Poractant Alfa Versus Beractant for Neonatal Respiratory Distress Syndrome: A Retrospective Cost Analysis

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OBJECTIVES The objectives of this study were to determine the average medication cost per patient of poractant alfa and beractant, and to compare the outcomes of treatment with these agents.

METHODS We conducted a retrospective, observational, cohort study of patients who received surfactant, before and after an institutional formulary change from beractant to poractant alfa. The primary outcome was the average medication cost per case. Secondary measures were clinical outcomes, including duration of respiratory support, length of hospital stay, and the occurrence of complications.

RESULTS A total of 114 patients were enrolled; 38 were treated with poractant alfa and 76 patients were treated with beractant. Baseline characteristics were similar between groups. The average medication cost per patient was $\$1756.44 \pm \1030.06 and $\$1329.78 \pm \705.64 for poractant alfa and beractant, respectively ($p = 0.011$). Patients treated with poractant alfa had a shorter length of stay (45.0 ± 30.5 days) than patients treated with beractant (65.1 ± 37.1 days) ($p = 0.010$). Rates of pneumothoraces, pulmonary hemorrhage, necrotizing enterocolitis, intraventricular hemorrhage, and mortality did not differ significantly between groups.

CONCLUSIONS We found an unanticipated increase in drug cost with poractant alfa compared to beractant.

ABBREVIATIONS INSURE, INTubation-SURfactant-Extubation; LOS, length of stay; RDS, respiratory distress syndrome

KEYWORDS beractant; neonatal respiratory distress syndrome; neonates; pharmacoeconomic; poractant alfa; surfactant

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Introduction

Respiratory distress syndrome (RDS) is a significant complication of prematurity. Administration of exogenous surfactant is the mainstay of RDS treatment; however, the optimal surfactant product and dosing strategy remain a subject of ongoing research and debate. Two commonly used products in the United States and Europe are beractant and poractant alfa. Studies comparing beractant to poractant alfa have demonstrated varied results regarding the efficacy of the products. Based on available data, the American Academy of Pediatrics does not recommend any specific surfactant product based on clinical superiority.¹ Conversely, current European consensus guidelines specifically note that there is a survival advantage with the use of poractant alfa compared to beractant; however, it is unclear whether this difference is related to differences in dosing or surfactant preparation.² To date, no trial has shown any surfactant product to be clearly superior.

For economic and medication safety reasons, it is advantageous for institutions to choose a single formulary surfactant product. No published trials have

shown either product to be more cost-effective when used in clinical practice. The only pharmacoeconomic trial comparing poractant alfa and beractant was a cost minimization analysis that used predictive modeling and data from clinical trials to extrapolate cost.³ In March 2015, our health system introduced a change of formulary surfactant product from beractant to poractant alfa. The motivation for this change was an internal consideration of the cost minimization analysis by Marsh and colleagues.³ This series of 3 economic models of comparing poractant alfa to beractant projected a cost savings using poractant alfa, driven by a less frequent need for redosing with poractant. To date, no data comparing the overall cost of the 2 products have been published. This study aimed to evaluate cost and outcomes data in a retrospective cohort of patients before and after a change in surfactant product at an urban community teaching hospital with a 35-bed, level III, neonatal intensive care unit.

Materials and Methods

We conducted a single center, retrospective, observational, cohort study of patients who received surfactant before and after a formulary change from

Table 1. Patient Characteristics (N = 114)

Characteristic	Beractant (n = 76)	Poractant alfa (n = 38)	p value
Gestational age, wk*	28.2 ± 3.2	29.3 ± 4.3	0.185
Birth weight, kg*	1.3 ± 0.8	1.4 ± 0.7	0.240
Sex, n (%), male	50 (65.8)	20 (52.6)	0.174
Race, n (%)†	30 (39.5)	20 (52.6)	N/A
White	40 (52.6)	18 (47.4)	
Black	2 (2.6)	0 (0)	
Other			
Insurance status, n (%)‡	45 (59.2)	19 (50)	N/A
Private	29 (38.2)	18 (47.4)	
Medicaid	1 (1.3)	0 (0)	
Self-pay			
Antenatal steroid use, n (%)	38 (50)	18 (48.6)	0.893
Genetic/congenital abnormalities, n (%)	7 (9.2)	3 (7.9)	0.815
Initial FiO ₂ *	0.60 ± 0.27	0.58 ± 0.30	0.753
INSURE surfactant delivery	6 (7.8)	5 (13)	0.375

INSURE, INTubation-SURfactant-Extubation; N/A, not applicable

* Mean ± SD.

