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Original Article

A Comparison of the Effect of Beractant (Beracsurf) and Proctant Alpha (Curosurf) in Neonatal Respiratory Distress: A Randomized Controlled Trial

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Abstract

Background: Surfactant treatment has revolutionized the management of respiratory distress syndrome (RDS) in preterm infants. The present study compared the effectiveness and adverse effects of two natural surfactants, Beracsurf and Curosurf, in premature infants with RDS who required surfactant administration.

Methods: Eighty-four newborns were enrolled in this double-blind randomized controlled trial study, which was conducted in Shiraz, Iran, from 2021 to 2022. The study included all preterm neonates with RDS, who required intubation for stabilization, were on continuous positive airway pressure (CPAP), required oxygen of more than 30% to maintain saturation 90-95%, or had CPAP failure. Using a simple random allocation method, the participants were randomly assigned to receive either Beractant as the case group or Proctant Alpha as the control group. The study assessed outcomes such as hospital length, number of surfactant administration, duration of respiratory support, complications, and mortality in both groups. Data were analyzed using SPSS software and applying independent *t* tests, Mann-Whitney tests, and Chi square tests.

Results: Eighty-four neonates were enrolled in the study, with 37 in the control group and 47 in the case group. The duration of hospital stay in the control group was 18.07±13.04 days, while it was 23.59±14.03 days in the intervention group (P=0.07). There were no differences between the two groups in terms of the fraction of inspired oxygen (FIO_2) (P=0.46), and complications (P=0.82). However, the intubation period in the Curosurf group was significantly lower (P=0.03). The mortality rate in the Curosurf group was 24.3% (95% CI=10.5%-38.1%); while in the Beracsurf group, it was 10.6% (95% CI=1.8%-19.5%) (P=0.09).

Conclusion: Beracsurf had comparable efficacy to Curosurf and could be considered a viable alternative.

Trial registration number: IRCT20120126008827N3.

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Keywords ● Beractant ● Infant, premature ● Pulmonary surfactants ● Respiratory distress syndrome, newborn

What's Known

- Surfactant therapy is highly effective in treating neonatal respiratory distress, representing a significant advancement in neonatal care worldwide. Due to their efficacy and safety, established surfactants, such as Curosurf, are widely utilized.

What's New

- Beracsurf, an Iranian surfactant, demonstrates comparable efficacy to Curosurf in treating neonatal respiratory distress. It provides a cost-effective alternative with no additional disadvantages, making it a viable option for neonatal treatment.

Introduction

Neonatal Respiratory Distress Syndrome (NRDS) is inversely proportional to gestational age and birth weight, with higher

incidence and severity in extremely low birth weight and premature infants.[1] To improve survival rates and reduce acute and chronic complications, NRDS patients are treated with a combination of conservative, medicinal, and supportive interventions.[2] Continuous positive airway pressure (CPAP) is the primary intervention recommended in the delivery room for neonates with respiratory distress who are breathing spontaneously. This approach aims to minimize ventilation injuries, bronchopulmonary dysplasia (BPD), and surfactant administration.[3] In cases of CPAP failure or when intubation is indicated, early selective surfactant therapy is the optimal management strategy.[4] Although intubation can increase the risk of BPD and bronchoalveolar damage, the role of prophylactic surfactant therapy is no longer recommended in centers that routinely use CPAP to provide positive end-expiratory pressure (PEEP).[5]

Pulmonary surfactant reduces surface tension at the air-liquid interface of bronchioles, preventing atelectasis and improving gas exchange.[6] It also decreases mortality rates, duration of hospitalization, and the incidence of air leaks such as pneumothorax, along with other respiratory complications.[7]

Currently, two main types of natural surfactants are available: bovine and porcine-derived. Beracsurf is the first Iranian surfactant and a biosimilar form of Survanta (Abbott, US), with each mL containing 25 mg of phospholipid and surfactant proteins SP-B and SP-C.

Beractant is derived from minced bovine lung extract and contains components such as dipalmitoylphosphatidylcholine, palmitic acid, and tripalmitin, making it more similar to human surfactant. It also contains surfactant protein B (SP-B) and surfactant protein C (SP-C).[8] In contrast, Proctant (Curosurf) is extracted from porcine lungs and purified to remove neutral lipids, containing 99% polar lipids and 1% low molecular weight hydrophobic proteins, such as SP-B and SP-C.[8, 9]

Numerous studies have demonstrated that natural surfactants perform better than synthetic ones, with no significant differences among various natural surfactants.[10, 11] Recently, two studies specifically compared the efficacy and safety of Beracsurf with other surfactants.[12, 13] Consequently, the present study aimed to compare the outcomes of preterm neonates with RDS requiring surfactant, between groups receiving Beracsurf and Curosurf.

