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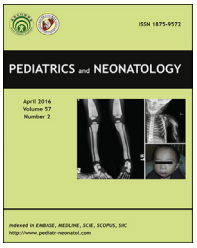

ORIGINAL ARTICLE

Comparison of Three Different Administration Positions for Intratracheal Beractant in Preterm Newborns with Respiratory Distress Syndrome

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Key Words
administration position;
beractant;
preterm infant;
respiratory distress syndrome

Background: The aim of this study was to compare the efficacy and adverse effects of various intratracheal beractant administration positions in preterm newborns with respiratory distress syndrome.
Methods: This study was performed on preterm newborns with respiratory distress syndrome. The inclusion criteria were being between 26 weeks and 32 weeks of gestational age, having a birth weight between 600 g and 1500 g, having received clinical and radiological confirmation for the diagnosis of respiratory distress syndrome (RDS) within 3 hours of life, having been born in one of the centers where the study was carried out, and having fractions of inspired oxygen (FiO_2) $\geq$ 0.40 to maintain oxygen saturation by pulse oximeter at 88–96%. Beractant was administered in four positions to Group I newborns, in two positions to Group II, and in neutral position to Group III.
Results: Groups I and II consisted of 42 preterm infants in each whereas Group III included 41 preterm infants. No significant differences were detected among the groups with regards to maternal and neonatal risk factors. Groups were also similar in terms of the following complications: patent ductus arteriosus (PDA), pneumothorax, intraventricular hemorrhage (IVH),

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chronic lung disease (CLD), retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), death within the first 3 days of life, death within the first 28 days of life, and rehospitalization within 1 month after discharge. Neither any statistically significant differences among the parameters related with surfactant administration, nor any significant statistical differences among the FiO_2 levels and the saturation levels before and after the first surfactant administration among the groups were determined.

Conclusion: In terms of efficacy and side effects, no important difference was observed between the recommended four position beractant application, the two position administration, and the neutral position.

1. Introduction

Respiratory distress syndrome (RDS) remains the most frequent cause of mortality and morbidity in preterm newborns. However, it is known that administration of exogenous surfactants improves alveolar oxygenation and reduces mortality and morbidity rates among preterm newborns with RDS.[1–4] Several types of surfactant preparations, including synthetic preparations, which are protein-free, and natural preparations, from bovine or porcine origin, have been used in the treatment of RDS.[5–9]

Beractant is a bovine-derived natural surfactant used in preventing and treating RDS in premature newborns. Survanta (AbbVie Inc., North Chicago, IL, USA) is the only beractant preparation administered worldwide. The Food and Drug Administration (FDA) has approved the administration of Survanta for prevention and treatment of RDS in newborns since 1991.[10] The manufacturing company acquired FDA approval for the product by defining the administration of the beractant preparation as follows: for a homogenous distribution of Survanta throughout the lungs, each total dose is divided into four quarter-doses, also known as aliquots (4 aliquots = 1 total dose). However, there are some difficulties concerning the administration of the surfactant in four positions. In the application of certain surfactant preparations, infants are not obliged to be in position.[10] In addition, the fact that surfactant can be administered in a neutral position has also established a tendency in neonatologists to apply surfactant in positions other than the four positions offered by the manufacturer. In different countries, many neonatologists use the beractant either in the two positions or in the neutral position, despite manufacturer's instructions. Although widespread in practicality, there are no data concerning the efficacy and diverse effects of the beractant application apart from those of the four positions in the early and late periods.

In this randomized controlled multicenter study, our aim was to compare the efficacy and side effects of beractant application in the four positions suggested by the manufacturer, in two positions, and in the neutral position in the early and late periods.

2. Methods

The following randomized controlled multicenter study was conducted in four different centers in Turkey. Preterm newborns were considered eligible for the study when they met the following inclusion criteria: being between 26 weeks and 32 weeks of gestational age, having a birth weight between 600 g and 1500 g, having received clinical and radiological confirmation for the diagnosis of RDS within 3 hours of life, having been born in one of the centers where the study was carried out, and having fractions of inspired oxygen (FiO_2) $\geq$ 0.40 to maintain oxygen saturation by pulse oximeter at 88–96%. Preterms with chromosomal defects, asphyxia, congenital heart and lung diseases, and those who had or needed chest compression or drug use in the delivery room, along with preterm babies who were delivered from mothers with membrane rupture for $>$ 2 weeks were all excluded from the study. The Institutional Ethics Committee of Inonu University, Malatya, Turkey approved the initiation of the study, and parental consent was obtained for all participants.

