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RESEARCH

Cost-effectiveness comparison of three different natural surfactant preparations in the treatment of preterm infants with respiratory distress syndrome

Pretermlerde respiratuvar distres sendromu tedavisinde kullanılan üç farklı doğal surfaktan preparatının maliyet etkinliğinin karşılaştırılması

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Abstract

Purpose: This study aimed to assess the cost-effectiveness of three natural surfactants by analyzing their initial impact on respiratory and blood gas variables and their associated costs.

Materials and Methods: This study included preterm infants with respiratory distress syndrome (RDS) born before the 32nd gestational week who received exogenous surfactant replacement therapy in a tertiary neonatal intensive care unit (NICU) between September 2019 and December 2022. Data from 985 patients were retrospectively obtained from medical records.

Results: Among the enrolled patients, 575 received Poractant Alfa (58%), 343 received Beractant (35%), and 67 received Calfactant (7%). No significant differences were observed between the surfactant groups in terms of short-term pulmonary improvement, complications, clinical outcomes, or costs. However, in subgroup analysis based on birth weights, Calfactant (331.57±162.54 $) was found to be significantly more cost-effective than Beractant (507.50±175.50 $) and Poractant Alfa (472.44±93.73 $) for infants weighing 750-999 grams. Furthermore, for infants weighing 1000-1499 grams, both Beractant (497.47±168.55 $) and Calfactant (531.54±293.20 $) were significantly less costly than Poractant Alfa (669.36±265.23 $).

Conclusions: This study demonstrated comparable short-term respiratory improvements, complications, and clinical outcomes among surfactant groups, emphasizing the potential influence of cost on surfactant choice. A novel model for selecting surfactant preparations based on birth weights was proposed, suggesting the use of Calfactant for infants weighing 750-999 grams and considering the use of Poractant Alfa for infants weighing 1000-1499 grams.

Öz

Amaç: Bu çalışma, üç doğal surfaktanın maliyet-etkinliğini, respiratuvar ve kan gazı değişkenleri üzerindeki başlangıç etkileri ve ilişkili maliyetleri analiz ederek değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Bu çalışmaya, Eylül 2019 ile Aralık 2022 tarihleri arasında üçüncü basamak yenidoğan yoğun bakım ünitesinde (YYBÜ) eksojen surfaktan replasman tedavisi almış, 32. gebelik haftasından önce doğmuş respiratuvar distres sendromu (RDS) tanılı preterm bebekler dahil edilmiştir. 985 hastaya ait veriler tıbbi kayıtlardan retrospektif olarak elde edilmiştir.

Bulgular: Çalışmaya dahil edilen hastaların %58'i (n=575) Poraktant Alfa, %35'i (n=343) Beraktant ve %7'si (n=67) Kalfaktant almıştır. Surfaktan grupları arasında kısa dönem pulmoner iyileşme, komplikasyonlar, klinik sonuçlar veya maliyetler açısından anlamlı bir fark gözlenmemiştir. Ancak, doğum ağırlıklarına göre yapılan alt grup analizinde, 750-999 gram ağırlığındaki bebeklerde Kalfaktant'ın (331,57±162,54 $), Beraktant (507,50±175,50 $) ve Poraktant Alfa'ya (472,44±93,73 $) göre anlamlı şekilde daha maliyet-etkin olduğu bulunmuştur. Ayrıca, 1000-1499 gram ağırlığındaki bebeklerde Beraktant (497,47±168,55 $) ve Kalfaktant'ın (531,54±293,20 $) Poraktant Alfa'ya (669,36±265,23 $) göre anlamlı şekilde daha düşük maliyetli olduğu görülmüştür.

Sonuç: Bu çalışma, surfaktan grupları arasında benzer kısa dönem respiratuvar iyileşme, komplikasyonlar ve klinik sonuçlar gözlemlendiğini, ancak maliyetin surfaktan seçiminde potansiyel olarak önemli bir rol oynayabileceğini göstermiştir. Doğum ağırlıklarına dayalı surfaktan seçimi için yeni bir model önerilmiştir. Buna göre, 750-999 gram ağırlığındaki bebekler için Kalfaktant'ın, 1000-1499 gram ağırlığındaki bebekler için ise Poraktant Alfa'nın tercih edilmesi önerilmektedir.

