

Comparison of two surfactant preparates derived from the same animal for the treatment of respiratory distress syndrome

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Abstract

Aim: Respiratory distress syndrome (RDS) is a lung failure that starts after birth. Because of deficiency of surfactants in alveoli, this becomes one of the most important causes of morbidity and mortality in preterm neonates. In this study, we tried to compare the outcomes of two types of natural surfactant, derived from same animal and aimed to manage the anxiety of clinicians while they are choosing the most appropriate preparate for RDS treatment.

Material and Methods: Newborns hospitalized in Baskent University Ankara Hospital Neonatal Intensive Care Unit between January 2017 and August 2018 and administrated with calfactant and beractant for RDS treatment were retrospectively examined.

Results: A total of 57 neonates were enrolled into the study. It was indicated that 38 (66.7%) of neonates were administered beractant and 19 (33.3%) were administered calfactant. We did not find any significant difference between beractant and calfactant groups, according to their genders, gestational weeks, their intubation situations, the duration of the oxygen requirement, antibiotic usages and the durations of mechanical ventilation. It was determined that calfactant-administered neonates needed statistically more repeat dose, than those in the beractant group ($p= 0.029$).

Conclusions: We examined two natural surfactant preparates derived from same animal. Calfactant which has some conflicting reports was newly introduced to our unit for RDS treatment. This study aimed to identify the most appropriate treatment modality for RDS. It would be more instructive to plan larger and more creative studies to examine possible differences among natural surfactant preparates.

Keywords: Beractant; calfactant; surfactant

INTRODUCTION

Respiratory distress syndrome (RDS) in newborns is a lung failure that starts after birth, which clinically gets worse within hours and days. Because of deficiency of surfactants in alveoli, this becomes one of the most important causes of clinical diseases and mortality, especially in preterm neonates. Moreover, RDS can be detected in term newborns and paediatric patients because of genetic lack of the surfactants, pneumonia, meconium aspiration syndrome, hypothermia and sepsis (1-3). The surfactant that is required for normal lung functioning starts to be produced after the 20th gestational week by Type 2 cells in the fetal lung. The production of surfactants starts after this week and increases as of 24th gestational week, thus preventing collapse by decreasing the surface tension at alveolar level and providing a

gas transaction (1). There have been many efforts to overcome RDS. According to many studies, it had been demonstrated that several surfactant preparates that had been administered through the intratracheal method had statistically significantly eased RDS and its complications (4). There are three natural surfactant preparates being used in Turkey; therefore, two of them have been approved by Food and Drug Administration (FDA) for treatment of RDS in newborns: calfactant (Infasurf; ONY, Inc., Amherst, NY) and beractant (Survanta; Abbvie, North Chicago, IL). Our unit has been using beractant since 2003 and calfactant since January 2017. Beractant (Survanta®) is a modified bovine minced lung surfactant extract, containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins. Each milliliter of beractant contains 25 mg of phospholipids. Its' recommended

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dosage is 100 mg phospholipid/kg (5,6). Calfactant (Infasurf®) is also derived from a bovine (calf) lung lavage surfactant extract that includes phospholipids, neutral lipids, and hydrophobic surfactant associated proteins B and C (SP-B and SP-C). Each milliliter of infasurf contains 35 mg total phospholipids. Its recommended dosage is 100 mg phospholipid/kg (7,8). Despite the fact that both preparations have similar contents, their phospholipid and apoprotein proportions are different. It was demonstrated that both surfactant prepares expedite the gas transaction in the lung, shorten the disconnection time from a mechanical ventilator and ease air leak syndromes (9). There are two strategies being used for administration of surfactants to a newborn lung (2,10). In the protective approach, a surfactant is being implemented within 15 minutes immediately after the birth. By contrast, according to the rescue approach, an endotracheal surfactant is administered for the neonate, who is connected to a mechanical ventilator and/or who needs 40% and more FiO₂ and/or whose PaO₂ values are low in the arterial blood sample and/or whose chest radiography is compatible with that of a chest with RDS (10). In our unit, we use the rescue approach for surfactant administration. In this study, we tried to compare the efficacy and outcomes of two different types of natural surfactant prepares and aimed to manage the anxiety of clinicians while they are choosing the most proper prepare for RDS treatment.

