Health Economics and Outcomes of Surfactant Treatments for Respiratory Distress Syndrome Among Preterm Infants in US Level III/IV Neonatal Intensive Care Units

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OBJECTIVE To compare length of stay (LOS), costs, mechanical ventilation (MV), and mortality in preterm infants treated in the Neonatal Intensive Care Unit (NICU) with beractant (BE), calfactant (CA), and poractant alfa (PA) for Respiratory Distress Syndrome (RDS).

METHODS This study evaluated preterm infants born between 2010 and 2013 with RDS diagnosis, gestational age of 25 to 36 weeks, birthweight of ≥ 500 g, and age of ≤ 2 days on first surfactant administration. Multivariable regression was used to evaluate all NICU outcomes.

RESULTS Of 13,240 infants meeting the study criteria, 4136 (31.2%) received BE, 2502 (18.9%) received CA, and 6602 (49.9%) received PA. Adjusted analyses estimated similar mean LOS (BE 26.7 days, CA 27.8 days, and PA 26.2 days) and hospital costs (BE: \$50,929; CA: \$50,785; and PA: \$50,212). Compared to PA, BE and CA were associated with greater odds of MV use on day 3 (OR = 1.56 and 1.60, respectively) and day 7 (OR = 1.39 and 1.28, respectively; all $p < 0.05$). Adjusted NICU mortality was significantly higher only with CA vs PA (OR = 1.51; $p = 0.015$).

CONCLUSION Adjusted NICU LOS and costs were similar among BE, CA, and PA. Infants receiving PA were less likely to be on MV at 3 and 7 days, and PA treatment was associated with lower odds of NICU mortality when compared to CA.

ABBREVIATIONS APR-DRG, All Patient Refined Diagnosis Related Group; BE, beractant; BW, birthweight; CA, calfactant; ICD-9 (-CM), *International Classification of Diseases*, 9th revision (clinical modification); GA, gestational age; GLM, generalized linear model; HCUP, Healthcare Cost and Utilization Project; LOS, length of stay; MV, mechanical ventilation; NICU, neonatal intensive care unit; PA, poractant alfa; RDS, respiratory distress syndrome; ROM, risk of mortality; SOI, severity of illness

KEYWORDS beractant; calfactant; costs; length of stay; mechanical ventilation; mortality; poractant alfa; respiratory distress syndrome; surfactant

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Introduction

Respiratory Distress Syndrome (RDS) in preterm infants is due to insufficient production of surfactant.¹ Its incidence is inversely related to gestational age (GA) and birthweight (BW). This condition is seen in 60% of infants born at <28 weeks of gestation and in 30% of infants born between 28 and 34 weeks of gestation but is only observed in $<5\%$ of infants born after 34 weeks of gestation.¹ The management of RDS consists of antenatal steroids, surfactant replacement, oxygen administration, positive-pressure ventilation, and nutritional support.^{2,3} Respiratory distress syndrome in preterm infants is associated with significant morbidity and mortality.^{2,4}

In the United States, RDS is seen in about 1% of

pregnancies and affects 20,000 to 30,000 infants each year.² The costs to treat RDS in preterm infants are substantial, and the economic burden reflects the required high level of care provided by Level III and IV Neonatal Intensive Care Units (NICUs).^{5–8} The Healthcare Cost and Utilization Project (HCUP) reported⁹ an average cost of hospitalization for RDS of \$55,000, compared to \$3,200 for all newborns in 2011, with hospital stays of 31.3 days and 3.4 days, respectively. Length of stay (LOS) and costs for RDS documented in this briefing are approximately twice that of preterm and low-BW infants. For newborns who died during hospitalization (including preterm, low-BW, and RDS infants) the average stay was 7.4 days, with an average cost of \$28,600.⁹