All newborns in the study were diagnosed with RDS both clinically and radiologically. Tachypnea ($>$ 60 breaths/min), retractions, nasal flaring, grunting, the need to maintain the oxygen saturation at $\geq$ 86% with $FiO_2 \geq 0.40$ in addition to the chest radiograph results with $\geq$ 2 Grade 2 RDS findings confirmed the RDS diagnosis. The classification of pulmonary X-ray findings for RDS included the following criteria: Grade 1, slight reticular (slightly granular) decrease in transparency of the lung with no certain difference from normal findings; Grade 2, soft decrease in transparency with an air–bronchogram overlapping the heart; Grade 3, gradual but strong decrease in transparency, as well as a blurry diaphragm and heart; and Grade 4, practically homogenic lung opacity.[11]

The patients were randomized into three different groups according to surfactant administration positions. In Group I, the surfactant was administered in four positions whereas it was administered in two positions in Group II, and in the neutral position in Group III (Figures 1–3). In Group I, the manufacturer's suggested positions were followed: head and body inclined 5–10° down with the head turned to the right; head and body inclined 5–10° down

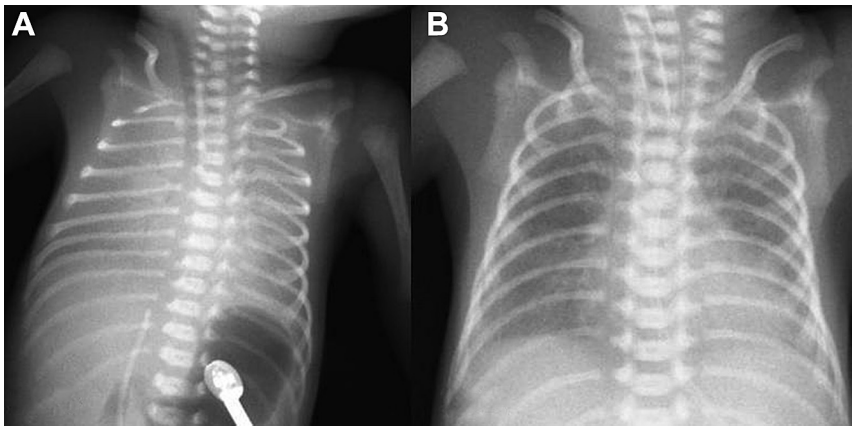

Figure 1 Chest X-rays (A) before and (B) after first surfactant administration in Group 1.

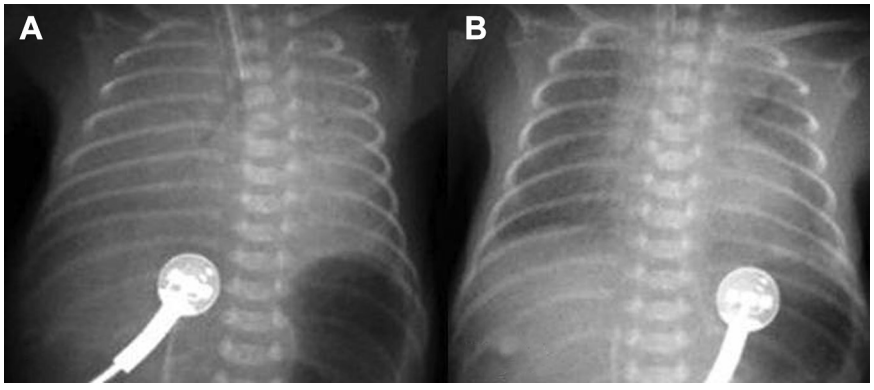

Figure 2 Chest X-rays (A) before and (B) after first surfactant administration in Group 2.