† Four patients had missing data.

‡ Two patients had missing data.

beractant to poractant alfa. A list of patients was generated from the pharmacy information system, and electronic medical records were evaluated to retrieve outcomes data. Patients receiving surfactant for treatment of RDS within the first week of life were included; patients were excluded if they received surfactant for any other indication or their first dose was received at another institution. The standard of practice at our institution is to use surfactant for RDS in patients who are intubated for the purpose of mechanical ventilation or by the INTubation-SURfactant-Extubation (INSURE) method. The use of surfactant for RDS prophylaxis was not routine during the study period. Patients in the beractant group were randomly chosen from all patients who received surfactant in the year before the formulary change, March 2014 to February 2015, by using a random number generator. The poractant alfa group included all patients who received surfactant since the change, March 2015 to October 2015. The study was approved by the hospital's institutional review board; written informed consent was not required owing to the observational design.

Poractant alfa was dosed at 200 mg/kg for the first dose and then at 100 mg/kg every 12 hours, for up to 2 additional doses. Beractant was dosed at 100 mg/kg every 6 hours, for a total of up to 4 doses. Per institutional guidelines, redosing was considered to be appropriate if the required FiO₂ at the time of the next dose was greater than 30%, and all doses were to be based on birth weight. Adherence to conditions for redosing were recorded. Redosing was considered to be appropriate if the interval was at least 12 hours for

poractant alfa or 6 hours for beractant, the FiO₂ at the time of redosing was at least 30%, and birth weight was used to calculate the patient's dose.

Data collection consisted of baseline demographics, the surfactant cost per case, as calculated from product dispensing data and average wholesale price in 2016 dollars, total hospital costs (charge data), and the outcomes of treatment. Specific outcomes that were collected were duration of mechanical ventilation (hours), duration of non-invasive respiratory support (hours), total duration of respiratory support (hours), duration of oxygen requirement (hours), length of stay (LOS), total number of doses of surfactant given, and the occurrence of complications such as pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, intraventricular hemorrhage, and mortality.

The study was powered to detect a difference in drug cost as the primary endpoint. Previous studies reported the cumulative dose per patient was 218 mg ± 115 mg for beractant and 273 mg ± 87 mg for poractant alfa.⁴ Average wholesale price in 2016 United States dollars was used for all calculations, assuming the smallest full vial to generate each dose was used in all cases.⁵ Poractant alfa cases and beractant cases were included in a 1:2 ratio. The number of patients in each group was based on a known available sample size in the poractant group. With an alpha error rate of 0.05 and a total sample size of 114 (38 poractant alfa cases and 76 beractant cases), the study was estimated to have 94% power to detect a difference in cost of \$171.82.

Statistical Analysis. Descriptive statistics were generated to characterize the study group. Continuous

Table 2. Cost Analysis in United States Dollars

Parameter	Beractant	Poractant alfa	p value
Average hospital charges	290,158 ± 228,257	258,083 ± 197,332	0.462
Average medication cost	1329.78 ± 705.64	1756.44 ± 1030.06	0.011
Dose 1	694.22 ± 272.89 (n = 76)	1293.67 ± 609.95 (n = 38)	<0.001
Dose 2	615.85 ± 231.62 (n = 45)	657.60 ± 278.93 (n = 19)	0.533
Dose 3	641.34 ± 279.26 (n = 22)	727.26 ± 363.68 (n = 7)	0.976
Dose 4	661.81 ± 189.15 (n = 7)	N/A	N/A
Proportion receiving 1 dose	29 (38.2%)	19 (50%)	0.22