Administration of animal-derived (bovine and porcine) surfactants at birth or shortly thereafter has greatly

reduced the morbidity, mortality, and costs associated with treatment of RDS in preterm infants.^{110–13} The use of these surfactants is well established as an effective treatment for RDS.¹¹⁴ To date the only 3 commercially available surfactants in the United States are beractant (BE; Survant, AbbVie, Inc, North Chicago, IL), calfactant (CA; Infasurf, ONY Biotech, Amherst, NY), and poractant alfa (PA; Curosurf, Chiesi Farmaceutici SpA, Parma, Italy). Much of the available literature^{10,15,16} related to the various exogenous surfactants accrues from several prospective, randomized, controlled studies comparing surfactant with placebo and surfactants with each other. However, there appears to be a paucity of comparative economic data among the available surfactants in the United States. Although 2 more recent retrospective studies^{17,18} compared clinical outcomes of the above 3 natural surfactants, they did not assess healthcare resource utilization or costs. No comparative study has specifically focused on these outcomes within the most critical and most resource-intensive time period following the development and treatment of RDS, which is the time in the NICU. Furthermore, this analysis differs from previous retrospective analyses in that it captures data more reflective of the change in standards of care for RDS patients, which has shifted toward non-invasive ventilation with selective surfactant administration and rapid extubation.^{11,19–21}

The overall purpose of this study was to retrospectively assess the associations between the use of surfactants (BE, CA, and PA) and LOS, costs, mechanical ventilation (MV), use on hospital days 3 and 7, and mortality during the index NICU period of treatment in a large patient population representative of real-world settings in the United States.

Materials and Methods

Study Design and Patient Population. A retrospective observational study was conducted using the Premier Healthcare Database (Premier, Inc, Charlotte, NC). The study was designed to assess the association of surfactant treatment with either BE, CA, or PA on healthcare resource use and clinical outcomes in preterm infants diagnosed with RDS and treated in Level III or Level IV NICUs of the hospitals in which they were born. Healthcare resource used included LOS and costs. Clinical outcomes included MV and mortality.

Infants born from January 1, 2010, through December 31, 2013, with an *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9) diagnosis code for RDS (ICD-9 769), a GA of ≥ 25 and < 37 weeks, and a BW of ≥ 500 g were identified. Completed weeks of gestation were categorized into 2-week intervals from 25 to 26 weeks through 35 to 36 weeks, and BW was categorized into 250-g groups from 500 to 749 g to ≥ 1750 g, as identified by ICD-9 diagnosis codes (Table S1). Preterm infants who were ≤ 2 calendar days of age on the first day of surfactant administration were

included in the assessment. Infants with more than one surfactant therapy, serious congenital abnormalities (as identified by ICD-9 diagnosis codes [Table S2]) (Figure 1), or missing cost data were excluded.

Data Source. The Premier database is a large US hospital-based, service-level, all-payer database that contains information on more than 6 million annual hospital discharges representing approximately 20% of annual inpatient discharges. The data are statistically deidentified and HIPAA compliant. Institutional review board approval for this study was not required, based on US Title 45 Code of Federal Regulations, Part 46, because the study used existing data, and because recorded information could not be identified directly or through identifiers linked to individuals.²²

Study Variables and Measured Outcomes. Study variables included patient and hospital characteristics. Patient demographics included age, sex, and race/ethnicity. Patient severity was captured by the 3M All Patient Refined Diagnosis Related Group (APR-DRG) severity of illness (SOI) and risk of mortality (ROM) levels, which were determined by algorithms based on age and clinical severity of primary and secondary diagnoses assigned to the hospitalization.²³

Outcomes data coincided with days attributed to the NICU and were limited to the first (index) set of consecutive NICU days if an infant had more than one distinct string of days in the NICU. Length of stay and costs, use of MV, and mortality were examined for the overall study population and 3 distinct surfactant-treated cohorts. Some analyses were stratified by the GA intervals (Table S3). To adjust for the differences in timing of costs across several years, cost values were standardized to 2013 US dollars based on the average consumer price index per year provided by the US Bureau of Labor Statistics.²⁴ Use of MV during the index NICU period was determined at day 3 and day 7.^{25,26} Mortality was assessed only during the index NICU period.