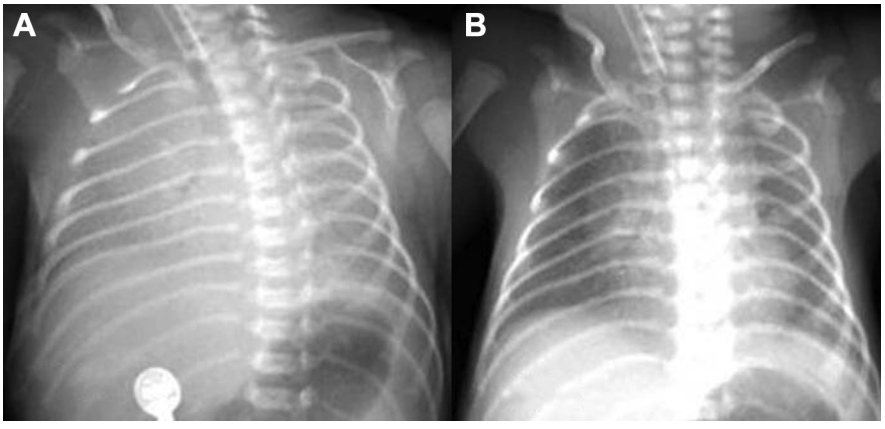

Figure 3 Chest X-rays (A) before and (B) after first surfactant administration in Group 3.

with the head turned to the left; head and body inclined 5—10° up while the head is turned to the right; and head and body inclined 5—10° up while the head is turned to the left. The two positions administered in Group II were as follows: head and body inclined 5—10° up with the head turned to the right and head and body inclined 5—10° up with the head turned to the left. Group III patients in the neutral position were positioned in supine position with head and feet level and in line and without turning the head sideways. According to the manufacturer's dosage suggestions, all patients in each group were administered a total dose of 100 mg of phospholipids/kg birth weight (4 mL/kg) divided into four quarter-doses. Beractant was taken into the disposable injectors with a large gauge needle (at least 20 G) without shaking. Following attachment of the injectors to 5 French end-hole catheters premeasured according to the lengths of endotracheal tubes of each baby, at the discretion of the clinician, the endotracheal tube

was suctioned before administering surfactant. The infant was allowed to stabilize before proceeding with dosing. In Group I, after injection of each quartile dose (1 mL/kg) of surfactant in 2 seconds, the catheter was rapidly withdrawn from the endotracheal tube, and the babies were manually ventilated for 30 seconds at a rate of 60 breaths/min via a hand bag with sufficient oxygen to prevent cyanosis. The same process was repeated for each position. After the last quarter dosing and 30 seconds of manual ventilation, the infant was extubated if the need for FiO_2 was $< 40\%$; if it was over, he/she was mechanically ventilated. Also in Group II, a quarter dose of surfactant was administered while the head of the baby was on the right in the same position defined above, and 30 seconds of manual ventilation was applied, keeping the position of the baby unchanged. After the second quarter dosing in the same position, the baby was ventilated for 30 seconds. The same procedure was followed for the left position of the head. Thirty seconds of ventilation was applied after the last quarter dosing, and continuous positive airway pressure (CPAP) or mechanical ventilation was chosen according to the need for FiO_2. In Group III, after each quarter dosing in a neutral position, the catheter was withdrawn and the baby was ventilated for 30 seconds. Following the last quarter dosing, as in the previous groups, the baby was ventilated for 30 seconds, and CPAP or a mechanical ventilator was applied. Additional doses (up to 3 doses) of beractant were given if the newborn required mechanical ventilator support or if $FiO_2 \geq 0.40$ was required to maintain the oxygen saturation at $\geq 86\%$ by pulse oximeter, plus radiological RDS Grade ≥ 3. The additional doses were administered in accordance with the positions in each group.

Details concerning patients' sex, gestational age, birth weight, Apgar scores, type of delivery, as well as maternal risk factors including maternal age, prenatal steroid administration, chorioamnionitis, multiple pregnancies, and preeclampsia were obtained. In addition, data such as total mechanical ventilation and CPAP duration, required surfactant doses, lowest saturation levels, heart rate during surfactant administration, FiO_2 and saturation levels before and after the initial surfactant applications, RDS grades in chest X-ray, and total hospitalization duration for all infants were recorded. The groups were also compared for the following complications until 1 month after their discharge: patent ductus arteriosus (PDA), pneumothorax, intraventricular hemorrhage (IVH), chronic lung disease (CLD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), death within the first 3 days of life, death within the first 28 days of life, and rehospitalization within 1 month after discharge.

