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The Effect of the Iranian Surfactant (Beraksurf) in the Treatment of Respiratory Distress Syndrome in Premature Neonates

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a type of lung development defect that is commonly seen in preterm births. Deficiency of pulmonary surfactant due to immaturity is the principal cause of RDS in premature infants. This study was conducted with the aim of Iranian surfactant (Beraksurf)'s effect in treating RDS in premature neonates.

Methods: In this study, all infants who were premature and had RDS were included in the study. Also, the infants were examined based on primary and secondary outcomes. Primary outcomes include the duration of need for nasal continuous positive airway pressure (NCPAP), number of surfactant administration, and secondary outcomes including bronchopulmonary dysplasia (BPD), pneumothorax, and pulmonary hemorrhage.

Results: A total of 162 neonates with a mean gestational age of 31.28 ± 2.58 weeks were evaluated. The 120 people (74.1%) used medicine only on the first day, 19 people on other days, and 23 people on the first and second day. Also, 141 children (87.6%) were discharged from the hospital and unfortunately, 20 children (12.4%) died. The prevalence of pneumothorax, BPD, and pulmonary hemorrhage was 1.8%, 1.2%, and 1.2% respectively. Also, 69.7% needed less than five days of mechanical ventilation and 30.2% needed more than 5 days of mechanical ventilation.

Conclusion: Considering getting better treatment results from taking Beraksurf, as well as fewer side effects and the fact that this drug is Iranian, and due to its easier access and cheaper price, we can pay more attention to the prescription of this drug.

Introduction

Respiratory distress syndrome (RDS) is common in preterm neonates, occurring in about 80% or more of those born at or < 28 weeks and in 98% of those with 24 weeks gestational age.[1] The most prominent clinical findings of RDS are chest retractions, tachypnea, nasal flaring, and grunting.[2] Many of these neonates develop RDS secondary to surfactant deficiency.[3] For premature neonates with RDS, delivery of surfactant via brief intubation has been the standard technique of surfactant administration.[1] Exogenous surfactant delivered to the trachea as rescue therapy is an important means of reducing the risk of adverse outcomes such as BPD, death, and air leak syndrome (ALS) and serious complications.[4] The guidelines showed that natural (animal-derived) surfactants are preferred over synthetic surfactants because the natural types are associated with a lower rate of adverse outcomes.[4] Respiratory protection, nasal continuous positive airway pressure (NCPAP), endotracheal mechanical ventilation (EMV), and surfactant prescription are the basis of management in RDS.[5]

The cause of surfactant deficiency in premature neonates is pulmonary immaturity and inadequate production. Pulmonary surfactant is a mixture of lipid and protein produced by type II alveolar cells that reduces alveolar surface tension and prevents atelectasis.[3] Endogenous surfactant can be isolated from lung lavage material by differential centrifugation, and analysis of surfactant from different mammalian species has shown a well-conserved composition. Approximately 85% of surfactant is composed of phospholipids. Phosphatidylcholine (PC) is the most abundant in about 75% of the total phospholipid fraction, and more than half of this phospholipid is represented by the saturated form of dipalmitoyl phosphatidyl choline (DPPC).[6] Beraksurf® is a pulmonary surfactant containing bovine lung extract which used for the treatment or prophylaxis of RDS in premature infants. Beraksurf manufactured as sterile, pyrogen-free intratracheal suspension and it should be administered intratracheally only. Beraksurf® with the generic name of Beractant is a generic form of a pulmonary surfactant named Survanta.[7]

The diagnosis of RDS is based on clinical symptoms with chest radiographic findings, and arterial blood gas (ABG) results. Radiographic findings of RDS are granular patterns of lung parenchyma with atelectasis and peripheral air bronchogram.[2]