N/A, not applicable

variables were described by using the mean and standard deviation. Categorical variables were described as frequency distributions. Differences in cost between the 2 groups were assessed by using Student's *t* test. Differences in ventilation and oxygenation requirements were assessed by using the Mann-Whitney *U* test because the data were not normally distributed. Differences in categorical clinical outcomes were assessed by using chi-squared analysis. All data were analyzed with SPSS v. 23.0 (International Business Machines Corp, Armonk, New York) and a *p* value of 0.05 or less was considered to indicate statistical significance.

Results

There were 127 patients who received surfactant between March 2014 and October 2015. Of these, 114 patients were enrolled: 38 patients were treated with poractant alfa; and 76 patients were treated with beractant, who were randomly selected from a sample of 89. There were no baseline differences in gestational age, birth weight, sex, race, insurance status, antenatal steroid use, presence of genetic or congenital abnormalities, indication, or initial FiO_2 requirement (Table 1).

Patients received an average of 1.68 ± 0.77 doses of poractant alfa and 2.01 ± 0.97 doses of beractant, which was not significantly different (*p* = 0.072). The percentage of patients receiving only 1 dose of surfactant was 50% in the poractant alfa group and 38.2% in the beractant group, which was not significantly different (*p* = 0.22). Redosing was appropriate in 17 of 26 doses (65%) of poractant given and 48 of 75 doses (64%) of beractant given (*p* = 0.93). The most common reason redosing was considered inappropriate was FiO_2 less than 30%. The second most common reason doses were considered inappropriate was that the patient's current weight, rather than birth weight, was used for the calculation of the dose. No patients received late doses of surfactant. The average medication cost was \$1756.44 ± \$1030.06 and \$1329.78 ± \$705.64 for poractant alfa and beractant, respectively (*p* = 0.011) (Table 2). The average hospital charges were \$258,083 ± \$197,332 and \$290,158 ± \$228,257 for poractant alfa and beractant, respectively (mean difference \$32,075, *p* = 0.462).

Patients treated with poractant alfa had a shorter LOS than those treated with beractant (*p* = 0.010) (Table 3). For patients treated with poractant alfa, duration of mechanical ventilation, duration of respiratory support, and duration of oxygen requirement were shorter; however, these were not statically significant. Patients who died or were transferred to another facility were not included in the duration of oxygenation and LOS calculations. Rates of pneumothoraces, pulmonary hemorrhage, necrotizing enterocolitis, intraventricular hemorrhage, and mortality did not differ significantly between groups. These data points were missing for 1 patient in the beractant group and 2 patients treated with poractant alfa.

Discussion

Our study aimed to evaluate differences in cost and outcomes with poractant alfa versus beractant in the management of neonatal RDS. The primary finding was an unanticipated increase in drug cost with poractant alfa over beractant. We had projected a reduction in drug costs secondary to a decreased need for redosing with poractant alfa versus beractant, as projected in the cost minimization analysis published by Marsh et al.³ However, the shorter length of hospital stay observed in the poractant alfa group resulted in an overall lower cost of care for the hospital admission. Length of stay was 20 days shorter in the poractant alfa group, which is unlikely to be explained by change in surfactant alone. While the overall trend toward shorter duration of respiratory support with poractant alfa is consistent with previous studies, the magnitude of the change is more than could be expected from change in surfactant alone.⁶⁻⁹ The magnitude of the difference we observed was likely influenced by confounding variables such as differences between the study groups and changes in clinical practice that occurred during the study period.

