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Comparison of the Results of Simultaneous Surfactant Administration and Nasal Continuous Positive Airway Pressure (INSURE) and Non-administration of Surfactant for the Treatment of Infants with Respiratory Distress Syndrome

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Abstract

Background: Various strategies have been suggested for the treatment of neonatal respiratory distress syndrome (NRDS).
Objectives: Nowadays, most of the high-risk pregnancies are successfully ended although they normally result in the delivery of premature and preterm neonates. The rate of NRDS increases in these neonates, which consequently demands for more interventions to save them.
Methods: This was a case-control study in which, 52 neonates of 27 - 32 weeks' gestation and birth weight 1000 - 3000 g were treated with Curosurf (a natural surfactant) and NCPAP (Nasal continuous positive airway pressure) as the case group. The control group consisted of 52 matched neonates untreated with surfactant and NCPAP.
Results: Studying 6 common NRDS-induced complications (pneumothorax, pulmonary hemorrhage, chronic lung disease, intraventricular hemorrhage, sepsis and patent ductus arteriosus) showed that there were no significant differences between the case and control groups ($P > 0.05$). Also, there were no significant differences in mortality and ventilator usage rates and duration of hospitalization ($P > 0.05$). In total, 9 neonates in the case group (17%) and 16 in the control group (30%) died consequently.
Conclusions: The results showed that surfactant therapy had no significant effect on mortality and ventilator usage rates, duration of hospitalization, and NRDS-induced complications.

Keywords: Surfactant, Neonate Respiratory Distress Syndrome, Mortality

1. Background

Since alveolar surface generally is formed during the weeks 30-33 of intrauterine life, preterm infants born before this period usually suffer from respiratory complications. Even infants of gestational age under 32 weeks may experience neonatal respiratory distress syndrome (NRDS) mainly due to the lack of surfactant (1). NRDS, as the most common respiratory disorder in preterm infants, is related to the lack of surfactant and is the most important reason for death in preterm infants (2). The prevalence of this disease declines as gestational age increases (3). As a result, the lung collapses, and its compliance is reduced (2). In most cases, detection is based on clinical findings of radiographic trials. Classical examples of the clinical symptoms of this disease include grunting, retraction of intercostal and subcostal spaces, moaning, cyanosis, and increased need for oxygen (3). Treatment of NRDS involves, first of all, the administration of foreign (exogenous) surfactant with mechanical ventilation (MV) (4, 5). The reduction of neonatal mortality rate using exogenous surfactant through 40% endotracheal (ET) tube has been observed (1, 6). Surfactant administration is helpful within the first two hours after birth; this has been well demonstrated for NRDS (2). Two strategies for surfactant therapy have been defined. Surfactant administration via ET tube following long-term MV is a common method. This has been effective in lung barotrauma, pneumothorax, long-term hospitalization, and hypoxia followed by ET suction. Trained staff and specialized equipment are, thus, vital (2). Using nasal continuous positive airway pressure (NCPAP) plus surfactant in the initial stage after birth reduces the need for MV,

and it also decreases some of the complications (1, 7-11). On the other hand, INtubation-SURfactant-Extubation (INSURE) is considered as an innovative method for treatment of NRDS. In this method, intubation is carried out along with surfactant administration (12-15). However, surfactant administration requires infant intubation and ET tube placement (16). There is no doubt that laryngoscope and ET tube placement are among the most common methods used in neonatal intensive care unit (NICU) (3, 17, 18). Excess physical stimulation in the larynx, for example through the use of the laryngoscope, causes pain and stress in infants (because after the week 24 of pregnancy, the infant feels pain). On the other hand, infants under six months experience greater pain due to the absence of nerve pathways responsible for pain reduction (3, 10, 19). Alternative methods are, therefore, preferred to avoid the imposed pain and stress by ET tube placement and also considering the fact that the use of the laryngoscope may cause dangerous complications such as severe blow leading to hypopharyngeal hole, pseudo diverticulum, hemorrhage, necrosis of the mucosa, vocal cord trauma, and laryngeal edema or dislocation of arytenoid cartilage (if the infant is awake, these complications will be even more severe) (20-22). Other hemodynamic complications due to the pain during intubation are: increases in the mean blood pressure to 33 mmHg and the heart rate to 30 pulses more than the base rate (which is due to the release of catecholamines and cortisol) and also changes in cerebral blood flow velocity (CBFV). These physio-hormonal changes may also lead to a sudden reduction in blood pressure and heart rate and even result in the stimulation of vagus nerve during intubation. It should be noted that although infants who are awake can resist intubation, this may lead them to experience increased cardiovascular instabilities. Nonetheless, these sudden changes in the heart rate and blood pressure of the infant as well as the increased need for oxygen may cause hypoxic-asphyxia, intraventricular hemorrhage (IVH), and intracranial hemorrhage (ICH). During ET tube placement, it has been observed that the increased pressure on the anterior fontanelle leads to intracranial pressure (ICP) (3). The basic treatment of NRDS is associated with surfactant and artificial respiratory support using various methods. NCPAP and MV are well known due to their effects on the reduction of mortality rate related to NRDS (23, 24). However, the early application of NCPAP and surfactant is effective in reducing the need for MV and can lead to fewer complications, shortened hospitalization time, and lowered additional costs of the hospital stay (1, 16, 25, 26). The early application of continuous positive air way pressure (CPAP) using surfactant therapy has been shown to improve outcome in infants with NRDS. The strategy of using only NCPAP in mild to severe NRDS remains 40 to 60 percent of patients in need of MV (12, 27, 28).

