

# Comparison of Efficacy and Pharmacoeconomic Outcomes Between Calfactant and Poractant Alfa in Preterm Infants With Respiratory Distress Syndrome

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**OBJECTIVES** In order to evaluate the impact of the surfactant of choice selection, primary end points were to compare the average number of doses per patient, need for mechanical ventilation on day 3, hospital length of stay, and in-hospital mortality between calfactant and poractant alfa in preterm infants with respiratory distress syndrome (RDS). Secondary outcomes included administration complications, development of bronchopulmonary dysplasia (BPD), and estimated average per patient cost among the study population.

**METHODS** A retrospective chart review was performed at a level IV neonatal intensive care unit between January 2020 and December 2021 to compare the efficacy, safety, and pharmacoeconomic outcomes following a surfactant of choice switch from calfactant to poractant alfa in preterm infants with RDS.

**RESULTS** Final analysis included 253 premature infants with gestational age (GA) between 22 and 36 weeks who met inclusion criteria. A total of 118 patients who received calfactant required higher average number of doses, 1.5 vs 1.3 doses ( $p = 0.031$ ), and had more administration complications than 135 patients who received poractant alfa (10.2 vs 2.2%,  $p = 0.008$ ). The need for redosing, mechanical ventilation on day 3, hospital length of stay, in-hospital mortality, and development of BPD were comparable between both groups. However, the estimated average per patient cost for poractant alfa was 32% higher than calfactant (\$1,901 vs \$1,439,  $p < 0.001$ ).

**CONCLUSIONS** Despite the pharmacoeconomic disadvantage, preterm infants who received poractant alfa needed fewer doses and were less likely to have administration complications compared with those who received calfactant.

**ABBREVIATIONS** APGAR, appearance, pulse, grimace, activity, and respiration; BPD, bronchopulmonary dysplasia; GA, gestational age; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome

**KEYWORDS** calfactant; Curosurf; Infasurf; poractant alfa; premature infants; respiratory distress syndrome; surfactant

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## Introduction

Respiratory distress syndrome (RDS) is a severe and potentially fatal cause of respiratory failure due to the insufficient surfactant production in preterm infants, and it has been associated with significant morbidity, mortality, and economic burden.<sup>1–4</sup> This condition is inversely related to gestational age (GA) because it was observed in 60% of infants <28 weeks GA, and only in <5% of infants >34 weeks GA.<sup>2</sup> Lung surfactant is one of the management strategies for RDS besides antenatal steroids, positive pressure ventilation, and nutrition support. The use of surfactants had been shown to reduce morbidity, need for mechanical ventilation, incidence of pulmonary air leak, and risk of chronic lung disease or death at 28 days of life in preterm infants.<sup>2,5–7</sup> Thus, the American Academy of Pediatrics recommended the

use of surfactants in preterm infants, especially in those <30 weeks GA with severe RDS after initial stabilization.<sup>6,7</sup> There are currently 3 animal-derived lung surfactant replacement products approved for the treatment of RDS in the United States: beractant, calfactant, and poractant alfa.<sup>8–10</sup> Porcine-derived surfactant, poractant alfa, contains a higher concentration of phospholipids, and a lower volume of administration compared with the bovine-derived products beractant and calfactant.<sup>10</sup>

The use of beractant had been falling out of favor in recent years. As shown in the 2015 systematic analysis, consisting of randomized or quasi-randomized trials by Singh et al,<sup>11,12</sup> authors concluded that poractant alfa significantly reduced mortality, and need for re-dosing when being compared with beractant in preterm infants with RDS. In a retrospective, observational, cohort study

comparing all-cause, in-hospital mortality between 3 animal-derived surfactants from 2005 to 2009 using The Premier Database, poractant alfa was associated with lower mortality compared with both beractant and calfactant treatments in preterm infants with RDS.<sup>13</sup> Using the same database, a retrospective observational study between 2010 and 2013 by Sekar et al<sup>14</sup> compared beractant, calfactant, and poractant alfa for RDS, and concluded that preterm infants receiving poractant alfa were less likely to be on mechanical ventilation at 3 and 7 days among the 3 surfactants, and they had lower odds of neonatal intensive care unit (NICU) mortality compared with those on calfactant. However, there was a lack of information on the precise cause of death and antenatal steroid dosing, which was considered one of most important risk factors for development of RDS in both of these studies.