Statistical Analyses. Descriptive statistics were performed for each of the BE, CA, and PA surfactant-treated cohorts. Continuous data were expressed as mean, standard deviation, and median. Means were compared by Student *t*-tests. Categorical data were expressed as frequencies and percentages and compared using chi-squared tests. Missing data were removed from analysis.

Adjusted analyses were performed using multivariable regressions for outcomes of index NICU LOS, cost, MV use on days 3 and day 7, and mortality. Continuous outcomes were modeled using generalized linear models (GLMs) with log link and Gamma distribution. Count outcomes were modeled using GLM regressions with log link and negative binomial distribution. Dichotomous outcomes such as presence of MV at day 3 and at day 7, as well as mortality, were modeled using logistic regression. The inclusion of a random center (hospital) effect in the models²⁷ accounted for

Figure 1. Attrition diagram. Left panel shows attrition of the total newborn population from January 1, 2010, through December 31, 2013, receiving surfactant within 2 days of birth, treated in a level III or IV NICU, and diagnosed with RDS. Right panel further shows the attrition of these newborns receiving only one surfactant and meeting inclusion criteria for gestational age, birthweight, and born without serious congenital abnormalities and receiving surfactant during the index NICU stay. FDA-approved dosages (based on birthweight): beractant 100 mg/kg (initial and repeat doses); calfactant 105 mg/kg (initial and repeat doses); poractant alfa 200 mg/kg (initial dose), 100 mg/kg (repeat dose).

the multilevel structure due to the clustering of infants within hospitals. All models included the same patient and hospital-level covariates, as follows: surfactant used (BE, CA, or PA); GA (ranging from 25 to 36 weeks in 2-week increments); BW (500–749, 750–999, 1000–1249, 1250–1499, 1500–1749, or 1750+ g); male sex (yes/no); race and ethnicity (black, Hispanic, white, or other); APR-DRG SOI (0, 1–2, or 3–4); APR-DRG ROM (0, 1–2, or 3–4); hospital bed size (1–199, 200–299, 300–499, or 500+ beds); population served (urban or rural); provider area (Midwest, Northeast, South, or West); primary payer category (commercial/managed care, Medicaid, or Medicare/self-pay/other assistance/other); and teaching status of hospital (yes/no).

Data analysis was performed using SAS software version 9.4 (Copyright, SAS Institute Inc, Cary, NC). An alpha value of <0.05 was considered statistically significant. Whereas the conclusions of the study are based on the adjusted results, unadjusted analyses are presented to provide context for the choices of covariates and model structure, including the importance of accounting for the hospital effect.

Results

Study Populations. Of the identified 13,240 preterm

infants with RDS meeting study criteria, 4136 (31.2%) received BE, 2502 (18.9%) received CA, and 6602 (49.9%) received PA (Figure 1). All preterm infants were treated in the hospitals in which they were born. A total of 209 hospitals provided data for the study. Beractant, CA, and PA preterm infants were treated at 90, 51, and 120 hospitals, respectively.

Patient Demographics and Clinical Characteristics.

For the overall population, almost 75% of the infants had a GA between 27 and 34 weeks, with more than one-third weighing ≥ 1750 g (Figure 2A and B). There were no statistical differences observed in the distribution of GA and BW among the 3 surfactant groups (Table 1).

For the overall group, most infants were male (57.6%), and the majority were white (53.0%) or black (18.4%). Most were insured through Medicaid (49.5%) or commercial/managed care insurance companies (47.2%). Approximately three-fourths of the infants were classified with an APR-DRG SOI of “major” (49.4%) or “extreme” (27.0%) and an ROM of “minor” (41.5%) or “moderate” (34.7%). Although no sex differences between the surfactant cohorts were observed, significant differences in distribution of race (all $p < 0.0001$), primary payer categories (all $p < 0.02$), SOI (all $p < 0.003$), and ROM (all $p < 0.02$) were observed (Table 1).

Figure 2. Distribution of gestational age (A) and birthweight (B) intervals plotted against percent of preterm infants for the overall study population.