Several studies have attempted to demonstrate the great potential of INSURE method for early surfactant therapy followed by the application of NCPAP in reducing the need for MV (29, 30).

2. Objectives

The aim of this study was to evaluate the effectiveness of INSURE method followed by NCPAP in infants with NRDS hospitalized in NICU.

2.1. Background Surfactant

The pathogenesis of NRDS in the absence of surfactants was first described by Avery and Mead in 1959 (31, 32). Afterward, Enhorning and Robertson reported the improvement of the pulmonary hysteresis loop after surfactant deposition in the trachea of rabbit fetuses in 1972 (31, 33). In 1980, Fujiwara et al. showed the first clinical benefit of the use of surfactant in infants with NRDS (31, 34). Since then, several randomized controlled trials (RCTs) using 12 different revolutionary surfactant products have been carried out in infants (31).

2.2. Surfactant Therapy Dose

Some human studies related to surfactant pharmacokinetics have been published. Initial tests have shown that a starting dose above 200 mg/kg leads to faster production and more stable improvements in the oxygenation when compared to a dose below 100 mg/kg of poractant (grade 2A) (35). Other experiments have also demonstrated similar benefits of administering a high dose above 100 mg/kg of poractant (36, 37). In a recent study exploring surfactant pharmacokinetics in humans using carbon-13 labeling, Cogo et al. showed that administering a high dose above 200 mg/kg leads to a significantly longer half-life in comparison with a dose below 100 mg/kg of poractant (38).

3. Methods

3.1. Study Population

This is a cohort study. In 2012, the samples were collected from the NICU of Amir al-Momenin hospital affiliated to Semnan University of Medical Sciences and divided into two groups of 52 people. Taking into account the quantitative conditions of sample size with first type error (α) at 0.05 level and second type error (β) at 0.020 level (power 80%), the number of samples for each group was considered to be 54. The study groups were: INSURE treatment group and surfactant non-administration group.

Inclusion criteria were: gestational age of 26 to 37 weeks (birth weight of 1000 to 3000 g), RDS score > 8, and radiological signs of NRDS at the age ≥ 30 minutes at birth (Table 1). Respiratory distress syndrome (RDS) scoring system is an index designed to objectively assess the clinical severity of hyaline membrane disease, in which the intensity of 5 symptoms including cyanosis, retraction, grunting, air entry-make baby cry and listen to breath sounds while baby cries, and respiratory rate are scored as 0, 1, and 2. The score was measured after allowing the infant to stabilize for at least 5 minutes at a constant FiO_2 (suitable for the infant). An RD score above 8 is defined as moderate to severe dyspnea (39, 40) (Table 1).

Table 1. RDS Scoring

Clinical Symptoms	0	1	2
Number of respiration per minute	Less than 60	60 to 80	More than 80
Cyanosis	Not in ambient air	Not under the hood	Yes under the hood
Intercostal retraction	No	Moderate	Severe
Respiratory sounds	Good	Reduced	Not heard
Granting	No	Only with Stethoscope	Without Stethoscope

Exclusion criteria included absence of clinical symptoms or chest radiography without NRDS. Anesthetic preparation of neonates for endotracheal intubation consisted of the administration of intravenous atropine 20 μg/kg, intravenous fentanyl 3 μg/kg to 5 μg/kg (slow infusion), and intravenous succinylcholine 2 mg/kg.