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Keywords:. Premature infants, neonatal respiratory distress syndrome, pulmonary surfactants, cost effectiveness

Anahtar kelimeler: Prematüre bebekler, neonatal respiratuvar distres sendromu, pulmoner surfaktanlar, maliyet etkinliği

INTRODUCTION

Respiratory distress syndrome (RDS) is a common pulmonary disorder among preterm infants. As gestational age decreases, it becomes increasingly common and challenging to manage. The basic pathology of this disease is characterized by insufficient surfactant biosynthesis due to the immaturity of type 2 pneumocytes[1]. In addition to invasive and non-invasive respiratory support techniques, the administration of exogenous surfactants is a well-established and frequently employed intervention for RDS. Improvement in alveolar surfactant deficiency, alveolar-capillary gas exchange, and respiratory effort began shortly after surfactant administration. Consequently, RDS severity and mortality are generally reduced[2,3].

Although both artificial and natural surfactant preparations are available, natural surfactants are preferred owing to their superior efficacy[4]. The Food & Drug Administration (FDA) has approved three commercial animal-derived natural surfactant preparations, namely Beractant (Survanta®; AbbVie Inc, Chicago, Illinois), Calfactant (Infasurf®, ONY Inc., Amherst, NY, USA), and Poractant alfa (Curosurf®, Chiesi Farmaceutici SpA, Parma, Italy).

No significant differences in clinical efficacy were observed between the preparations. Currently, studies are being conducted to evaluate the effectiveness of surfactant preparations. There are uncertainties, especially regarding the short-term effects following surfactant application. Clinicians using surfactants have concerns that they believe are due to the application volumes, contents, and application methods of surfactant preparations. Therefore, the short-term effects and side effects of natural surfactant preparations need to be investigated [3,4].

In addition, conflicting results have been reported in the few studies evaluating the cost-effectiveness of surfactant. The general clinical approach is to use the clinically effective surfactant preparation in the short and medium term rather than the surfactant preparation with the lowest cost. The search for the most effective surfactant preparation at the lowest cost and with the fewest side effects must continue. Therefore, financial burden is a forthcoming point in deciding which preparation to choose, particularly in low-income and developing countries. However, there is a lack of studies evaluating their cost-effectivities, and the findings are controversial[3,4].

The hypothesis of our study is that some surfactant preparations may be cost-effective according to birth weight in premature infants. Our results may provide advantages to clinicians in surfactant selection, especially in low-income countries. The objective of our investigation was to evaluate the cost-effectiveness of these three distinct natural surfactants by analyzing their short-term impact on respiratory and blood gas variables as well as their associated expenditures.

MATERIALS AND METHODS

Study design

This study included preterm infants with RDS who were born before the 32nd gestational week (GW) and received exogenous surfactant replacement therapy in our tertiary neonatal intensive care unit (NICU) between September 2019 and December 2022. We included patients born in our tertiary center and discharged from our NICU as well as those who died in our NICU. Those born in another health center and transferred to our NICU, those transferred from our NICU to another NICU for continuation of treatment, and those still under treatment during the study period were excluded from the study. All data were obtained from hospital medical records and evaluated retrospectively. To ensure the reliability of the records and to protect the privacy of the patients, all data were kept confidential and not shared anywhere. All stages of the study were carried out by two specialist physicians. The same treatment protocols were applied to all patients throughout the study period.

Patients with major congenital anomalies, surfactant protein B deficiency, congenital lung anomalies, who received repeated doses of different surfactant preparations, who did not receive surfactant, or who died in the delivery room were also excluded. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and

was approved by Ankara Bilkent City Hospital No. 2 Clinical Research Ethics Committee (date: 07.06.2023 and number: E2-23-3710). Informed consent was obtained from parents or legal guardians of the participating children.

Procedure

The retrospective analysis encompassed the collection of patient data from medical records, incorporating variables such as gender, GW, birth weight, mode of delivery, maternal age, maternal morbidities (including but not limited to Diabetes mellitus (DM), preeclampsia, chorioamnionitis), antenatal steroid usage, APGAR scores at 1st and 5th minutes, acute phase reactants (C-reactive protein (CRP), interleukin (IL)-6), additional medical conditions associated with prematurity (such as Early and late onset sepsis (EOS and LOS), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD)), duration of days on supplemental oxygen, days on invasive and non-invasive ventilation support, pulmonary complications (including but not limited to pneumothorax, pulmonary hemorrhage), time to the first surfactant administration, number and type of surfactants, respiratory support parameters (positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), mean airway pressure (MAP), fraction of inspired oxygen (FiO2), oxygen saturation (SaO2)), and blood gas parameters (power of hydrogen (pH), partial pressure of carbon dioxide (pCO2), bicarbonate (HCO3), base deficit (BD), lactate) before surfactant administration, as well as at 1st and 6th hours post-surfactant treatment. Other recorded metrics included the length of the NICU stay and mortality rates. Furthermore, the cost associated with the administered surfactants was meticulously calculated and documented in United States dollars (USD).