Recorded CLD was confirmed using the National Institute of Health diagnostic criteria for CLD.[12] Clinical findings of systemic infection with positive blood culture helped to diagnose neonatal sepsis. In addition, cranial ultrasonography was used to detect IVH, and grading was carried out using Papile's classification.[13] Patent ductus arteriosus (PDA) was considered clinically significant if a defect was confirmed by echocardiogram with ductal size > 2 mm and a left atrial diameter/aortic root ratio of > 1.5 mm together with left ventricular enlargement. NEC was also among diagnosed problems; NEC was classified according to Bell's[14] criteria. ROP was confirmed by following the international classification.[15]

Only conventional ventilation was used in this study. The ventilator strategies and initiating and weaning procedures were standardized. The standard initiating settings for mechanical ventilation were as follows: peak inspiratory pressure (PIP) of 15–20 cmH_2O, positive end expiratory pressure (PEEP) of 4–6 cmH_2O, flow rate 6–8 L/min, ventilator rate 30–40/min, and an aspiratory/expiratory ratio of 1:2. The weaning was started when the infant required FiO2 < 0.30, and the patient was able to cope with satisfactory blood gases at a flow rate of < 20/min and PIP ≤ 15 cmH_2O once clinically and radiologically stable.

A descriptive analysis was performed for demographic and clinical characteristics of the patients. For nonparametric values such as the lowest saturation rate during administration of surfactant and the saturation level before surfactant application, we used the Kruskal-Wallis test. For the other parametric values, one-way analysis of variance test was used. Pearson's Chi-square test was performed for the categorical variables. All statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA), and the statistical significance was set at $p < 0.05$.

3. Results

In this study, 132 preterm newborns were included from January 2013 to February 2014 at four different centers in Turkey. Seven of these infants were immediately excluded from the study because of misdiagnosis or inappropriate surfactant administration methods (Figure 4). Finally, a total of 125 preterm newborns with RDS were included. Groups I and II included 42 infants in each, whereas Group III included 41 infants. The details concerning patients' characteristics are shown in Table 1. There were no significant differences among the three groups with regards to gestational age, birth weight, sex, type of delivery, Apgar scores, antenatal steroid administration, RDS grade, positive pressure ventilation requirement at delivery room, maternal age, and some maternal risk factors.

Similarly, there were no notable differences among the groups in terms of surfactant application-related issues and ventilation support needs (Table 2). Any serious complications such as pneumothorax, need for resuscitation, or perforation in the trachea or the esophagus in any of the groups during the surfactant administration process were recorded. Comparing the extubation success rates in the first 72 hours of the operations, we did not observe any significant difference ($p = 0.88$).

The first 3 days and overall mortality rates were similar in the three groups (Table 3). Other follow-up outcomes including hospitalization duration, NEC, CLD, CLD-free survival, ROP, Grade 3–4 IVH, PDA, sepsis, pneumothorax, pulmonary hemorrhage and rehospitalization rates within the 1st month after discharge were also similar in the three groups (Table 3).

4. Discussion

Throughout our study, we found no significant differences with regards to the administration of the beractant among