3.2. Intervention

INSURE treatment group: For surfactant administration in this group, the infant's head was placed in a tracheal intubation state. The intubation was performed under direct laryngoscopy using endotracheal tube appropriate for the infant's weight. A syringe filled with surfactant heated to body temperature was attached to the feeding tube and placed inside the driven ET tube to 5.0 cm below the tip of the tube. Surfactant was then administered within 1 - 3 minutes. The surfactant administration was stopped if the heart rate fell below 100 b/min, oxygen saturation ($SPaO_2$) was below 80%, or there was cough or choking. After the infant's condition became stable again by applying bag-mask ventilation, the administration resumed. Following the surfactant administration, the infants received NCPAP of 4 - 8 cm H_2O through the ventilator. Subsequent surfactant administration was applied 12 to 24 hours after the first administration when $Fio_2 > 0.40$ was required for maintaining $SpaO_2 > 85\%$. The infants were intubated, and MV started if the infants under NCPAP had $SpaO_2$ below 85%, or if the analysis of arterial blood gases (ABG) showed $PaO_2 < 50$ mmHg, $PaCO_2 > 60$ mmHg, and pH < 7.2 while the infants were receiving $FiO_2 > 0.40$ (based on a/Ao_2 ratio <0.22). When $FiO_2 < 0.40$ mmHg, $PaO_2 > 50$ mmHg, and $PaCO_2 < 60$ mmHg were achieved, the infants under NCPAP were weaned from the device and placed in an Oxyhood (5-7 Li/Min O_2).

Surfactant non-administration group: Given that this method was implemented until 2008 and considering the hypothetical effects of surfactant on reducing the mortality rate, the samples for this group were selected on a retrospective basis; that is, the infants were first evaluated by examining respiratory distress records, and those with respiratory distress score of eight or more were included in the study. In addition, the infants in this group were matched with those in the case group in terms of birth weight, gestational age, and maternal steroid intake during pregnancy. The relevant data were extracted from medical records of patients and written in a form prepared for this purpose.

4. Results

In this study, the infants in the two groups of surfactant administration and surfactant non-administration were compared in terms of basic characteristics (Table 2) (viz., gender, gestational age, birth weight, and type of delivery). The findings showed that, out of 52 infants in each group, there were 29 males (56%) and 23 females (44%) in the group receiving surfactant, and 31 males (60%) and 21 females (40%) in the group not receiving surfactant. However, the difference between the groups was not statistically significant (P = 0.691). In addition, there was no statistically significant difference (P = 0.626) between the average birth weight of infants in the case group (1605 ± 479.6 g) and that of the control group (1559.2 ± 484 g). Out of the 52 infants in the case group, 11 cases (21%) had normal delivery, and 41 cases (79%) had cesarean delivery. In the control group, 17 out of 52 infants (33%) had normal delivery while 35 cases (57%) had cesarean delivery; no statistically significant difference was detected in this regard (p = 0.185). The mean gestational age was 31 ± 2.3 weeks in the case group and 31.4 ± 2.4 in the control group; the difference was not statistically significant (P = 0.357). Moreover, 12 cases in the first group (23.1%) and 10 cases in the second group (19.2%) had not received two doses of steroids before birth; a between-group difference that was not statistically significant (P = 0.215). After intervention, the infants in

both groups were compared in terms of clinical characteristics (see Table 3). It was found that the difference in the average duration of hospital stay in NICU was not statistically significant between the case and control groups (13.4 ± 10.1 and 11± 8.3 days, respectively, P = 0.215). Also, as indicated in Table 3, out of 52 infants in each group, 2.5 ± 7.6 in the case group and 2.2 ± 3.8 in the control group required mechanical ventilation. Although the mortality rate was not significantly different between the groups, the number of deaths was higher among infants receiving INSURE than those not receiving (Table 3). Nevertheless, no significant difference in chronic lung disease (CLD) and sepsis was observed between the two groups.

5. Discussion

NRDS is a progressive condition that threats neonates during the first hours and days of life. In more severe cases, it may require mechanical ventilation. Numerous complications of mechanical ventilation in infants (pulmonary air-leakage (PAL), intraventricular hemorrhage (IVH), CLD, etc.) have led to several studies on the administration of surfactant using INSURE method and the simultaneous use of NCPAP in the early hours of birth. Some of these studies have documented satisfactory results.