Definition of premature morbidities

Infants with a birth weight below the 10th percentile for gestational age were designated as small for gestational age (SGA)[5]. Patients with positive blood culture growth within the first 72 hours were defined as having EOS, whereas those with positive blood culture growth obtained after the 72nd hour were considered as having LOS[6]. Individuals with increased blood flow in their ductus arteriosus that requires medical treatment were classified as hemodynamically significant PDA patients[7]. According to the Volpe classification, patients with Stage 3 intraparenchymal bleeding were identified as having severe IVH[8]. Those requiring more than 21% FiO2 or respiratory support at or after postnatal week 36 or at discharge were evaluated as having moderate/severe BPD[9]. Premature infants with retinopathy treated with laser or intravitreal therapy were categorized as having severe ROP[10].

Surfactant treatment strategies

In adherence to the guidelines stipulated by our national RDS protocol, surfactant is administered in our NICU to premature infants meeting the following criteria: neonates with a GW less than 32 weeks who were intubated in the delivery room, those exhibiting a FiO2 requirement of ≥40%, or those with a MAP requirement exceeding 7 cmH2O[11].

The application dosages of the three natural surfactant preparations employed in our unit adhered to the recommended guidelines provided by both manufacturers and our national regulatory framework. The initial application dosages for surfactant preparations are delineated as follows: Beractant (Survanta®; Abbvie, North Chicago, IL) at 100 mg/kg (4 ml/kg), calfactant (Infasurf®; ONY, Inc., Amherst, NY) at 105 mg/kg (3 ml/kg), and poractant alfa (Curosurf®, Chiesi USA, Inc., Cary, NC) at 200 mg/kg (2.5 ml/kg). While the application dosages of beractant and calfactant remained constant in subsequent administrations, successive dosages of poractant alfa following the initial application were administered at 100 mg/kg (1.25 ml/kg). Repeat dosages were administered with the same preparation no sooner than 12 h after the initial application. Patients were limited to a maximum of three surfactant administrations.

Statistical analysis

Statistical analysis was conducted utilizing the SPSS software for Windows (version 20.0; IBM, Chicago, IL, USA), a statistical package program. Data distributions were assessed using both histograms and the Kolmogorov–Smirnov test. Comparisons among the three distinct surfactant groups were performed using ANOVA with the Bonferroni test or Kruskal Wallis test. Pearson's chi-square test was performed for categorical data. Student's t-test was used for continuous data. Normally distributed data are presented as means and standard deviations, whereas abnormally distributed data are presented as

medians and interquartile ranges. Categorical data are expressed numerically and as percentages. Considering cost-effectiveness of surfactant preparations, it was found that at least 46 patients per group were required, with an effect size of 0.50, type I error of 0.05, and power of 0.80. The statistical significance threshold was set at a p-value <0.05, based on the statistical analysis results. Prism software (Prism 8, GraphPad Software, San Diego, California, USA) was used to analyze and graph data.

RESULTS

During the study period, 6858 premature infants were admitted to our NICU, and 1735 of them were born before the 32nd GW. While 24 of the 1735 patients had major congenital anomalies, two patients had lung hypoplasia. Repeated doses of different surfactant preparations were administered to 56 patients, whereas 527 patients did not receive surfactant. Eighty-nine patients were referred from another center, and data on 52 patients were unavailable. Finally, 985 eligible patients (456 (46%) were female) (Poractant Alfa group: n=575 (58%); Beractant group: n=343 (35%); Calfactant group: n=67 (7%)) were included in the study. The mean GW of the patients was 26.7 ± 2.8 GW, and the mean birth weight was 997 ± 470 g.