In contrast to previous findings, Trembath et al<sup>15</sup> performed a comparative effectiveness study of 3 animal-derived surfactants for RDS at 322 US NICUs from 2005 to 2010. All surfactants demonstrated comparable effectiveness in the prevention of air leak syndromes, bronchopulmonary dysplasia (BPD), and mortality. Similarly, Jeon et al<sup>16</sup> conducted a retrospective review comparing poractant alfa and calfactant in preterm infants at 24 to 31 weeks of gestation with RDS. Both surfactants had a similar incidence of surfactant redosing, pulmonary air leak, duration of mechanical ventilation, and poststeroid therapy. In addition, poractant alfa was found to have higher incidence of pulmonary hemorrhage, postnatal diuretic therapy, and moderate to severe BPD. The recent 2018 retrospective study by Zayek et al<sup>17</sup> concluded that poractant alfa did not reduce the need for redosing as reported by the manufacturer, and the per patient drug cost was also 38% higher than calfactant. However, this study did not assess other efficacy end points, including mechanical ventilation, morbidity, or mortality.

Medical City Dallas Hospital had been using calfactant as a lung surfactant of choice since 1998.<sup>18</sup> With recent literature showing better efficacy outcomes for poractant alfa,<sup>14,15</sup> consensus was made to switch from calfactant to poractant alfa starting January 2021. Nonetheless, literature regarding the selection of most efficacious surfactant is still conflicting and not definitive, thus requiring further investigation, especially at a level IV NICU that provides the highest level of care. To that end, the goal of this study was to compare the efficacy, safety, and pharmacoeconomic outcomes of calfactant and poractant alfa in RDS management.

## Materials and Methods

**Study Design.** This study was a retrospective chart review to compare the efficacy, safety, and pharmacoeconomic outcomes of calfactant and poractant alfa in preterm infants with RDS at Medical City Dallas Hospital between January 2020 and December 2021.

Preterm infants (GA between 22 and 36 weeks) with RDS who received the first dose of surfactant at age  $\leq 2$  days were included. Patients were excluded if they were  $>36$  weeks, or had meconium aspiration syndrome, chromosomal abnormality, or life-threatening major congenital anomalies, such as hydrops fetalis, cardiac defects, or pulmonary hypoplasia. Surfactants were dosed based on the manufacturer's labeling.<sup>9,10</sup>

Primary end points were to compare the efficacy outcomes (average number of doses per patient, need for mechanical ventilation on day 3, hospital length of stay, and in-hospital mortality) between calfactant and poractant alfa in preterm infants with RDS. The secondary end points included the comparison of safety as well as pharmacoeconomic outcomes: administration complications, development of BPD, and estimated average per patient cost among the study population.

**Definition.** The diagnosis of RDS and decision to use pulmonary surfactant were based on patient severity as determined by chest radiography, blood gas analysis, and oxygen requirement. In this study, calfactant was a surfactant of choice from January to December 2020, and then it was transitioned to poractant alfa from January to December 2021. The switch was a complete transition, and there was no overlapping period in order to avoid selection bias. The estimated average per patient cost for surfactants was calculated based on the average wholesale price.

The RDS treatment dosing via endotracheal was 105 mg/kg/dose (3 mL/kg/dose), and the same dose may be repeated at 12-hour intervals (up to 3 additional doses, maximum total dose: 420 mg/kg or 12 mL/kg) for calfactant. In the poractant alfa group, the treatment dose was 200 mg/kg/dose (2.5 mL/kg/dose), and 100 mg/kg/dose (1.25 mL/kg/dose) may be repeated at 12-hour intervals (up to 2 additional doses, maximum total dose: 400 mg/kg or 5 mL/kg).<sup>9,10</sup> Based on the National Institute of Child Health and Human Development, for those born at  $<32$  weeks GA, BPD was diagnosed based on supplemental oxygen support ( $>21\%$ ) for  $\geq 28$  days at 36 weeks postmenstrual age or discharge, whichever came first. For those born with GA  $\geq 32$  weeks, BPD referred to the requirement of supplemental oxygen support  $<21\%$  for 28 days to 56 days postnatal age or discharge, whichever came first.<sup>19–22</sup> Administration complications were defined as endotracheal tube or airway occlusion, oxygen desaturation, bradycardia, or pneumothorax requiring intervention.

**Study Population.** Preterm infants with RDS were retrospectively reviewed through Meditech, our electronic medical record. Data were recorded using patient charts from January 2020 to December 2021. Patients were screened based on previously discussed inclusion and exclusion criteria.