BE, beractant; CA, calfactant; PA, poractant alfa cohorts.

Hospital Characteristics. Most preterm infants were treated in hospitals in the south (50.4%) and in urban locations (94%). The distribution of provider regions was different among the 3 treatment cohorts (all $p < 0.0001$), but the difference in the distribution of urbanicity between BE and CA was not statistically significant. Just over half (53.4%) of the infants were treated in teaching hospitals. The distribution of non-teaching and teaching hospitals was different between all surfactant groups (Table 2; all $p < 0.0001$). Except for the BE cohort, in which more than half were treated in non-teaching hospitals (52.0%), the majority of CA and PA infants were treated in teaching hospitals. Most (83.6%) of the infants were treated in hospitals with more than 300 beds. Distribution by bed size was different between

surfactant groups (all $p < 0.0001$), although most infants were treated in larger hospitals with 300 or more beds (Table 2).

Measured Outcomes. Index NICU Length of Stay. Descriptive Analysis. Mean unadjusted LOS for the overall population was 32.4 ± 30.3 days (Table 3). Mean unadjusted LOS was significantly shorter for BE (30.9 ± 28.9 days) when compared to both CA (33.0 ± 33.3 days, $p = 0.0090$; $\Delta 2.1$ days) and PA (33.0 ± 29.8 days, $p = 0.0002$; $\Delta 2.1$ days). No significant difference in unadjusted LOS was noted between CA and PA.

Adjusted Analysis. No significant differences in mean adjusted LOS were found between surfactant treatments (data not shown). Mean adjusted LOS (all $p > 0.05$) was 26.7 days (95% CI 24.4–29.1) for BE; 27.8

Table 1. Patient Characteristics of the Overall Study Population and Surfactant Cohorts

	Overall Study Population (N = 13,240)	Beractant (BE) (N = 4136)	Calfactant (CA) (N = 2502)	Poractant Alfa (PA) (N = 6602)	p value		
	n (%)	n (%)	n (%)	n (%)	BE vs CA	BE vs PA	CA vs PA
Gestational age (wk)					0.3224	0.0902	0.0611
25–26	1950 (14.7)	629 (15.2)	399 (16)	922 (14)			
27–28	2421 (18.3)	785 (19)	460 (18.4)	1176 (17.8)			
29–30	2484 (18.8)	771 (18.6)	450 (18)	1263 (19.1)			
31–32	2472 (18.7)	773 (18.7)	473 (18.9)	1226 (18.6)			
33–34	2308 (17.4)	673 (16.3)	447 (17.9)	1188 (18)			
35–36	1605 (12.1)	505 (12.2)	273 (10.9)	827 (12.5)			
Birthweight (g)					0.7430	0.0395	0.1803
0500–0749	918 (6.9)	303 (7.3)	188 (7.5)	427 (6.5)			
0750–0999	2087 (15.8)	661 (16)	412 (16.5)	1014 (15.4)			
1000–1249	2072 (15.7)	690 (16.7)	387 (15.5)	995 (15.1)			
1250–1499	1766 (13.3)	543 (13.1)	312 (12.5)	911 (13.8)			
1500–1749	1469 (11.1)	450 (10.9)	279 (11.2)	740 (11.2)			
1750+	4928 (37.2)	1489 (36)	924 (36.9)	2515 (38.1)			
Sex					0.5157	0.6421	0.2313
Female	5601 (42.3)	1762 (42.6)	1077 (43.1)	2762 (41.8)			
Male	7632 (57.6)	2372 (57.4)	1425 (57)	3835 (58.1)			
Unknown	7 (0.1)	2 (0.1)	0	5 (0.1)			
Race/ethnicity					<0.0001	<0.0001	<0.0001
Black	2438 (18.4)	888 (21.5)	472 (18.9)	1078 (16.3)			
Hispanic	441 (3.3)	242 (5.9)	45 (1.8)	154 (2.3)			
Other	3350 (25.3)	1004 (24.3)	574 (22.9)	1772 (26.8)			
White	7011 (53)	2002 (48.4)	1411 (56.4)	3598 (54.5)			
Primary payer category					<0.0001	0.0108	<0.0001
Commercial/managed care	6249 (47.2)	1873 (45.3)	1249 (49.9)	3127 (47.4)			
Medicaid	6549 (49.5)	2125 (51.4)	1112 (44.4)	3312 (50.2)			
Medicare	71 (0.5)	33 (0.8)	2 (0.1)	36 (0.6)			
Other	137 (1)	19 (0.5)	83 (3.3)	35 (0.5)			
Self-pay/other assistance	234 (1.8)	86 (2.1)	56 (2.2)	92 (1.4)			
APR-DRG severity of illness					0.0027	<0.0001	<0.0001
1 = Minor	538 (4.1)	150 (3.6)	108 (4.3)	280 (4.2)			
2 = Moderate	2570 (19.4)	666 (16.1)	463 (18.5)	1441 (21.8)			
3 = Major	6545 (49.4)	2136 (51.6)	1171 (46.8)	3238 (49.1)			
4 = Extreme	3570 (27)	1179 (28.5)	756 (30.2)	1635 (24.8)			
Not Available	17 (0.1)	5 (0.1)	4 (0.2)	8 (0.1)			
APR-DRG risk of mortality					<0.0001	0.0147	<0.0001
1 = Minor	5499 (41.5)	1704 (41.2)	901 (36)	2894 (43.8)			
2 = Moderate	4597 (34.7)	1456 (35.2)	875 (35)	2266 (34.3)			
3 = Major	2603 (19.7)	825 (20)	605 (24.2)	1173 (17.8)			
4 = Extreme	524 (4)	146 (3.5)	117 (4.7)	261 (4)			
Not available	17 (0.1)	5 (0.1)	4 (0.2)	8 (0.1)			