Basal characteristics such as GW, birth weight, sex, maternal age, frequencies of maternal DM, maternal preeclampsia, chorioamnionitis, antenatal steroid use, cesarean section, SGA, APGAR scores at the 1st and 5th, initial IL-6 and CRP values, and the first surfactant application time were not different between the Poractant Alfa, Beractant, and Calfactant groups (Table 1).

Table 1. Basal characteristics of the patients

Variables	Poractant Alfa (n=575)	Beractant (n=343)	Calfactant (n=67)	p
Gestational age, weeks *	26.7±2.5	26.2±2.2	26.2±2.2	0.053
Birth weight, g *	976±435	999±325	1001±336	0.064
Maternal age, years a*	28.5±6.2	28.4±5.8	29.4±6.1	0.400
Maternal diabetes mellitus, n (%)	23 (4.0)	19 (5.5)	3 (4.4)	0.161
Maternal preeclampsia, n (%)	87 (15.1)	45 (13.1)	12 (17.9)	0.071
Chorioamnionitis, n (%)	39 (6.7)	12 (3.4)	4 (5.9)	0.088
Antenatal steroid, n (%)	458 (79.6)	260 (75.8)	48 (71.6)	0.184
Cesarean section, n (%)	513 (89.2)	289 (84.2)	61 (91.0)	0.107
Male gender, n (%)	307 (53.4)	188 (54.8)	34 (50.7)	0.208
Small for gestational age, n (%)	113 (19.6)	44 (12.8)	13 (19.4)	0.249
Apgar 1st min., **	4 (4)	4 (5)	4 (3)	0.483
Apgar 5th min., **	6 (2)	6 (4)	6 (2)	0.175
First surfactant application time, minutes. *	21 (13)	24 (14)	22 (11)	0.121
IL-6, pg/ml *	35 (143)	26 (94)	36 (96)	0.108
CRP, mg/L *	1 (37)	1 (32)	1 (20)	0.114

CRP: C-Reactive Protein; IL-6: Interleukin-6; *Mean ± standard deviation, **median (interquartile range).

In the follow-up, the duration of stay in the NICU, frequencies of additional medical conditions such as hemodynamically significant PDA, moderate-to-severe BPD, severe IVH, NEC, ROP, EOS, LOS, as well as respiratory variables including the duration of invasive/non-invasive ventilation or oxygen therapy, the number of surfactant administrations, and intubation rates at 24 h, 72 h, and on the 7th day were not significantly different among the three surfactant groups. Respiratory complications, such as pneumothorax and pulmonary hemorrhage, and ultimately mortality rates, also showed no significant differences among the three surfactant groups (Table 2).

The single-dose surfactant usage rate was the highest in the calfactant group (82%). In the Beractant and Poractant alfa groups, the rates were 79% and 69%, respectively. The rates of using two doses of surfactant were found to be 22%, 18%, and 15% in the Poractant alfa, Beractant, and Calfactant groups, respectively. Among the patients in the Poractant alfa group, 9% required three doses of surfactant, while this rate was 3% in the other groups. No significant difference was observed among the surfactant groups in terms of the frequency of patients requiring repeated doses (p=0.472) (Figure 1).

Table 2. Patient follow-up data

Variables	Poractant Alfa (n=575)	Beractant (n=343)	Calfactant (n=67)	p
Number of surfactants, **	1 (1) (1-3)	1 (1) (1-3)	1 (1) (1-3)	0.472
Duration of MV, days *	3 (4)	3 (5)	3 (5)	0.109
Duration of NIV, days *	5 (9)	4 (8)	4 (9)	0.085
Duration of oxygen therapy, days *	30 (36)	29 (32)	33 (31)	0.132
Rate of intubation at 24 hours, n (%)	296 (51.4)	185 (53.9)	38 (56.7)	0.271
Rate of intubation at 72 hours, n (%)	158 (27.4)	116 (33.8)	21 (31.3)	0.319
Rate of intubation at day 7, n (%)	86 (14.9)	54 (15.7)	11 (16.4)	0.407
Pneumothorax, n (%)	38 (6.6)	27 (7.8)	6 (8.9)	0.126
Pulmonary hemorrhage, n (%)	21(3.6)	13 (3.7)	4 (5.9)	0.304
EOS, (%)	14 (2.4)	7 (1.8)	2 (2.9)	0.514
LOS, (%)	115 (20.0)	82 (23.9)	17 (25.3)	0.235
Severe (Stage≥3) IVH, (%)	49 (8.5)	41 (11.9)	7 (10.4)	0.677
Medically treated PDA, (%)	215 (37.4)	145 (42.2)	30 (44.7)	0.273
PDA ligation, (%)	28 (4.8)	15 (4.3)	4 (5.9)	0.370
NEC (Stage≥2)	23 (4.0)	9 (2.6)	3 (4.4)	0.266
ROP, (%)	33 (5.7)	21 (6.1)	5 (7.4)	0.301
Moderate to severe BPD, (%)	79 (13.7)	49 (14.2)	10 (14.9)	0.457
NICU stay, days *	31 (51)	33 (53)	32 (66)	0.486
Mortality, (%)	115 (20.0)	78 (22.7)	14 (20.8)	0.130