**Data Collection.** Retrospective collection of patients' clinical and demographic data included: date of birth; GA; sex; birth weight; appearance (skin color),

pulse, grimace (reflex irritability), activity (muscle tone), and respiration (APGAR) scores at 1 and 5 minutes; maternal data (antenatal steroids, gestational diabetes, gestational hypertension, and/or chorioamnionitis); number of surfactant doses; mechanical ventilation on day 3; hospital length of stay, in-hospital mortality; administration complications; BPD; and surfactant estimated costs. All patient data were collected and were documented in a password-protected flowsheet.

**Statistical Analysis.** Sample size calculation was based on the need for mechanical ventilation on day 3. With a target reduction to 25%, 80% power, and single side analysis, a total sample size of 266 would be required for the entire study duration. Data were extracted from patient charts and were loaded into the statistical analysis software (SAS 9.4M7, SAS Institute, Cary, NC). Continuous variables were tested for normality, and those testing as normal were subjected to parametric tests used for analysis. Data fields that were not normal were analyzed using non-parametric tests. Non-normally distributed data were presented as median (IQR) and compared using the Mann-Whit-

ney *U* test. Univariate analyses of binary and ordinal variables were compared using  $\chi^2$  statistics, whereas a *t* test was used to compare continuous variables. A *p* value <0.05 was considered statistically significant. However, with the inclusion of 253 patients in the final analysis, this study did not have enough patients to achieve power.

## Results

**Patient Characteristics.** A total of 335 patients with RDS were screened (see Supplemental Figure). Eighty-two patients were excluded for the following reasons: 25 patients were >36 weeks GA, 15 patients had meconium aspiration syndrome, and 42 patients had chromosomal abnormality or life-threatening major congenital anomalies. A total of 253 patients were included in the final analysis. There were 118 included in calfactant group, and the poractant alfa group had 135 patients. Baseline characteristics for our preterm infants with RDS are shown in Table 1. The median (IQR) GA was 29 weeks in both groups (*p* = 0.13), with comparable birth weight of 1160 g (780–1710) in the

**Table 1.** Demographic and Baseline Characteristics of Patients Receiving Calfactant vs Poractant Alfa

Parameters	Calfactant (n = 118)	Poractant Alfa (n = 135)	p value
Gestational age, median (IQR), wk n (%)	29 (26–31)	29 (26–32)	0.13
22–23 wk	9 (7.6)	4 (3)	
24–25 wk	19 (16.1)	19 (14.1)	
26–27 wk	21 (17.8)	26 (19.3)	
28–29 wk	20 (16.9)	23 (17)	
30–31 wk	24 (20.3)	20 (14.8)	
32–33 wk	12 (10.2)	22 (16.3)	
34–36 wk	13 (11)	21 (15.6)	
Birth weight, median (IQR), g n (%)	1160 (780–1710)	1320 (830–1825)	0.09
<500 g	7 (5.9)	3 (2.2)	
500–999 g	39 (33.1)	39 (28.9)	
1000–1499 g	34 (28.8)	41 (30.4)	
1500–1999 g	25 (21.2)	25 (18.5)	
2000–2499 g	5 (4.2)	16 (11.9)	
2500–2999 g	6 (5.1)	4 (3)	
>3000 g	2 (1.7)	7 (5.2)	
Sex, n (%)			0.036
Female	61 (51.7)	52 (38.5)	
Male	57 (48.3)	83 (61.5)	
APGAR score at 1 min, median (IQR)	5 (3–6)	5 (3–7)	0.21
APGAR score at 5 min, median (IQR)	7 (6–8)	7 (6–8)	0.75
Maternal antenatal steroids, n (%)	109 (92.4)	115 (85.2)	0.07
Maternal gestational diabetes, n (%)	16 (13.6)	19 (14.1)	0.9
Maternal chorioamnionitis, n (%)	6 (5.1)	6 (4.4)	0.81
Maternal gestational hypertension, n (%)	36 (30.5)	48 (35.6)	0.4
Maternal pregnancy with $\geq 1$ complication, n (%)	8 (6.8)	11 (8.1)	0.68

APGAR, appearance, pulse, grimace, activity, and respiration

calfactant group and 1320 g (830–1825) in the poractant alfa group ( $p = 0.09$ ). The calfactant group had more female patients, whereas there were more male patients in the poractant alfa group ( $p = 0.036$ ). There was no difference in GA, birth weight, APGAR scores, or maternal complications.

**Primary End Points.** Efficacy outcomes for preterm infants with RDS are shown in Table 2. Patients who received calfactant required a higher average number of doses than those who received poractant alfa (1.5 vs 1.3 doses,  $p = 0.031$ ), but they had a comparable need for surfactant redosing (37.3% vs 28.1%,  $p = 0.12$ ). The need for mechanical ventilation, the hospital length of stay, and in-hospital mortality were similar between both groups.