In terms of seven complications examined in this study (viz., pneumothorax, pulmonary hemorrhage, chronic lung disease, intraventricular hemorrhage, sepsis, and retinopathy), no statistically significant differences were observed between the case group receiving surfactant and the control group not receiving surfactant (P > 0.05). There were also no significant differences between the two groups in terms of the need for MV, length of hospitalization in NICU, and mortality rate (P > 0.05). In the cases in which the mother had received corticosteroids, a major constraint was incomplete documented information, especially with regard to some of the infants in the surfactant non-administration group (i.e., the control group). Given that the administration of corticosteroids 48 hours before delivery can affect the course of the disease, the missed data in this regard would lead to the interference with adequacy of group matching and introduction of bias into the results. The other notable point in the present study was the lack of POST NICU at the hospital, which in turn, led to a longer hospitalization of the infants of both groups in the NICU. Therefore, given the higher costs associated with special sections compared to ordinary ones, the accurate comparison of hospitalization in NICU was not possible.

Bohlin et al. conducted a descriptive, retrospective study at two centers in Stockholm, Sweden, to compare MV using surfactant, response-based therapy, and the outcome of infants with NRDS at gestational age of 27 to 37 weeks (N = 420) over a 5-year period before and after the introduction of the INSURE strategy at one of the centers of Karolinska Hnddinge in 1998. The results showed that applying INSURE reduced the number of infants requiring MV by 50% (P < 0.01) and led to the early administration of surfactant and a general increase in the use of surfactant. In addition, it was shown that the treatment based on the INSURE method improved oxygenation, and only 17% of infants required more than one dose of surfactant. However, in the current study, 15 infants (29% of infants in the case group) required more than one dose of Curosurf (a natural surfactant), and there was no difference between the two groups in terms of the need for MV (13).

In a randomized double-blind study, Reninger et al. examined the effects of surfactant administration using transient intubation in infants with gestational ages of 29 to 35 weeks with mild to severe NRDS requiring oxygen during NCPAP. The infants were randomly divided into a surfactant group involving intubation, surfactant administration, and immediate extubation (n = 52) and a control group in which there was no surfactant administration (n = 53). In the surfactant recipient group, 30 infants (58%) were male, 23 cases (44%) were born by cesarean delivery, and the minimum and maximum gestational age was 27 and 35.4 weeks, respectively (the mean gestational age of 32.4 ± 19 weeks). In the control group, 33 infants (62%) were male, 27 cases (51%) were born by cesarean delivery, and the minimum and maximum gestational age was 27.4 and 35.7 weeks, respectively (the mean gestational age of 32.1 ± 16 weeks). The minimum and maximum infants' birth weight was 855 g and 3555 g, respectively, with an average of 1853 g. The need for MV was 70% in the control group and 50% in the surfactant recipient group (P < 0.05). The surfactant recipient group had a lower Fio2 after the intervention. However, there were no changes in the overall consumption of surfactant, duration of oxygen therapy, length of stay in the hospital, and bronchopulmonary dysplasia. In the present study, the number of male infants was also higher than the number of females in both groups, and the mean gestational age (± standard deviation) was 31.4 ± 2.4 weeks in the surfactant recipient group and 31 ± 2.3 weeks in the control group. In both groups under study, the highest and lowest gestational ages were 37 and 27 weeks, respectively. The mean birth weight (± standard deviation) was 1605 ± 479.6 g in the case group and 1559.2 ± 484 g in the control group. The highest and lowest birth weights in the infants of both groups were 3000 and 1000 g, respectively. In the current study, the need for MV was 43.3% in the INSURE treatment group and 47.2% in the control group; the difference was not significant (P > 0.05). In terms of duration of hospitalization and bronchopulmonary dysplasia, no significant differences were detected

Table 2. Baseline Characteristics[a,b]

Variable		First Group (n = 52)	Second Group (n = 52)	Significance
Gender	Male	29 (56)	31 (60)	0.691
	Female	23 (44)	21 (40)	
Delivery	NVD	11 (21.15)	17 (33)	0.185
	C/S	41 (78.85)	35 (67)	
Birth Weight		1605 ± 479.6	1559.2 ± 484	0.626
Gestational Age, wk		31.4 ± 2.4	31 ± 2.3	0.357

[a]Values are expressed as mean ± SD or No. (%).
[b]First group underwent INSURE and then NCPAP; second group without INSURE.