BPD: bronchopulmonary dysplasia, EOS: early onset sepsis, IVH: intraventricular hemorrhage, LOS: late onset sepsis, MV: mechanical ventilation, NEC: necrotizing enterocolitis, NIV: non-invasive ventilation, PDA: patent ductus arteriosus, ROP: retinopathy of prematurity; *Median (interquartile range), **median (interquartile range) (minimum-maximum).

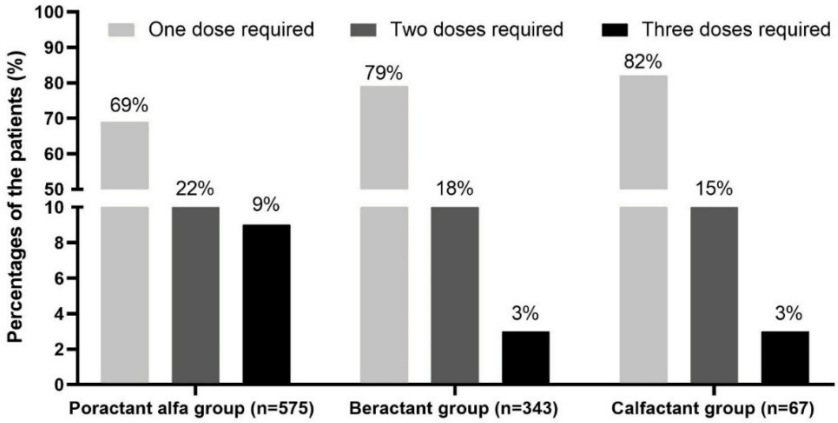

Figure 1. Frequencies of one dose, two doses, and three doses requirements in surfactant groups.

No statistically significant differences were discerned among the three surfactant groups concerning respiratory support parameters and blood gas results, both prior to and at the 1st and 6th hours after post-surfactant administration (Table 3).

Table 3. Blood gas values and respiratory support parameters of patients during the first six hours after surfactant administration.

Variables	Poractant Alfa (n=575)	Beractant (n=343)	Calfactant (n=67)	p
Before surfactant				
PIP, cm H_2O	20.3±3.8	19.0±2.7	18.5±1.5	0.673
PEEP, cm H_2O	6.1±0.7	6.2±0.5	6.4±0.3	0.108
MAP, cm H_2O	9.1±0.9	9.0±0.9	9.0±0.7	0.706
FiO_2, %	53.5±11.9	57.9±11.5	52.9±21.5	0.092
SaO_2, %	91.0±8.2	91.2±9.4	94.0±5.6	0.057
pH	7.25±0.13	7.26±0.07	7.26±0.08	0.188
pCO_2, mmHg	55.1±18.1	55.4±12.8	57.8±13.3	0.182
HCO_3, mmol/L	18.8±4.2	18.2±3.8	18.3±3.4	0.127
BD, mmol/L	-7.7±4.7	-7.5±3.1	-8.8±2.7	0.304
Lactate, mmol/L	5.2±3.1	4.4±2.4	6.2±3.2	0.083
1st hour after surfactant				
PIP, cm H_2O	18.6±2.5	18.3±2.4	18.3±1.6	0.134
PEEP, cm H_2O	6.1±0.7	6.1±1.2	6.1±0.5	0.125
MAP, cm H_2O	8.9±1.1	8.9±0.8	8.7±0.5	0.206
FiO_2, %	39.6±10.7	41.1±10.1	36.0±10.0	0.100
SaO_2, %	93.3±7.9	92.8±9.1	94.0±1.6	0.173
pH	7.25±0.14	7.27±0.10	7.27±0.06	0.134
pCO_2, mmHg	49. 1±12.4	48.5±10.7	50. 0±11.1	0.427
HCO_3, mmol/L	19.4±3.7	19.2±3.3	19.0±4.1	0.660
BD, mmol/L	-7.2±3.8	-7.1±4.0	-7.5±3.2	0.249
Lactate, mmol/L	4.8±2.8	4.2±2.1	5.4±3.1	0.091
6th hour after surfactant				
PIP, cm H_2O	18.3±2.4	18.3±2.4	18.0±1.4	0.115
PEEP, cm H_2O	6.0±0.8	6.1±1.7	6.0±0.3	0.620
MAP, cm H_2O	8.9±0.8	8.9±0.7	8.7±0.4	0.285
FiO_2, %	33.7±10.8	33.7±13.1	31.6±7.0	0.102
SaO_2, %	94.7±5.1	94.7±4.8	94.1±2.9	0.393
pH	7.29±0.12	7.28±0.15	7.27±0.08	0.114
pCO_2, mmHg	40.3±14.5	41.9±12.1	42.3±13.0	0.259
HCO_3, mmol/L	19.6±3.7	19.3±4.2	19.3±4.8	0.217
BD, mmol/L	-6.7±4.1	-7.0±5.6	-7.2±4.6	0.301
Lactate, mmol/L	4.1±1.6	3.9±1.9	5.0±3.2	0.079