Patients and Methods

This study was a double-blind randomized controlled trial with a sample size of 84 newborns with respiratory distress syndrome (RDS) requiring surfactant administration over 12 months (April 2021-May 2022) in the neonatal intensive care units (NICU) of Hafez and Namazi Hospitals, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). This study was registered in the Iranian Registry of Clinical Trials (IRCT20120126008827N3). Moreover, the study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.569) and conformed to the relevant ethical guidelines and regulations. All the patients' parents or their legal guardians provided written informed consent before their enrollment.

The sample size of the study was estimated based on a study by Mussavi and colleagues,[14] with a power of 80%, a significance level of 0.05, and a standard deviation of 0.20. Accounting for a 10% dropout rate, the estimated sample size was initially set at 90, (based on surfactant administration rates of 1.08±0.33 vs 1.55±1.12).

For preterm deliveries, a pediatrician or pediatric resident was present in the delivery room. Based on clinical assessment and the neonatal resuscitation program,[15] neonates might require intubation for stabilization. Early CPAP was considered for those with difficult breathing or persistent cyanosis despite oxygen administration. Infants with gestational age (GA) between 24 and 37, diagnosed with RDS and requiring intubation for stabilization, as well as those who required CPAP for stabilization and had a fraction of inspired oxygen (FIO_2) more than 30% to maintain oxygen saturation between 90-95%[2] met the criteria for surfactant administration in both the intervention and control groups.

The exclusion criteria were the presence of congenital anomalies, such as congenital cyanotic heart diseases, digestive system anomalies, the presence of chromosomal abnormalities, and not providing written informed consent by parents or legal guardians.

Randomization and Allocation Concealment

Participants were randomly assigned to different groups using a simple random allocation method. A random number sequence was generated using Stata software (version 12, StataCorp LLC Company, USA), by an independent person who was not involved in the study. This ensured that the sequence was both unbiased and unpredictable. Allocation concealment was maintained by using numbered, opaque, and sealed envelopes. These envelopes were prepared in advance

and kept securely. At the time of randomization, the first researcher opened the envelopes in the sequence to assign the participant to either the intervention group (Beracsurf [Tekzima Company, Alborz, Iran]) or the control group (Curosurf [Chiesi Company, Italy]).

Blinding Procedure

This study was double-blind, in which neither the parents of the newborns nor the data collectors, assessors, and analysts knew which type of surfactant each neonate received. This was accomplished by ensuring that the surfactants were administered in identical syringes and using coded labels that could only be decoded after data analysis was complete.

Surfactant Administration

Surfactant was administered by a pediatrician or neonatologist who was knowledgeable about its application. For neonates on CPAP, the INSURE method (Intubation, Surfactant administration, and Extubation) was used.[16] If the neonates were already intubated, surfactant was administered through the endotracheal tube.

Newborns in the control group received 2.5 mL/Kg of Curosurf as the initiation dose which could be repeated every 12 hours up to three doses, and the newborns in the intervention group received 4 mL/Kg of Beracsurf as the initiation dose which could be repeated every 6 hours up to four doses.

The primary outcomes of the study were length of hospital stay, duration of intubation, invasive mechanical ventilation (ventilator), and non-invasive CPAP. The secondary outcome was the numbers of surfactant administration, the Fio_2, and complications such as patent ductus arteriosus (PDA); which was assessed via echocardiography in neonates exhibiting signs of PDA, such as a bounding pulse, wide pulse pressure, or worsening respiratory conditions; intraventricular hemorrhage (IVH), which was assessed via sonography in clinically unstable neonates, and those who were born before 32 weeks of gestational age.[17] In sonography, IVH is graded as follows: Grade I is characterized by germinal matrix hemorrhage, Grade II by intraventricular hemorrhage without ventricular dilation, Grade III by intraventricular hemorrhage with ventricular dilation, and Grade IV by intraparenchymal hemorrhage, sepsis (using blood culture and clinical assessment), pneumothorax (using chest X-ray, and assessed by clinical symptoms), and pulmonary hemorrhage (using chest X-ray, and assessed by clinical symptoms). The mortalities in both groups were also recorded.