Many factors could have impacted the increase in cost observed with poractant alfa. The increased proportion of patients requiring only 1 dose of surfactant with poractant alfa, which was observed in previous studies, was not observed in this study.⁷⁻⁹ Although we showed no difference in the proportion of patients

Table 3. Outcomes

	Beractant (n = 63)	Poractant alfa (n = 32)	p value
Duration (mean $\pm$ SD)			
Mechanical ventilation, hr*	511.9 $\pm$ 637.1	371.5 $\pm$ 568.9	0.297
Respiratory support, hr*	730.8 $\pm$ 1060.4	612.3 $\pm$ 1012.6	0.389
Non-invasive respiratory support, hr*	521.5 $\pm$ 743.1	409.4 $\pm$ 643.6	0.594
Oxygen requirement, hr*	1201.5 $\pm$ 1042	747.3 $\pm$ 757.5	0.075
Hospital stay, days*	65.1 $\pm$ 37.1	45.0 $\pm$ 30.5	0.010
Complication, n (%)	n = 75	n = 36	
Pneumothorax	9 (12.0)	6 (16.7)	0.501
Pulmonary hemorrhage	4 (5.3)	0	N/A
Necrotizing enterocolitis	5 (6.7)	3 (8.3)	0.751
Intraventricular hemorrhage	12 (16.0)	6 (16.7)	0.929
Mortality	10 (13.3)	2 (5.6)	0.217

N/A, not applicable

receiving only 1 dose of poractant alfa, this could be due to our institution's previous practice with beractant. A high percentage of doses after the first dose were given to patients not meeting at least 1 of the recommended criteria for redosing. While this percentage was similar between groups, this could have impacted the difference in cost observed. It is also important to note that the cost calculation in this study used the price for the nearest-sized whole vial(s) required to make each patient's surfactant dose, which generates waste. Pharmacies that batch surfactant doses would likely see a decrease in cost relative to that reported in this study, and that cost may be influenced by other factors such as product stability.

Previous studies comparing beractant to poractant alfa have demonstrated varied results. Some studies have shown comparable efficacy^{10,11} or increased short-term benefits, such as shorter duration of intubation, without changes in mortality with poractant alfa.^{6,7} However, others have shown a need for fewer doses and improved mortality with poractant alfa, when compared to beractant.^{8,9} A recent meta-analysis by Singh and colleagues¹² demonstrated a reduction in mortality and need for redosing with poractant alfa, when compared to beractant. However, another recent meta-analysis by Zhang and colleagues¹³ did not find a difference. Interpretation of all of the aforementioned data is limited because of significant changes in neonatal ventilation techniques that have occurred since these studies were conducted. Such changes in practice also limit the interpretation of the results of the present study. Changes in ventilation practices during the study period, which could have contributed to this difference, include increased use of early continuous positive airway pressure and implementation of nasal synchronized intermittent mandatory ventilation, beginning in early 2015, which would have affected the poractant

alfa cohort more than the beractant cohort.

This study is limited by its single center, retrospective design. Collection of data was dependent on the accuracy of the medical record; some data were missing and some information may not have been accurate. As the beractant and poractant alfa cohorts were treated at different times, there were differences in clinical practice we could not control for, such as changes in ventilation techniques, and there may have been other confounding factors that were not able to be identified. While differences in baseline characteristics did not reach statistical significance, there were other variables that could have influenced the results. Patients in the beractant group were younger, smaller, and more likely to be male; these are all poor prognostic factors in the setting of prematurity.¹⁴ It is also possible that other unmeasured confounders factored into the difference in LOS. The reduced LOS associated with poractant alfa was not associated with improvement in important RDS-related outcomes such as pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, or intraventricular hemorrhage.

Conclusions

Controlling costs and improving value in health care is increasingly important, and this is the first study comparing the cost of beractant and poractant alfa. Our results provide valuable insight into the difference in medication cost observed in practice between the 2 agents. The drug cost savings predicted with poractant alfa was not observed in this study.³ However, our observation of significantly shorter length of hospital stay and decreased overall cost of care associated with poractant alfa raises further questions regarding the impact of agent selection and complexities of outcomes. Owing to the retrospective nature of this study and

changes in standard of care during the study period, it remains unclear what impact the choice of surfactant had on the differences in cost we observed. Future randomized controlled trials comparing these agents, using current standards of care in neonatal ventilation, would be required to recommend the use of one agent over the other.

ARTICLE INFORMATION

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