Despite the increase in RDS cases, RDS-related infant mortality rates have decreased significantly in developed countries, but in resource-limited settings, RDS remains one of the most common causes of death among preterm infants.[8] Caihong Qiu et al., in a meta-analysis compared the efficacy of pulmonary surfactant in RDS in premature neonates. The relative risk of RDS in premature neonates with six different pulmonary surfactants including beractant (Survanta), poractant (Curosurf), surfactant A (Alveofact), lucinactant (Surfaxin), calfactant (Infasurf), and colfosceril (Exosurf) was analyzed. They concluded that other pulmonary surfactants were more effective in reducing mortality from RDS in preterm infants compared to bracteates. Surfactant A drugs seem to have the best effect in reducing mortality from RDS in premature infants.[9]

Therefore, the benefit of surfactant administration for the treatment of RDS is confirmed. Currently, surfactants are available in Iran under different brand names and there is a difference of opinion about their effectiveness. One of the well-known types of this drug in the Iranian market is surfactant with the Beraksurf brand name, which is significantly used in neonates with RDS. However, many studies have not been conducted to identify the efficacy and safety of this drug in infants with respiratory distress. Therefore, in this study, we decided to investigate the effect of Beraksurf in the treatment of RDS in premature infants. Further evaluations with longer follow-up duration are needed for evaluating the effect of Beraksurf.

Materials and Methods

Study population: This is a cross-sectional-analytical study that was performed on preterm neonates. All infants under 34 weeks were admitted to the NICU of Shahid Sadoughi Hospital in Yazd in 2021 and received Beraksurf.

Method: In this study, after the admission of infants with RDS in the NICU and evaluation of the infants in terms of the need for surfactant, as well as obtaining permission from the parents to use surfactant (Iranian Beraksurf), these patients were included in this study.

Dose of drug: Each dose of Beraksurf is 100 mg/kg or 4 mL/kg body weight at birth. This Beraksurf is from Teksima Karaj-Tehran company.[7] The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Beraksurf suspension into the endotracheal tube.

Inclusions in this study: All neonates who are premature (gestational age 34 weeks and less) and have RDS and have received surfactant administration.

Exclusion criteria: including infants with congenital pulmonary abnormalities, after the end of hospitalization, infants were examined based on primary and secondary symptoms and complications. The primary outcomes measured in these patients include the duration of ventilator use, CPAP duration and the number of surfactants used. Secondary outcomes included BPD, IVH, PDA and pneumothorax. In the end, after completing the required information, the results were entered into SPSS 22 software and analyzed (version 22, IBM Corporation, Armonk, NY).

Implementation method: The questionnaire related to the research for infants, which includes the entry and exit criteria, was completed by the children's assistant, and after collecting the questionnaires, it was first entered manually in the EXCEL software. For blinding, another researcher entered the data into SPSS software based on the entered information and analyzed it statistically. The results obtained for quantitative variables were expressed as mean and standard deviation (Mean ± SD) and for qualitative variables as frequency and percentage, and the comparison between qualitative variables was also done using the Chi-square test. A significance level of less than 0.05 was considered.

Results

The demographic characteristics, Apgar frequency and premature rupture of membranes (PROM) of the subjects are shown in Table 1.

Table 1. Demographic Characteristics of Preterm Infants

Characteristics	Beraksurf group (n = 162)	Total
Gender n (%)		162 (100%)
Male	83 (51.2%)	
Female	79 (48.8%)	
Gestational age (mean)	31.28 ± 2.58	161
Gestational age (weeks)		
26 - 29 weeks	47 (29.2%)	
30 - 36 weeks	114 (70.8)	
Birth weight, g	1446.39 ± 769.2	157
≤ 1000	43 (27.4%)	
1001 - 2000	96 (61.1%)	
≥ 2001	18 (11.5)	
Mode of delivery	n (%)	161
Normal vaginal delivery	67 (41.6%)	
Caesarean section	94 (58.4%)	
Apgar frequency		162
≤ 7	52 (32.1%)	
≥ 8	110 (67.9%)	
PROME	26 (16.1%)	161
Normal (Non-PROME)	135 (83.9%)	