Statistical Analysis

The data were analyzed using SPSS software, (version 26, IBM, USA). Quantitative data such as birth weight, maternal age, and gestational age were expressed as mean±SD. Qualitative data, such as the incidence of adverse events, were summarized as numbers and percentages. Analytical tests such as independent *t* test, Mann-Whitney, and Chi square tests were performed to distinguish the significant difference between groups. The generalized estimating equation (GEE) model was employed for the FIO_2 as the response variable, and the group, mode, time, and number of administrations as independent variables. This model allowed us to control for various factors and gain a better understanding of how each variable affected FIO_2. The GEE approach was chosen due to its robustness in handling correlated data, which is typical in repeated measurement studies. $P<0.05$ was considered statistically significant.

Results

A total of 120 neonates were enrolled in the study. After excluding 36 neonates who did not meet the inclusion criteria, 84 neonates were ultimately evaluated. Among them, 37 neonates (44.04%) received Curosurf, while 47 (55.95%) neonates received Beracsurf. The CONSORT diagram is presented in figure 1.

Gender analysis indicated similar sex distribution between the two groups. Moreover, other basic characteristics such as birth weight, gestational age, and maternal age were the same between the two groups. The Apgar score in the 1st and 5th minutes after birth was measured, and it was matched between the two groups (table 1).

CPAP period and intubation period, as the primary outcomes, were used to compare the two groups and their efficacy in treating RDS. The results indicated that only the intubation period was significantly longer in the Beracsurf group, and the other parameter was the same (table 2). The mean duration of the intubation period was 36.71±18.25 hours in neonates who received Curosurf and 37.61±27.6 hours in neonates who received Beracsurf (P=0.03). The mean duration of CPAP was 48.61±30.10 hours and 46.22±34.33 hours, respectively (P=0.98).

According to table 3, the value of FIO_2 decreased over time significantly (0.26 per hour). A single additional dosage of surfactant results in a 5-unit increase in FIO_2, which might indicate a worsening condition in those requiring higher doses. There were some differences between the types of modes. There was no statistically significant difference between the two groups (P=0.14).

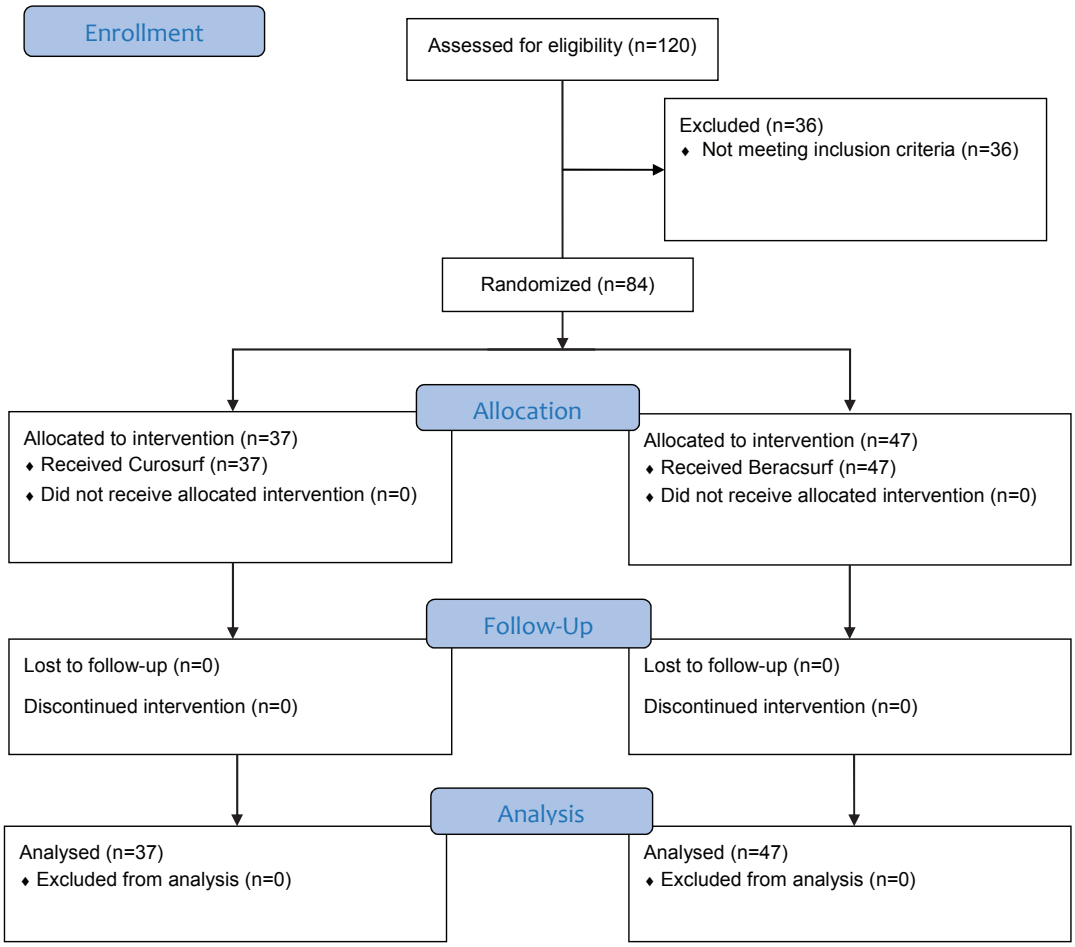

Figure 1: The CONSORT flow diagram depicts the participant's flow through the phases of this trial.