BD: base deficit, FiO_2: fraction of inspired oxygen, MAP: mean airway pressure, PIP: peak inspiratory pressure, PEEP: positive end expiratory pressure, SaO_2: oxygen saturation

In our study, similar to the baseline characteristics and follow-up data, no significant differences in costs were observed among the three surfactant groups. Subgroup analyses based on birth weight revealed similar surfactant costs among the three surfactant groups for infants weighing less than 750 g. In infants with birth weights ranging from 750 to 999 g, the use of Calfactant was significantly more cost-effective compared to Beractant and poractant alfa (Poractant alfa vs Calfactant: $p < 0.001$; Beractant vs Calfactant: $p = 0.001$). For infants with birth weights between 1000 and 1499 g, both Beractant and Calfactant were significantly less costly than poractant alfa (Poractant alfa vs. Beractant: $p < 0.001$; Poractant alfa vs. Calfactant: $p < 0.015$). The cost profiles were similar across the groups in infants with birth weights ranging from 1500 to 2000 grams (Table 4).

Table 4. Cost comparisons of surfactant groups according to the birth weights of patients.

Birth weight	Poractant alfa (A)		Beractant (B)		Calfactant (C)		p	Comparison of binary groups	
	n	CPPC	n	CPPC	n	CPPC		Groups	p
Total	575	554.91±228.08 $	343	529.05±249.76 $	67	499.09±288.04 $	0.092	A vs B B vs C A vs C	0.118 0.429 0.066
1500-2000 g	80	744.45±167.03 $	72	731.53±360.334 $	5	753.2±292.35 $	0.124	A vs B B vs C A vs C	0.774 0.137 0.152
1000-1499 g	149	669.36±265.23 $	67	497.47±168.55 $	33	531.54±293.20 $	<0.001*	A vs B B vs C A vs C	<0.001 0.460 0.015
750-999 g	101	472.44±93.73 $	60	507.50±175.50 $	12	331.57±162.54 $	<0.001*	A vs B B vs C A vs C	0.101 0.001 <0.001
<750 g	245	457.40±186.92 $	144	451.49±177.60 $	17	429.09±227.45 $	0.813	A vs B B vs C A vs C	0.759 0.634 0.622

CPPC: Calculated per Patient Cost in USD

Since there was no significant difference between the preparations regarding respiratory improvement, complications, and clinical outcomes, we proposed a new birth weight-based approach for selecting surfactant preparations, considering the financial differences in Figure 2. Because significant cost differences were found between the groups in the birth weight subgroup analysis, all baseline characteristics and follow-up data examined previously within the total cohort were also compared by birth weight group, and no significant difference was found.