PROM: Premature rupture of membranes

Table 2. Frequency of Day of Consumption of Drug

Frequency of day of consumption of drug	N = 162	%
Day 1	120	74.1
Day > 1	19	11.7
Two days	23	14.2

Finally, 162 neonates were included in this census study. Out of all the patients, 83 (51.2%) were male and 79 (48.8%) were female. The mean of gestational age was 31.28 ± 2.58 and mean of neonatal birth-weights in this study was 1446.39 ± 769.2. Also, 67 (41.6%) patients had a Normal vaginal delivery, and 94 (58.4%) had a cesarean section. In general, 52 neonates (32.1%) had an Apgar score of less than 7 and 110 neonates (67.9%) had an Apgar score of more than 8 at 5 minutes. No infant had a major congenital anomaly.

Table 3. Primary Outcomes

Variables	(n = 162) N (%)
NCPAP, day	
≤ 5	101 (62.7)
≥ 6	60 (37.3)
Duration of hospitalization (day)	N (%)
≤ 10	76 (46.9%)
≥ 11	86 (53.1%)
Discharge	141 (87.6)
Milk of mother	122 (73.3)
None of milk of mother	40 (24.7)

Consumption of drug and primary outcomes: 120 patients (3.7%) in the Beraksurf group started their treatment on the first day, and 19 (6.3%) received Beraksurf on the second day, and 23 people received Beraksurf on both days (Table 2). primary outcomes showed, that 101 (62.7%) patients needed NCPAP for ≤ 5days and 60 (37.3%) patients needed NCPAP for ≥ 6 days (Table 3).

Secondary outcomes and complications are shown in Table 4. In the Beraksurf group, the prevalence of pulmonary hemorrhage, BPD, pneumothorax, and mortality were 1.2, 1.2, 1.8, and 12.4%, respectively (Table 4).

Table 4. Secondary Outcomes (The Frequency of Complications and Mortality)

Variables	Beraksurf group (n = 162)
Pulmonary hemorrhage	1.2%
BPD, n (%)	1.2%
Pneumothorax, n (%)	1.8%
Mortality, n (%)	20 (12.4%)

BPD: Bronchopulmonary dysplasia

We also assess the need for NCPAP according to gestational age. The results showed that 116 neonates were <32 weeks' gestation and 47.7% of them needed NCPAP for more than 5 days. Also, 46 neonates were >32 weeks' gestation and only 13% of them needed NCPAP for more than 5 days, which shows that mature babies do not need NCPAP for a long time (Table 5).

Table 5. Determining and Comparing the Need for NCPAP According to Gestational Age

Need for NCPAP	≤ 5 days	> 5 days	Total
< 32 weeks' gestation	61 (52.6%)	55 (47.7%)	116
> 32	40 (87%)	6 (13%)	46
Total	101 (62.3%)	61 (37.7%)	162

Discussion

Respiratory distress syndrome (RDS) rapidly worsens if not treated in the first hours and will lead to an increase in infant mortality.[10] Also, RDS and Jaundice are the most common causes of hospitalization in neonates.[11,12] Surfactant replacement has been accepted as a standard procedure for the treatment of acute RDS in infants worldwide. Currently, two classifications of natural and synthetic surfactants are commonly used.[13,14] Although the administration of surfactants can be associated with side effects such as obstruction of the pulmonary hemorrhage, sepsis, pneumothorax, intracerebral hemorrhage, and as a result, mortality.[15] But on the other hand, it is very effective by improving oxygen supply and reducing the adverse consequences of acute RDS such as neurodevelopmental disorders.[16]

The results of our study on the effectiveness of Beraksurf in the treatment of RDS in preterm infants admitted to the NICU

are that among these 162 people, 49% were boys and 51% were girls. In our study, 101 patients (62.7%) required NCPAP for < 5 days and 60 (37.3%) required NCPAP for > 6 days. In our study, 69.7% required less than 5 days of mechanical ventilation and 30.2% required more than 5 days of mechanical ventilation. Also, 2 of 162 subjects (1.2%) had pulmonary hemorrhage. Also, in the previous study, we talked about the effect of budesonide with surfactant in the treatment of RDS, and in that study, the mortality rate was close to this study and was about 11.4%, which was not significant, and other complications were also not significant between the control and intervention groups.[17]