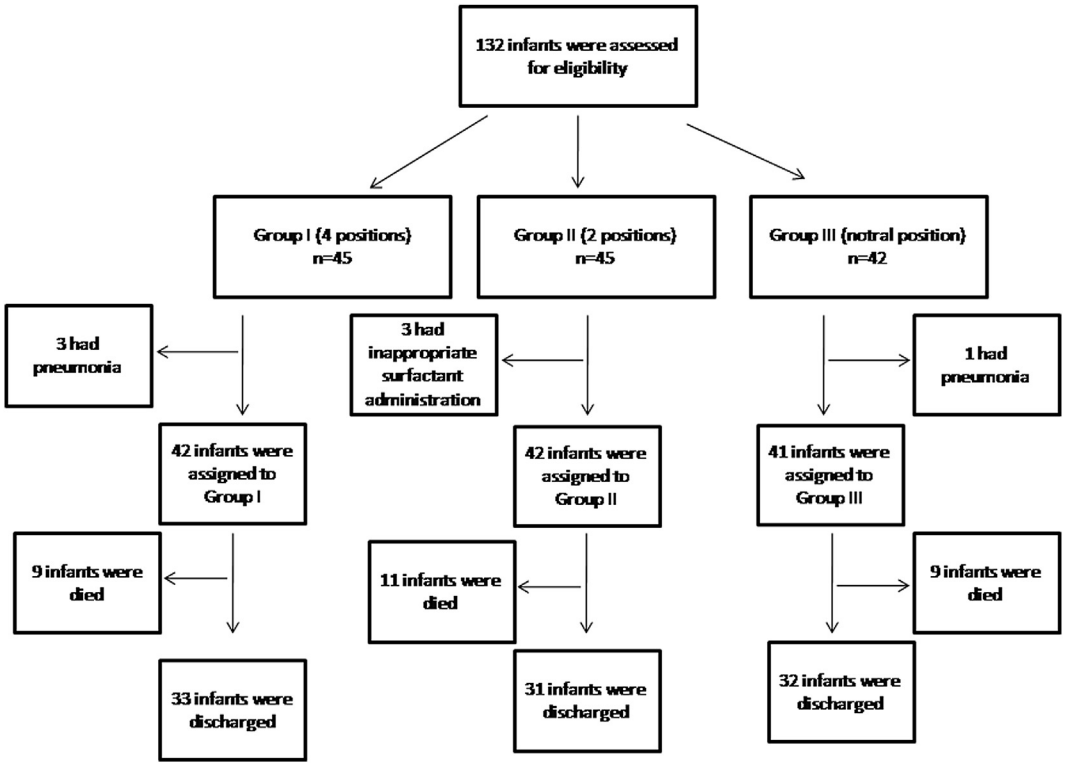

Figure 4 Flow diagram of the patients included in the present study.

the four positions as recommended by the manufacturer, the two positions, and the neutral position in terms of application, efficacy, and possible complications in the early and late periods.

The main idea behind the four positions included in the manufacturer's instructions is to get the surfactant to as many alveoli as possible. The four position administration allows the fluid to come into contact with the upper and lower quadrants of the lungs, and the right and left lobes.[16] It is assumed that the gravity will help the surfactant to be redistributed between the two lungs after the instillation. In other words, this method is intended to facilitate the surfactant to access the various lobes of the lungs. Moreover, these were the positions validated during the clinical trials for FDA approval of the drug. AbbVie (Chicago, IL, USA), the manufacturing company or independent researchers have not conducted any clinical trials to test other positional permutations since then. Current clinical recommendations on the positioning of infants during surfactant instillation of beractant vary according to the

Table 1 Demographic characteristics of the patients.

	Group I $n = 42$	Group II $n = 42$	Group III $n = 41$	p
Gestational age (wk)	28.6 ± 1.81	28.5 ± 1.73	28.1 ± 1.68	0.27
Birth weight (g)	1099 ± 225	1143 ± 220	1068 ± 158	0.51
Male	24 (57.1)	23 (54.8)	18 (43.9)	0.43
Caesarean section	34 (81)	34 (%81)	30 (73.2)	0.61
Apgar score at 1 min	4 (2–7)	4 (2–8)	4 (2–7)	0.39
Apgar score at 5 min	7 (5–9)	7 (5–9)	7 (5–9)	0.84
Antenatal steroid use	22 (52.4)	21 (50)	19 (46.3)	0.85
Number of surfactant administration	1.35 ± 0.61	1.35 ± 0.57	1.34 ± 0.57	0.98
Maternal age (y)	27 ± 5.1	27.1 ± 6.3	28.8 ± 5.3	0.19
Preeclampsia	11 (26.8)	13 (31)	11 (26.8)	0.87
PPV in delivery room	15 (35.7)	12 (28.6)	19 (46.3)	0.24
RDS grade	2.35 ± 0.93	2.57 ± 0.83	2.58 ± 0.89	0.39

Data are presented as n (%), median (range), mean ± SD.
PPV = positive pressure ventilation; RDS = respiratory distress syndrome.

Table 2 Surfactant administration related primary outcomes.