MATERIAL and METHODS

Newborns hospitalized in Baskent University Ankara Hospital Neonatal Intensive Care Unit (NICU) between January 2017 and August 2018 and administrated with calfactant and beractant for RDS treatment were retrospectively examined. The study included all newborns with RDS whose care conditions were similar and who were treated with surfactants, except the ones who had major congenital abnormalities, congenital heart and congenital pulmonary diseases and chromosomal defects. Demographic and clinical features of neonates and their mothers were retrospectively examined maternal status (maternal age, gestational diabetes, early membrane rupture, chorioamnionitis, eclampsia and preeclampsia, and antenatal steroid), gestational weeks, birth weight, state of delivery, gender, Apgar Scores of first and fifth minutes, usage of antibiotics, number of days of respiratory support, neonatal infections, air leak syndrome, repeat of surfactant, reintubation in first 72 hours after extubation, bronchopulmonary dysplasia (BPD), length of hospitalization, and mortality. The name of the surfactant prepare that was administered, if any presence of intubation and; if so, its duration, the presence of mechanical ventilator and; if so, its duration, FiO₂ level at postnatal 72nd hour and day of 7, mean airway pressure (MAP) at postnatal hour 72nd and day 7, oxygen requirement at their 28th postnatal day and 36th gestational week and early and late complications of RDS (BPD, necrotizing enterocolitis (NEC) (≥ 2 stage), intraventricular hemorrhage (IVH) (≥ 3

stage), retinopathy of prematurity (ROP) (eligible for laser photocoagulation) were recorded. We defined BPD in infants of modalities as early as respiration conditions were suitable. Repeat doses were given to babies whose MAPs were above 7 and/or FiO₂ is above 30% (15).

Statistical Analysis

Statistics SPSS 25 Version 25.0 (IBM Corp, Armonk, NY, USA) statistical pocket program was used for the evaluation of data. Mean \pm standard deviation and percentage and frequency values were used for the variables. The variables were evaluated after the control of preconditions of normalcy and homogeneity of variants (Shapiro–Wilk and Levene test). During the process of data analysis, for the comparison of two groups of independent 2 group t test (Student's t test), and if preconditions were not fulfilled, the Mann–Whitney U test was used. Categorical data were analyzed by Fisher's Exact Test and Chi-squared test. In the case that suggested frequency was below 20%, to include this frequency to the analysis, the evaluation was made by the Monte Carlo simulation method. Categorical data were analyzed by Fisher's Exact Test and Chi-squared test. In the case that suggested frequency was below 20%, to include this frequency to the analysis, the evaluation was made by the Monte Carlo simulation method "p<0,05" were acknowledged for statistical significance. The power analysis of the study is found to be 81.37%.

RESULT

During the study period, 353 newborns were hospitalized. A total of 57 neonates were enrolled into the study. The neonates were between 680 g and 3380 g (mean: 1885 g) and between 23–39 weeks of gestation (mean: 32 weeks). Boys were 66.7% of all newborns (38/57), and 33.3% neonates were girls (19/57). Fifty-six of neonates were born through cesarean section (98.2%). It was indicated that 38 (66.7%) of neonates were administered beractant and 19 (33.3%) were administered calfactant. We did not find any significant difference between groups, when we compared their genders, birth methods, gestational weeks, birth weights, fifth minute Apgar scores (Table 1). Apgar 1 median was 7 (6–9) [median (minimum-maximum)], and Apgar 5 median was 8 (6–10) [median (minimum-maximum)]. Apgar 1 and maternal age have revealed a statistically significant difference between groups ($p = 0.04$ and $p = 0.04$, respectively) (Table 1). No significant difference was determined between groups, on behalf of the gestational week and neonatal infections ($p = 0.90$ and $p = 0.38$, respectively). The examination of maternal status, as gestational diabetes, early membrane rupture, chorioamnionitis, eclampsia, and preeclampsia, antenatal steroid, also indicated no statistically significant differences between groups ($p > 0.05$). No statistically significant difference was found between groups, when compared according to their intubation situations and their durations the duration of the oxygen requirement, antibiotic usages and their durations, durations of mechanical ventilation ($p > 0.05$) (Table 1). In the case

where groups were compared for their 72nd hour and 1st of FiO₂ levels, there was no statistically significant difference (respectively, $p = 0.176$ and $p = 0.466$). A comparison of MAP levels at the 72nd hour and the 1st week for groups indicated no difference ($p = 0.255$ and $p = 0.345$, respectively). When comparisons were made between their oxygen requirements at the groups' 28th postnatal day (mild BPD) and 36th gestational week (moderate/severe BPD), no statistically significant difference was found between the groups ($p = 0.635$ and $p = 0.590$, respectively). No significant difference was found in terms of reintubation in 72 hours after extubation ($p = 0.565$) (Table 1). It was determined that calfactant-administered

neonates needed statistically more repeat dose than those in the beractant group ($p = 0.029$). Calfactant and beractant were compared according to early and late complications of surfactant deficiency. No difference was found air leak syndrome, BPD, NEC, and IVH, ROP ($p = 0.476$, $p = 0.776$, $p = 0.476$, $p = 0.254$, and $p = 0.990$, respectively). The length of hospitalization in the calfactant group was 28.4 ± 17.5 , whereas the same parameter was 30.1 ± 17.6 in the beractant group. No statistically significant difference was determined between the groups ($p = 0.31$). Mortality rates were the same in the two groups and indicated no significant difference (Table 1).