**Secondary End Points.** Safety and pharmacoeconomic outcomes are presented in Table 3. The calfactant group had more administration complications than those who received poractant alfa (10.2 vs 2.2%,  $p = 0.008$ ). Of the 12 complications in the calfactant group, there were 6 oxygen desaturations, 5 instances of combination of oxygen desaturation and bradycardia, and 1 airway occlusion; however, there were only 3 complications in the poractant alfa group, 2 oxygen desaturations, and 1 combination of oxygen desaturation and bradycardia. The estimated average patient cost was 32% lower in calfactant than in those who received poractant alfa (\$1,439 vs \$1,901,  $p < 0.001$ ). Thus, calfactant's estimated 1-year total cost was \$86,834 lower than poractant alfa (\$169,785 vs \$256,619), whereas the development of BPD was similar between both groups (49% vs 51%,  $p = 0.54$ ).

**Table 2.** Comparison of the Primary End Points Between Calfactant and Poractant Alfa

Parameters	Calfactant (n = 118)	Poractant Alfa (n = 135)	p value
Average number of doses, mean $\pm$ SD	1.5 $\pm$ 0.8	1.3 $\pm$ 0.6	0.031
Surfactant redosing, n (%)	44 (37.3)	38 (28.1)	0.12
2 doses	29 (24.6)	31 (23)	
3 doses	12 (10.2)	6 (4.4)	
4 doses	3 (2.5)	1 (0.7)	
Mechanical ventilation on day 3, n (%)	93 (78.8)	107 (79.3)	0.08
Hospital length of stay, mean $\pm$ SD, days	81 $\pm$ 52	77 $\pm$ 74	0.67
In-hospital mortality, n (%)	7 (5.9)	7 (5.2)	0.79

## Discussion

Respiratory distress syndrome is a severe and potentially fatal cause of respiratory failure due to the insufficiency in surfactant production of preterm infants.<sup>1–4</sup> Exogenous surfactant is crucial in reducing morbidity, mortality, and economic burden in preterm infants with RDS. Thus, surfactant is currently being listed as an important treatment in the World Health Organization Model List of Essential Medicines for Children.<sup>23,24</sup> Literature regarding the selection of most efficacious surfactant is still conflicting and not definitive.<sup>11–17</sup> Medical City Dallas had used calfactant until December 2020, and switched over to the new surfactant of choice, poractant alfa, based on recently published literature<sup>14,15</sup> and physicians' previous experience at other institutions. We therefore sought to evaluate the differences in efficacy, safety, and pharmacoeconomic outcomes between calfactant and poractant alfa for RDS at this institution. Preterm infants received the first dose as soon as possible after birth or once the diagnosis of RDS was made. Based on the Medical City Dallas's NICU Administration of Surfactant Policy, up to 3 additional doses may be repeated if patients were still intubated receiving at least 30% to 40% inspired oxygen to maintain arterial oxygen saturation  $>88\%$ , or with a partial pressure of oxygen  $<60$  torr on  $>30\%$  inspired oxygen.<sup>18,25,26</sup> Fourth dose was generally less common unless patients continued to be in severe respiratory failure requiring high mechanical ventilator settings, and significant amount of supplemental oxygen. As shown in Table 3, the need for surfactant redosing was comparable between both groups (37.3% in calfactant vs 28.1% in poractant alfa,  $p = 0.12$ ) and was similar to the findings by Zayek et al.<sup>17</sup> There were 2.5% of patients in the calfactant group vs 0.7% of patients in the poractant alfa group who received the

**Table 3.** Comparison of Safety and Pharmacoeconomic Outcomes Between Calfactant and Poractant Alfa

Parameters	Calfactant (n = 118)	Poractant Alfa (n = 135)	p value
Administration complications, n (%)	12 (10.2)	3 (2.2)	0.008
Bronchopulmonary dysplasia, n (%)	49 (41.5)	51 (37.8)	0.54
Estimated average patient cost, mean $\pm$ SD, \$	1439 $\pm$ 932	1901 $\pm$ 1000	$<0.001$
Estimated 1-year total surfactant cost (\$)	169,785	256,619	N/A