	Group I	Group II	Group III	*p*
< 100/min pulse during surfactant administration	4 (9.5)	5 (11.9)	4 (9.8)	0.92
Minimum sPO_2 during surfactant administration (%)	77.7 ± 6.7	78.2 ± 7.5	80.4 ± 7.1	—
Endotracheal reflux of surfactant	4	5	5	0.72
FiO_2 before surfactant administration	59 ± 23	57 ± 18	56 ± 25	0.67
FiO_2 after surfactant administration	50 ± 13	49 ± 14	46 ± 12	0.30
FiO_2 difference (before & after surfactant administration)	10.1 ± 6.8	7.5 ± 6.3	7.6 ± 5.9	0.18
sPO_2 before surfactant administration	86.9 ± 4.3	87.7 ± 4.7	88.7 ± 4.4	—
sPO_2 after surfactant administration	91.1 ± 3.1	92.1 ± 3.2	92.4 ± 2.8	0.58
sPO_2 difference (before & after surfactant administration)	3.7 ± 2.9	4.3 ± 3.1	4.8 ± 3	0.55
FiO_2 on the 3rd day	43 ± 16	42 ± 14	44 ± 16	0.97
sPO_2 on the 3rd day	92 ± 2.8	92.5 ± 2.8	93 ± 2.9	0.35
Extubation success within 72 h	27 (64.3)	29 (69)	28 (68.3)	0.88
Total CPAP duration (h)	110 ± 132	103 ± 96	117 ± 107	0.63
Total mechanical ventilation duration (h)	72.8 ± 118.1	76.3 ± 99.6	69.5 ± 86.5	0.31

Data are presented as *n*, *n* (%) or mean ± SD.
CPAP = continuous positive airway pressure; FiO2 = fraction of inspired oxygen; sPO_2 = saturation of peripheral oxygen.

manufacturer. There are only a few publications that support other clinical practices, and the volume of published material that compares the four positions with other positions is very small.

A study by Zola et al[17], the sole study so far to compare the suggested four positions with other positions in newborn infants, relates the beractant administration experiments in infants with RDS through a catheter inserted into the endotracheal tube. In this research, infants were positioned in accordance with three different approaches: "in two positions along with the removal of the infant from the ventilator;" "in two positions and without the removal of the infant from the ventilator;" and in the manufacturer-recommended four positions.[17] The results of the study showed no significant differences among the groups with regards to the infant clinical outcomes (ventilation requirements, oxygenation, mortality, and the incidence of pulmonary air leaks) in the first 72 hours of life.[17] Applying the surfactant in the neutral position in a separate group and administering the surfactant in four fractional doses in each group constitute the most notable differences between the authors' analysis and the present study. However, since there were no significant differences among the groups after the application of the surfactant in the latter, it is safe to assume that both studies support the effective and accurate usage of the surfactant in other methods of positioning other than the four position administration recommended by the manufacturer.

It has been argued that surfactant application on neonatal piglets in four different positions "improved the outcome because of the rapid distribution of intratracheally administered surfactant to the lungs".[16] Davis et al[16] used radio-scintiscanning to determine the initial movement of a bovine surfactant labeled with Tc99m into the lungs of piglets with RDS. The bovine surfactant was instilled as a single intratracheal dose followed by distributional assessments for 30 minutes.[16] It was observed that the surfactant was rapidly and symmetrically distributed to

Table 3 Surfactant administration related secondary outcomes.

	Group I	Group II	Group III	*p*
Total hospitalization duration days	46.8 ± 23.2	44.2 ± 18.1	55.1 ± 25.4	0.09
Total mortality	21.4	26.2	22	0.85
Mortality within the 1st 3 days	4.8	4.8	4.9	1
Necrotising enterocolitis	9.8	9.8	9.8	0.99
Chronic lung disease	14.3	16.7	17.1	0.93
CLD-free survival	69	64.3	63.4	0.84
ROP	10	7.1	7.3	0.90
Grade 3–4 IVH	4.8	2.4	0	0.62
PDA	14 (33.3)	13 (31)	11 (26.8)	0.42
Sepsis	9.5	4.8	7.3	0.70
Pneumothorax	10.4	14.3	9.8	0.55
Pulmonary hemorrhage	7.1	9.5	7.3	0.90
Rehospitalization within 1 month after the discharge	7.1	4.8	9.8	

Data are presented as % or *n* (%).
CLD = chronic lung disease; IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.

all lung portions after instillations. Thus, the authors concluded that the surfactant lowered surface tension in proportion down to its interfacial concentration. At this point, the addition of the surfactant to one region creates surface tension gradients relative to other portions, and the spreading surfactant is continually directed to the lung periphery.[16] We speculate that interfacial spreading effect may facilitate the rapid delivery of the beractant into aerated lungs regardless of the position of administration.