Table 1: Baseline characteristics and risk factors of infants

Variables		Beracsurf (N=47)	Curosurf (N=37)	P value
		mean±SD	mean±SD	
Gestational age (week)		30.94±2.51	31.14±3.08	0.75*
Birth weight (g)		1546.74±619.23	1610.54±601.29	0.63*
Maternal age (year)		32.30±5.62	29.81±4.87	0.36*
Apgar score at 1 min		5.46±2.63	6.00±2.00	0.30*
Apgar score at 5 min		7.35±2.47	8.14±1.38	0.7*
Sex, n (%)	Male	27 (57.4%)	16 (43.2%)	0.19**
	Female	20 (42.6%)	21 (56.8%)	

*Assessed by *t* test. **Assessed by Chi square test; P<0.05 was considered significant.

Table 2: Primary outcomes

Variables		Beracsurf (N=47)	Curosurf (N=37)	P value*
		n (%)	n (%)	
Intubation Period (h)	No	16 (34.04)	26 (70.2)	0.04
	<24 h	11 (23.4)	3 (8.1)	
	<48 h	4 (8)	0 (0)	
	>72 h	9 (19.1)	8 (21.6)	
CPAP Period (h)	<24 h	17 (36.1)	11 (29.7)	0.98
	<48 h	11 (23.4)	13 (35.13)	
	<72 h	5 (10.6)	5 (13.5)	
	<96 h	7 (14.8)	4 (10.8)	
	>96 h	5 (10.6)	3 (8.1)	

*Assessed by the Mann-Whitney test, P value less than 0.05 is considered significant. CPAP: Continuous positive airway pressure; h: Hour

Table 3: Generalized estimating equation outputs for assessing the effects of groups on FIO_2 adjusted for other variables

Variables	Coefficient	Standard error	Z	P value	95% CI	
					Lower	Upper
Mode						
Hood	8.84	10.34	0.86	0.39	-11.42	29.10
CPAP	54.39	20.25	2.69	0.007	14.69	94.08
SIMV	24.94	2.81	8.88	<0.001	19.43	30.45
SIPPV	14.09	3.21	4.39	<0.001	7.80	20.39
Time	-0.26	0.04	-6.41	<0.001	-0.34	-0.18
Number of administrations	5.04	1.18	4.29	<0.001	2.74	7.34
Group						
Beracsurf	-3.37	2.30	-1.46	0.14	-7.89	1.14

*Assessed by a generalized estimating equation, P<0.05 was considered statistically significant. CPAP: Continuous positive airway pressure; SIMV: Synchronized intermittent mandatory ventilation; SIPPV: Synchronized intermittent positive pressure ventilation

Table 4: Generalized estimating equation outputs for assessing the crude effects of groups on FIO_2

Variables	Coefficient	Standard error	Z	P value	95% CI	
					Lower	Upper
Group						
Beracsurf	1.97	2.71	0.73	0.46	-3.34	7.28
Time	-0.23	0.04	-5.48	<0.001	-0.32	-0.15

*Assessed by a generalized estimating equation, P<0.05 was considered statistically significant.

Table 5: An exact test for comparison of the number of administered doses in two groups

Group	Number of administrations				Total	P value
	1	2	3	4		
Beracsurf, n (%)	26 (54.17%)	9 (18.75%)	9 (18.75%%)	4 (8.33%)	48 (100%)	0.35
Curosurf, n (%)	22 (61.11%)	10 (27.78%)	3 (8.33%)	1 (2.78%)	36 (100%)	
Total, n (%)	48 (57.14%)	19 (22.62%)	12 (14.29%)	5 (5.95%)	84 (100%)	

*Assessed by a generalized estimating equation, P<0.05 was considered statistically significant.

The crude coefficients for the group effect are presented in table 4. According to this finding, the patients who received Beracsurf had no statistically significant difference in FIO_2 during the study period compared with those who received Curosurf (P=0.46).

In both groups, the majority of patients received one dose, 54.17% in Beracsurf and 61.11% in Curosurf. However, no significant difference was observed between groups concerning the number of received dosages. In addition, the participants were recategorized based on the number of administrations to those who received only one dose, and the others who received more than one dose. Once more, there were no differences between the groups (table 5).