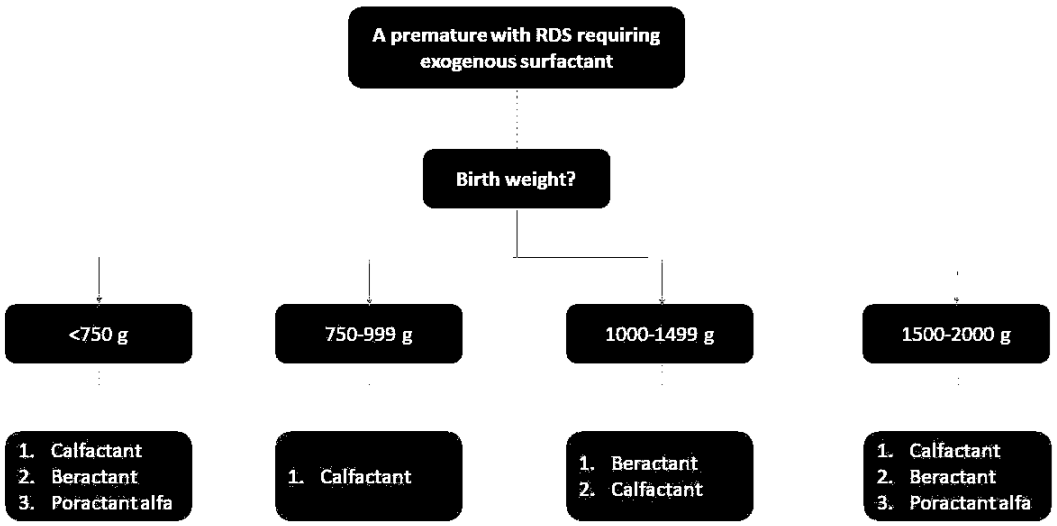

Figure 2. Our proposal model as a novel approach for selecting surfactant preparation.

DISCUSSION

In this study, we aimed to compare the short-term pulmonary effects and costs of three different natural surfactant preparations for treating premature RDS. Baseline characteristics, including demographic, clinical, and laboratory markers and clinical outcomes, were similar between the surfactant groups. Patients in each group were monitored for pulmonary involvement by measuring blood gas and ventilator parameters 6 h after surfactant administration. All the groups showed improvement, and there was no significant difference in respiratory improvement. Therefore, we considered that the short-term clinical effects of the three surfactants on pulmonary function were similar. Similarly, we found that costs were similar between groups. We then performed a subgroup analysis according to birth weight. RDS-related baseline and follow-up data were similar between groups. However, While Calfactant was significantly less costly than the others in the 750-999 g group, Poractant alfa was significantly costlier than the others in the babies born with a birth weight of 1000-1499 g.

Poractant alfa was used in more than half of our patients, while beractant was administered in approximately one-third, with only 7% falling into the calfactant group. Until 2017, only poractant alfa and beractant preparations were available in our country. The delayed availability of calfactants may have caused clinicians to be hesitant about their use for RDS treatment, resulting in lower clinical experience. Another point is that the required volume to achieve the effective treatment dose is lower for poractant alfa than for other preparations. In our study, this could be another possible reason for Poractant alfa being the most preferred surfactant[12]. The frequency of usage varies across clinics, depending on when the product was licensed in the country and the current unit's usage practices[3,13]. In a multicenter study, Beractant, Calfactant, and Poractant alfa use frequencies were 40%, 30%, and 30%, respectively. In line with our findings, the frequencies of composite outcomes such as air leak syndromes, BPD, and death were similar between these three surfactant groups[3].

In line with our findings, a prospective study demonstrated the short-term pulmonary improvement effect of exogenous surfactants by showing a significant decrease in PCO2, pH, MAP, FiO2, modified ventilatory indices, and respiratory severity scores in premature infants with RDS at 12th and 24th hour after administration. However, surfactant types were not compared to each other[14]. In another study, clinical efficacies of Calfactant, Poractant alfa, and Surfactant-TA on the patients with RDS whose demographic factors were similar were observed and reported to be equal[15]. Similar to our study, the benefits on the respiratory system of three different surfactants, Beractant, Calfactant, and Poractant alfa, were comparable[16].