Table 3. Frequency of Outcomes[a]

Variable	INSURE Group (n = 52)	Control Group (n = 52)	P Value
Need for mechanicalventilation	2.5 ± 7.6	2.2 ± 3.8	0.497
Pneumothorax	4 (7.7)	9 (17.3)	0.141
Duration of hospital stay (days) in NICU	13.4 ± 10.1	11 ± 8.3	0.215
IVH GRADE(1)	8 (15.4)	3 (5.8)	0.744
Pulmonary hemorrhage	10 (19.2)	7 (13.5)	0.597
CLD	2 (3.8)	0	0.495
Sepsis	2 (3.8)	0	0.495
PDA	17 (32.7)	25 (13)	0.517
Death	9 (17.3)	16 (30.8)	0.108

[a]Values are expressed as mean ± SD or No. (%).

between the two groups under study (P > 0.05) (4).

In Verder et al.'s study, preterm infants with mild to severe NRDS were randomly divided into NCPAP only-group (n = 33) and NCPAP plus surfactant group (n = 35). In the surfactant recipient group, the infants were transiently intubated, received Curosurf, and manually ventilated for two to four minutes. These infants were then extubated and exposed to NCPAP. Treatment failure involved the lack of extubation within one hour or re-intubation for ventilator treatment within five days. Indication of MV included decreased oxygen tension ratio to less than 0.15 or severe attacks of apnea or both. Subsequent surfactant administration was applied 12 and 24 hours later provided that the infants still required oxygen concentration greater than 60%. The NCPAP plus surfactant group particularly required MV to a lesser extent (15 out of 35 cases, 43%) than the NCPAP only-group (28 out of 33 cases, 85%) (P < 0.05). In addition, the results of the study showed IVH Grade 1 and 2 in five infants (14%), IVH Grade 3 or 4 in three infants (9%), pneumothorax in one infant (3.3%), and need for oxygen in 28 days after birth (CLD) in three infants (9%) of the surfactant recipient group. There were no cases of pulmonary hemorrhage or necrotizing enterocolitis (NEC), and there were no differences in the subsequent outcomes 28 days after birth in terms of mortality rate, intraventricular hemorrhage Grade 3 or 4, periventricular leukomalacia, or the need for oxygen. In the present study, as mentioned earlier, there was no significant difference between the two groups in terms of the need for MV. Moreover, IVH Grade 1 and 2 in nine infants (17.3%), IVH Grade 3 and 4 in two infants (3.8%), pneumothorax in four infants (7.7%), CLD in two infants (3.8%), and pulmonary hemorrhage in 10 infants (19.2%) were observed; the differences between the two groups under study were not, however, significant with respect to these complications (P > 0.05) (11).

In a retrospective study, Choi et al. compared the mortality rate of infants between surfactant pre-treatment group (control group) and surfactant post-treatment group (case group). The infants in the control group were selected from those born 1988 - 1991, while in the case group, the infants born between 1993 and 1996. Therefore, 4861 infants in the control group and 5430 infants in the case group were studied. Out of these infants, 204 in the control group and 414 in the case group were afflicted with NRDS. Surfacten was used as the surfactant of choice in this study. The mortality rate was similar in males and females, but the rate for the surfactant group (79%) was significantly lower than that for the control group (38%) (P < 0.05). In the present study, however, the mortality rate in the INSURE group was not significantly different from that of the control group (41).

In the above studies, the birth location of the infants under study was not mentioned. Birth at a hospital and transfer to another hospital can have negative effects on

the course of treatment due to dangers associated with transferring. Likewise, in the present study, out of nine infants in the surfactant recipient group who died, only three cases had been born in Amir al-Momenin hospital, i.e. the study location, and the rest had been referred from other hospitals. In contrast, out of the 16 infants in the control group who died, only two cases had been referred from other hospitals, and the rest had been born at the study hospital. This point might have affected the results of the present study when compared to those of previous studies. In addition, the type of surfactant used in the present study (viz., Curosurf) was similar only to the surfactant applied by Verder et al. Other factors that could be regarded as the sources of inconsistencies between the results of the current study and those obtained in the previous studies can be related to the fact that, in the present study, the control group was selected retrospectively, and the case group was selected prospectively. In addition, the treatment team as well as access to information was not equal in both groups.

Regarding that combination treatment regimen (simultaneous use of surfactant and CPAP) can bias the whole results, we recommend that a further study be conducted on the basis of the CPAP alone administration for control patients.

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Footnotes

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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