Table 1. The comparison of demographic and clinical features of beractant and calfactant groups

Demographic and clinical characteristics	Calfactant n=19	Beractant n=38	p
Gestational week, (weeks), ^a	31.4±3.2	32.4±3.5	0.290
Birth weight, (g), ^a	1793±705	1930±653	0.470
Intubation duration, (days), ^a	8.3±13	11.52±19.32	0.630
Mechanical ventilation duration, (days), ^a	9.42±10.71	13.58±19.02	0.380
Oxygen requirement, (days), ^a	16.74±19.52	20.47±23.99	0.560
Repeat dose surfactant, ^b	10 (52.6)	9 (23.6)	0.029*
Antibiotic duration (days), ^a	11±9.5	9.1±5.5	0.360
Mortality, ^b	1 (5.2)	2 (5.2)	0.455

* $P < 0.05$ was considered statically significant. ^a mean \pm SD, ^b n (%)

DISCUSSION

In this study, we demonstrated that there were no significant differences in demographic features and clinical outcomes of the calfactant and beractant groups. Both preparates were found to have the same effectivity, similar complications in percentages, and different repeat doses; calfactant-administered group was demonstrated to need more repeat doses. Many studies have proved that the natural surfactant preparates have similar efficacies, outcomes, and complications. Ramanathan compared different preparates and found no difference in efficacy between calfactant and beractant (16). Similarly, Trembath et al. examined animal-derived surfactant preparates and found no difference in BPD, NEC, IVH, air leak syndrome and mortality (13). All these results are comparable to our study; thus, all natural surfactant preparates have been demonstrated to have similar efficacies in the management of RDS and its complications. After finding similar efficacies among natural preparates, researchers tried to explain their economic outcome. Zayek et al. especially studied the pharmacoeconomic differences among calfactant and poractant alfa and determined an economic advantage for calfactant (17). Bloom et al. compared calfactant and beractant and established that the calfactant preparate was more efficient in the acute period of RDS (need for FiO₂ was decreased in first 48

hours and MAP was decreased) and had longer efficiency time than beractant (18). Bloom et al. continued their study by enrolling 749 infants in the prophylaxis trial and 1361 infants in the treatment trial and revealed no difference between calfactant and beractant in their repeat dose (19). Hastings et al. compared calfactant and beractant and found no statistically significant difference in dosage, FiO₂ level at the 72nd hour and complications. However, in the group that used calfactant as prophylaxis, the repeat dose was found to be much higher (20). One of the most recent studies compared three forms of natural surfactant preparates (poractant alfa, calfactant, and beractant) (21). Dilli et al. compared the lung ultrasonography (LUS) scores by surfactant types in preterms with RDS. They demonstrated that poractant alfa and beractant similarly diminished the need for oxygen in accordance to their LUS findings and seemed to be superior to calfactant. The rate of a repeat surfactant dose was also found to be higher in calfactant (22). Similarly, in our study, the repeated surfactant dose was found higher in the calfactant group. All forms of surfactant preparates are suitable in our hospital. They are alternately used according to the features of a patient's clinical situation and are administered by the same group of doctors using the INSURE method. During our experience, two surfactant preparates were equally as effective, with no side effects, but revealed that the calfactant group had a higher repeat

dose. Two preparates were derived from the same animal. They were both used in the same dosage (phospholipid/kg). However, one was the minced form (beractant), and the other one was the lavaged form (calfactant). The technical difference in derivation and combination of these two preparates, which were derived from the same animal (bovine), may be the cause of differences in studies trying to determine the efficacy and outcomes of the two preparates. We also speculate that different protocols and self-experiences of different clinics during treatment of preterms with RDS may alter the outcomes and efficacies of different surfactant preparates. The sample size of our study is small, thus making it hard to generalize the results. Prenatal protocols used by the Division of Perinatology of Baskent University's Ankara Hospital, for the risk of preterm labor, i.e., betamethazone administration, declined the overall RDS numbers among newborns in our NICU.

CONCLUSION

We examined two natural surfactant preparates: calfactant and beractant. Calfactant group was shown to need more repeat dose. It would be more instructive to plan larger and more creative studies to examine clinical effects and differences among natural surfactant preparates.

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