However, there are conflicting data in the literature regarding clinical outcome comparisons of different natural surfactant preparations. Pulmonary hemorrhage and moderate-to-severe BPD were found to be more common in those under Poractant alfa than in those under Calfactant in a study comparing Poractant alfa, Calfactant, and Surfactant-TA[15]. However, a systematic review reported that BPD and air leak syndrome frequency were not significantly different between patients administered beractant and those administered poractant alfa[17]. A recent study showed that mortality rates were similar between patients receiving Beractant and Calfactant[18]. In addition, Beractant and Poractant alfa were also shown to have equal mortality rates[17]. There were discrepancies between the two studies that evaluated mortality rates when comparing Poractant alfa, Calfactant, and Beractant. In the earlier of the two investigations, deaths occurred less often among infants who received Poractant alfa[19]. However, the more recently published study found significantly reduced mortality in the Calfactant treatment arm relative to the other surfactants[16]. On the other hand, a recent meta-analysis suggested that Surfactant A, Calfactant, Poractant alfa, Lucinactant, and Colfoscerilare are more effective in reducing the mortality of RDS in preterm infants than beractant[20]. We considered that the wide variability in the clinical outcome findings provided by the studies was due to the highly heterogeneous birth weights and GW of the included patients and the significant variation in long-term follow-up protocols among the centers.

There are a limited number of studies comparing the financial burden of different natural surfactant preparations, and they present contradictory findings. Zayek et al.[13] showed a significant pharmacoeconomic advantage of Calfactant compared to Poractant alfa. While Marsh et al.[21] pointed out the economic superiority of Poractant alfa to Beractant, a more recent observational cohort study offered the opposite[22]. Nevertheless, the most

extensive cohort study examining the expenditures associated with Poractant alfa, Beractant, and Calfactant, which is more recent than the previous ones, indicated non-significant variations between the formulations[23]. Furthermore, a recent comprehensive systemic review article similarly indicated no substantial cost discrepancies among these three surfactants[24]. In line with these current findings, we found no significant cost difference between the preparations in this study. However, we took one step further and performed a subgroup analysis based on the birth weights. Then, we showed that while Calfactant can be a more cost-effective option than the others for premature infants with a birth weight of 750-999 g, Poractant alfa has significant economic disadvantages compared to the others for RDS patients born 1000-1499 g.

Surfactant cost studies address surfactant usage rates, dose repetitions, and surfactant cost per unit. In addition, surfactant usage indications and costs vary between units over the years. Another factor affecting the use of surfactant type is the time the surfactant entered the country. Surfactant that is first approved for use in the country can be used more frequently by clinicians in that country[13,24]. This situation is also seen in the results of our study. Clinicians' decisions may change in light of new studies on surfactant preparations and current data. Therefore, each unit should conduct its own effectiveness and cost studies for surfactant. In fact, with the changing current data for surfactant, the unit should review its own data over time. In addition, more valuable data can be obtained with national cost and effectiveness studies and multi-center studies in addition to the data of each unit[13,15,24]. In this respect, we think that the results obtained with the subgroup analysis in our study may be an important start.

Although several studies have compared the clinical efficacies of different surfactants, this is the first study to examine the changes in blood gas and respiratory support parameters before and after the application of three different natural surfactants. Moreover, we performed a birth weight-based sub-analysis to compare the financial costs of these surfactants for the first time. This study presents novel findings. However, owing to the predominantly retrospective nature of our study, there are inherent limitations associated with inaccessible data. The main limitation is that we were unable to calculate the total hospital costs per patient, despite calculating the surfactant cost per patient. Furthermore, we could not assess the method of surfactant administration, its impact on respiratory distress scores, or its long-term effects.

In conclusion, our study, which included patients diagnosed with RDS treated with three different surfactant preparations and demonstrated similar baseline characteristics, we showed that short-term respiratory improvements, complications, and clinical outcomes were comparable among the groups. Therefore, we emphasize the potential prominence of the cost factor in the choice of preparation. However, we also found no significant difference in costs among preparations. Subsequently, when we conducted subgroup analysis based on birth weights, we found that the economic burden of Calfactant was significantly lower in infants weighing 750-999 grams, and in infants weighing 1000-1499 grams, both Calfactant and Beractant exhibited notably lower economic burden. Being the first to compare pre- and post-administration respiratory parameters and blood gas values of three different surfactant preparations, our study is remarkably noteworthy in revealing a similar clinical response among the preparations. Moreover, as the first study to perform subgroup analysis based on birth weight when comparing surfactant preparations from an economic standpoint and presenting a new birth weight-based approach to selecting preparations, our study presents valuable insights; however, it should be supported by future, particularly, multicenter studies. According to our findings, each country and each unit should evaluate its own surfactant cost, so that the results can shed light on the clinical applications of surfactant. It is especially important for middle and low-income countries.

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