	
	37.5% (6)	69.9% (65)	78.8% (89)	95% (19)	0.001

ventilator.

No side effects were seen in 66.1% (160) of the neonates. However, in 33.9% (82) neonates, side effects occurred, and in 11.2% (27 neonates), multiple side effects were seen.

The duration of MV ranged from 1-50 days. The average duration was 2.2 days, with the standard deviation of 6.6 days.

The average duration of MV application in the success group was 1.6 days (±5.5 days) and in the non-surviving group 8.1 days (±12.5 days).

From the 242 neonates under study, 91.3% (221) recovered and 8.7% (21) did not survive.

The average weight in the successful group was 2130 g (±698 g) and in the group of exitus patients was 939 g (±265 g).

The average GA in the successful group was 33.1 weeks (±3.1 weeks) and in the non-surviving group was 28 weeks (±2.3 weeks).

The factors that determined the outcome of this study were as follows (Table II):

Type of delivery: Babies born through C-section showed better results.

Weight: The heavier the baby, the better the results.

Gestational age: Older newborns showed better results.

Number of fetuses: In the presence of more than one fetus, the rate of success decreased.

Factors affecting the survival rate included:

Number of fetuses: For the singleton neonates, the survival rate was 94.3% (164) compared to 84.8% (57) survival with multiple fetuses (p=0.01).

MV dependency: In the group who did not originally need MV to survive, 98.3% (176 of 179 neonates) recovered. However, in the group that was dependent on MV to survive, only 71.4% (45 of 63 neonates) recovered (p<0.001).

Pregnancy complications: In the pregnancies in which the mother did not experience complications, recovery occurred in 178 of 188 neonates (94.7%). Yet, in the case of mothers with pregnancy complications, only 79.5% (43 of 54) recovered (p=0.002).

Type of surfactant: With Poractant alfa, the recovery rate was 88.7% (149 of 168 recovered) and with Beractant, the recovery rate was 97.3% (72 of 74 neonates recovered) (p=0.027).

Discussion

Surfactant therapy (INSURE method) can be used in a wider range of premature neonates (<37 weeks of GA) who suffer from RD rather than limiting its application to early

premature neonates with RDS[17]. All the neonates studied were defined as premature (<37 weeks). However, in a group of these neonates, the occurrence of the RD may have been caused by some factors other than prematurity, which included diabetic mother, birth asphyxia, failure of the mother to enter the "active phase of labor" before giving birth, meconium aspiration syndrome, and hypoxic-ischemic encephalopathy (HIE), and it is very important to treat these underlying factors as a preventative measure.

According to our findings, in general, the application of the INSURE method is one of the best approaches for the treatment of RD in neonates, without limiting its application to the neonates with GA under 32 weeks.

Since the application of the INSURE method shortens the duration of hospitalization and reduces the risk of long-term side effects and disabilities, we propose that the use of the INSURE method benefits most of the premature and also near-term neonates suffering from RD. Additionally, it reduces the costs of treatment. In order to gain the best results, the INSURE method should be applied within the first two hours after birth or within six hours at the latest to show its effectiveness. If improvement is attained, extubation and NCPAP should follow. For ethical reasons, we did not have a control group.

Type of delivery, weight, GA, and the number of fetuses determined the outcome of this study. The number of fetuses, MV dependency, pregnancy complications, and type of surfactant affected the survival rate.

There are two types of surfactants available for clinical use: natural and artificial. The natural surfactants are extracted from mammal lungs, while the artificial types contain phospholipid molecules similar to human surfactant. In our study, we used either of the two natural surfactant products available: Beractant (from cow) or Poractant alfa, which is derived from swine lungs. We concluded that Beractant resulted in better recovery in the neonates.

Furthermore, compared to the other types of surfactant used in other studies, death and pneumothorax occurred less frequently with Beractant. The authors of this study do not have any relation to any pharmaceutical industry.

Our current study showed that by using surfactant for RD, the death rate decreased (by 8.7%). Another factor that changed during the course of this study and affected the mortality rate was the use of corticosteroids before birth in high-risk pregnancies between weeks 24-34 of GA.

In the current study, since there was no control group, we could not evaluate the outcome of cases with no corticosteroids involved. In all scientific references, it is cautioned that pulmonary bleeding can occur as the result of surfactant administration. Otherwise, administration of surfactant is one of the best treatments in this group. In our study, in the presence of pulmonary bleeding (in 9 neonates), the outcome was fatal in 69%. Unfortunately, since foreign countries have imposed economic sanctions on Iran, the availability of imported drugs is not guaranteed. Hence, we did not use surfactant for the treatment of bronchoalveolar hemorrhage. Sepsis was the cause of 17.5% of neonatal deaths.

In conclusion, random prospective studies in controlled experiments to determine the advantages or disadvantages of using MV or surfactant in high-risk neonates are deemed necessary.

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