A study by Broadbent et al[18] on rabbits with RDS showed that positioning during surfactant application did not actually affect the distribution of the compound in the lungs and "that keeping the chest in the horizontal position might result in most even distribution of the surfactant in the two lungs". Another study that compared surfactant administration in a single dose with surfactant administration through slow tracheal infusion on rabbits showed that bolus application provided more accurate results.[19] A similar study concentrated on the different effects of surfactant application in three groups of sheep with RDS that were given surfactant in four positions with four boluses, two lateral positions with two boluses, and a 30 minute infusion. The study confirmed the surfactant distribution in the lungs in the groups that underwent bolus surfactant administration in two positions and in four positions without any significant difference among the bolus groups.[20] Taking all these animal-based tests into consideration, one may conclude that positioning in surfactant administration does not really have an effect on the surfactant distribution in the lungs while bolus applications are visibly more efficient compared to the infusion of the compound. That is also why the surfactant manufacturers, without any exceptions, instruct administration of the surfactant in bolus placements (all in a single dose, or the total dose in 2 or 4 aliquots) in several positions such as four position administration (Survanta), two position administration (Infasurf), or without any specific positioning (Curosurf).

The Fetus and Newborn Committee of the Canadian Pediatric Society guideline concluded that there was no evidence to support the practice of placing the infant in multiple different positions during the administration of surfactant.[21] The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn has similarly concluded that there is not sufficient evidence to recommend an optimal number of fractional doses of surfactant or what body position is best when surfactant is administered.[22] However, health care professionals have tried other computations of body positions over the years to find out which works best for their individual units. In Turkey, there are different approaches to positioning the infants during the administration of Survanta, one of the two accessible surfactants in the country. The common practice in Turkey is to place the surfactant intratracheally in two different positions or in neutral position with four equal aliquots. However, the present study, based on the data from four different centers in the country, has clearly shown that there are no significant differences among the three positioning approaches in beractant applications.

Surfactant administration procedures may be complicated and require the supervision of clinicians experienced in tracheal intubation, ventilator practices, and management of preterm infants. The most commonly reported complications include transient airway obstruction, bradycardia, oxygen desaturation, and pulmonary hemorrhage.[22–24] Throughout the study, we observed bradycardia (< 100 pulse/min) in approximately 10% of our patients from all three groups with an 8–10% decline in their saturation of peripheral oxygen (sPO_2) levels, although we did not need to apply chest compression or adrenalin upload in any of these patients. Furthermore, we did not find any relation between administering the beractant in different positions and surfactant placement-related complications.

Surfactant application decreases mortality and morbidity rates in RDS.[25] It has also positive results in many parameters like pneumothorax, pulmonary interstitial emphysema, and hospitalization duration.[3,22,26] Although CLD frequency has unexpectedly increased compared to the periods before surfactant administration, this increase has opened the way for high levels of life expectancy in younger infants, and so for more healthy infant discharges from hospitals with CLD. As far as these results are concerned, numerous comparative studies conducted with different surfactants have come up with various results.[6,8,27,28] Here, it is beneficial to keep in mind that beractant administration, similar to other surfactant compounds, reduces morbidity and mortality in infants with RDS or premature infants. However, there is not enough evidence with respect to the efficacy of administration methods other than the ones offered by the manufacturers on morbidity and mortality rates. Our study has shown no differences among the various beractant administration practices mentioned above with regards to mortality, mechanical ventilation and CPAP duration, hospitalization duration, rehospitalization within 1 month after the discharge, and prematurity- or RDS-related complications like NEC, CLD, ROP, IVH, and pneumothorax.

In conclusion, our study found no significant differences among the administration of the beractant in preterm infants with RDS in four positions as recommended by the manufacturer, two positions, and the neutral position in terms of effectiveness and adverse effects. Therefore, instead of relying solely on the manufacturer-instructed four positions, administering the beractant in two positions and in neutral position is equally reliable and safe, not to mention easier and more practical.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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