Nourollahi et al.,'s study is one of the similar studies in this field. They compared the effectiveness of Curosurf and Beraksurf in the treatment of RDS in premature infants. They concluded Beraksurf seems to be as effective as curosurf in premature neonates with RDS, but is less expensive than it. They did not mention the mortality rate of Beraksurf's group.[18] Najafian et al., compared efficacy and safety of two available natural surfactants in Iran including Curosurf and Survanta. They observed no significant difference in complications or mortality between those two groups; however, Curosurf was associated with less need of ET tube and NCPAP.[5] By separating the gestational age, in neonates who were less than 32 weeks compared to those who were more than 32 weeks, they needed less daily NCPAP, which is consistent with Najafian's study. In that study, neonates between 29 Up to 32 weeks, they needed less NCPAP than after 32 weeks (P = 0.008). In our work mortality rate was 12% that it was close to mortality rate of Najafian's study (10.7%). This mortality rate may be due to the fact that we conducted this study during the COVID-19 pandemic. Children with underlying conditions are at increased risk of severe COVID-19 related mortality than children without underlying illness.[19,20] The high mortality rate may be due to an unknown covid-19 infection. COVID-19 infection in infants has many complications, including cardiac complications.[21,22] Saeedi, et al., compared side effect of survanta and curosurf in decreasing mortality due to RDS in premature infants. They concluded that Survanta and Curosurf are similar in treatment of neonatal RDS. The mortality rate in Survanta group was 28% and in curosurf group was 26.6% that both of them is so higher than mortality rate in our study.[23] Their high mortality may be due to the fact that the study was conducted in 2008 and the equipment and neonatal care were not as advanced as they are now. Also, Mirzarahimi and Barak compared efficacy of Curosurf and Survanta in preterm infants with RDS. Their results showed in treatment of RDS in preterm infants each of two groups had similar side effects but the need for repeated doses in Curosurf group and need for ventilation in Survanta group is less than others.[24] Gharehbaghi et al., evaluated complications among preterm newborns treated with Beractant and Poractant Alfa. In their study, neonates who received Poractant had shorter duration of intubation than neonates treated with Beractant, without any difference in the duration of oxygen therapy or hospitalization. They concluded that there was no significant superiority of Poractant over Beractant.[25] Although our study showed a reduction in the need for mechanical ventilation in infants and relatively few complications, further studies are needed in this area. It is suggested to compare the effectiveness and side effects of Beraksurf with other surfactants available in Iran in future studies.

Conclusion

Considering that RDS is a common problem in premature neonates, there is a constant need for surfactants. Also, cheap and available surfactants are more preferable, so when prescribing surfactants, Beraksurf should be given more attention by doctors. In this phase of the clinical trial study, we examined the injection time, drug safety and side effects, as well as the effectiveness of Beraksurf. The need for mechanical

ventilation in Beraksurf group was low and the side effects were also acceptable. In this field, there is a need for more studies, especially comparison with other surfactants.

Conflict of Interest

Authors have no conflict of interest.

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Ethical Considerations

The present study was approved by Shahid Sadoughi University Ethics Committee (IR.SSU.MEDICINE.REC.1400.107).

Author's Contribution

Conceptualization, MH.L. and M.NS.; methodology, MH.L. and M.NS.; formal analysis, A.D. and MH.L.; investigation, A.D., MH.L., SR.M.; resources, A.D. and SR.M.; data curation, A.D. and SR.M.; writing original draft preparation, S.E.; writing review and editing, S.E., A.D.; supervision, MH.L. All authors have read and agreed to the published version of the manuscript.

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