N/A, not applicable

fourth surfactant dose. In addition, preterm infants in calfactant group required a greater average number of doses compared with poractant alfa (1.5 vs 1.3 doses,  $p = 0.031$ ), which was a finding different from that of Gerdes et al<sup>27</sup> (1.67 vs 1.72 doses), and Zayek et al<sup>17</sup> (1.6 vs 1.7 doses,  $p = 0.03$ ). This could be contributed to calfactant group had more micropreemies (22–25 weeks GA) than the poractant alfa group in this study, although the difference in patient population was not statistically significant. This added an unexpected finding to this study; even when the calfactant group had more micropreemies, only 66% of patients (29 of 44 patients) received the second dose, and it was less than 82% of patients (31 of 38 patients) who received poractant alfa's second dose. Although calfactant is a bovine lung lavage preparation, poractant alfa is derived from a minced porcine lung extract that contains the highest amount of polyunsaturated fatty acid phospholipids and plasmalogen, which had been shown to decrease mortality rate and risk for BPD.<sup>28,29</sup> Although this study did not detect a difference in mortality or BPD development between calfactant and poractant alfa, poractant alfa had lower incidence of administration complications, including endotracheal tube or airway occlusion, oxygen desaturation, and bradycardia. The higher phospholipid concentration in poractant alfa had been shown to allow for smaller administration volume, facilitate more rapid administration, favor less time to recovery, and decrease incidences of oxygen desaturation and bradycardia.<sup>23,27</sup>

In terms of mortality, Ramanathan et al<sup>13</sup> analyzed all-cause mortality in 14,173 preterm infants and found an approximately 50% reduction in odds of mortality of poractant compared with calfactant. Similarly, Sekar et al<sup>14</sup> concluded that preterm infants who received poractant had lower odds for mortality and needed less mechanical ventilation support compared with calfactant. Lower mortality risks of poractant alfa may be attributed to the higher initial doses, whereas calfactant used the same dose throughout the treatment course.<sup>23</sup> However, this study did not detect a difference between calfactant and poractant alfa for in-hospital mortality, even in the 22 to 23 weeks GA subgroup (22% vs 25%,  $p = 0.91$ ).

Adopting a surfactant intervention for RDS in clinical practice requires consideration for both cost-effectiveness, and clinical effectiveness. Despite poractant alfa being shown to be more clinically effective than calfactant at reducing death, need for oxygen, and mechanical ventilation, poractant alfa's average per patient cost was shown to be higher, and it may be not as cost-effective compared with calfactant in clinical practice.<sup>2,17</sup> Poractant alfa's cost of treatment was 38% higher than calfactant, and the 22-month cost difference could reach up to \$202,732.75 in the hospital.<sup>17</sup> At our level IV NICU, the estimated average patient cost for poractant alfa was also 32% higher than calfactant. With

a similar percentage of re-dosing between both groups, the higher pharmacoeconomic cost for poractant alfa could potentially be related to higher initial dosing, the higher number of patients in the poractant group, and more patients in 32 to 36 weeks GA as the dose volume increased according to body weight. Based on the 2016 Healthcare Cost and Utilization Project's statistical report, pediatric hospital stays or overall health care cost for extreme prematurity or RDS in the United States had the highest aggregate costs of \$6.53 billion, accounting for nearly 14% of all pediatric inpatient costs in 2016.<sup>30</sup> Thus, more evidence is needed to justify the correlation between pharmacoeconomic cost (cost-effectiveness), and patient's overall health care cost (clinical effectiveness).

This study had several limitations. It was a single-center, retrospective study with a small sample size, and there was a lack of power to detect significant difference between both treatment groups. There was also practice variation regarding the timing of surfactant redosing among physicians, thus it could not be confirmed that the NICU Administration of Surfactant Policy's criteria was strictly followed. Patient-specific respiratory data, such as inspired oxygen requirement or partial pressure of oxygen use, would have been beneficial to determine if patients met criteria for redosing. Furthermore, in-hospital mortality and other study end points described association and did not imply causation. Despite these limitations, this study presented novel findings regarding the efficacy, safety, and pharmacoeconomic outcomes of calfactant vs poractant alfa. The findings of this study could potentially be generalizable to US preterm infants with RDS at the highest level of NICU care. Larger data sets and prospective controlled trials would provide more clarity and better assist with surfactant selection in preterm infants with RDS.

## Conclusion

In summary, RDS is a continual cause of morbidity and mortality in preterm infants. Appropriate use and selection of a surfactant product is crucial in the management of RDS. Despite the pharmacoeconomic disadvantage, preterm infants who received poractant alfa needed fewer doses and were less likely to have administration complications compared with those who received calfactant.

## Article Information

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