The hospitalization period was 18.07±13.04 days in patients who received Curosurf and 23.59±14.30 days in patients who received Beracsurf. There was no statistically significant difference between the two groups (P=0.07). Although the difference in side effects, such as pulmonary hemorrhage, pneumothorax, IVH, and sepsis, was not significant (P=0.20, P=0.85, P=0.82, P=0.69, respectively), 11 (29.72%) neonates in the Curosurf group and 17 (36.17%) neonates in the Beracsurf group had no IVH. Based on the grade of IVH, the distribution of neonates with IVH grades 1, 2, 3, and 4 was 15 (40.5%), 4 (10.8%), 1 (2.7%), 1 (2.7%) in the Curosurf group, and 22 (46.8%), 2 (4.2%), 2 (4.2%), 0 (0%) in Beracsurf group, respectively. The difference between the groups was not statistically significant (P=0.82).

Of the neonates who received Curosurf, 9 (24.3%) (95% CI=10.5% to 38.1%) did not survive, compared to 5 (10.6%) (95% CI=1.8% to 19.5%) who received Beracsurf. However, the difference in mortality rates was not statistically significant (P=0.09).

Discussion

The present study compared the efficacy and side effects of two surfactants, Proctant Alpha (Curosurf) and beractant (Beracsurf). For the primary outcomes, there was no statistically significant difference between the two groups in terms of CPAP period, length of hospitalization, and FIO_2. However, the patients who received

Curosurf had a significantly shorter intubation period (P=0.03). Morbidity and mortality rates did not differ significantly between groups.

A recent study compared the efficacy and safety of Beractant with Proctant Alfa in two different periods while they were available on the market and found no significant difference between groups.[18]

Trembath and colleagues conducted a comparative RCT with a large sample size within 5 years, and the results indicated that there was no difference in the origin of surfactants in terms of adverse effects such as pneumothorax, pulmonary hemorrhage, and BPD.[19] Moreover, in the present study, the rate of pulmonary hemorrhage and pneumothorax was lower in the Beracsurf group than in the Curosurf group (11.6 vs 22.2, 4.7 vs 5.6). However, the difference was not statistically significant. Nourollahi and colleagues conducted a study and found no difference in mortality or morbidity rates, which was consistent with the findings of the present study.[13] In contrast, another study in Iran, compared Curosurf and Beracsurf and reported a lower mortality rate among neonates who received Beracsurf. It is worth mentioning that neonates receiving Curosurf in their study had lower GA and birth weight, which was significantly different from the Beracsurf group. Other complications indicated no significant variance between the groups in their study.[12]

The FIO_2 variation was set to evaluate two groups by quantitative analysis. The analysis revealed no significant difference between the groups based on FIO_2. These findings were consistent with those of Gharehbaghi and colleagues.[12] Malloy and colleagues reported that Proctant Alpha led to a lower FIO_2 requirement than Beractant.[20] Other studies yielded similar findings.[21-24]

In the present study, the intubation period was significantly shorter in patients who received Curosurf. In contrast to our findings, Mirzarahimi and colleagues reported a longer duration of ventilatory support in patients treated with Curosurf than those treated with Survanta.[24] Another previous study reported lower respiratory support in the first 72 hours and a more successful extubating rate in patients who received proctant.[25] Speer and colleagues also noted that patients treated with Curosurf had lower peak expiratory pressure and mean airway pressure.[22]

In terms of redosing, the present study indicated no significant difference between the groups. However, two other studies reported a higher requirement for repeating doses with beractant.[23, 24]

Few studies compared the advantages and disadvantages of Beracsurf with other available surfactants. Beracsurf, the only domestically produced surfactant in Iran, is more accessible and cost-effective. This study is advantageous as it adds to the limited body of research on Beracsurf. Furthermore, there were no significant differences between the groups in terms of birth weight, gestational age, and Apgar scores, which made the comparison more reliable. However, a limitation of this study was the limited availability of Curosurf during the study period, despite its increased availability in previous years.

Conclusion

The effects and side effects of two surfactants, Curosurf and Beracsurf, were found to be comparable. However, Curosurf had a shorter duration of intubation period. Considering that Beracsurf is produced and easily accessible in Iran, it is economically logical to use it as the preferred surfactant.

Authors' Contribution

Kh. S.N: concept and design, writing and editing the manuscript; H.B: collecting the data, writing and editing the manuscript; M.R: supervision, concept, and design, editing the manuscript; M.D: collecting data, writing, and editing the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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