Table 2. Hospital Characteristics of the Overall Study Population and Surfactant Cohorts

	Overall Study Population (N = 13,240)	Beractant (BE) (N = 4136)	Calfactant (CA) (N = 2502)	Poractant Alfa (PA) (N = 6602)	p value		
	n (%)	n (%)	n (%)	n (%)	BE vs CA	BE vs PA	CA vs PA
Provider area					<0.0001	<0.0001	<0.0001
Midwest	2522 (19.1)	832 (20.1)	309 (12.4)	1381 (20.9)			
Northeast	1745 (13.2)	494 (11.9)	590 (23.6)	661 (10)			
South	6673 (50.4)	2494 (60.3)	1456 (58.2)	2723 (41.3)			
West	2300 (17.4)	316 (7.6)	147 (5.9)	1837 (27.8)			
Population served					0.0734	<0.0001	0.0005
Rural	801 (6.1)	180 (5.3)	133 (5.3)	488 (7.4)			
Urban	12,439 (94)	3956 (95.7)	2369 (94.7)	6114 (92.6)			
Teaching status					<0.0001	<0.0001	<0.0001
Non-teaching	6169 (46.6)	2152 (52)	862 (34.5)	3155 (47.8)			
Teaching	7071 (53.4)	1984 (48)	1640 (65.6)	3447 (52.2)			
Hospital bed size					<0.0001	<0.0001	<0.0001
001–099	86 (0.7)	39 (0.9)	33 (1.3)	14 (0.2)			
100–199	493 (3.7)	148 (3.6)	106 (4.2)	239 (3.6)			
200–299	1597 (12.1)	446 (10.8)	410 (16.4)	741 (11.2)			
300–499	5681 (42.9)	1719 (41.6)	885 (35.4)	3077 (46.6)			
500+	5383 (40.7)	1784 (43.1)	1068 (42.7)	2531 (38.3)			

days (95% CI 25.2–30.8) for CA; and 26.2 days (95% CI 24.0–28.5) for PA.

Index NICU Total Costs. Descriptive Analysis. Cost findings for the overall and surfactant cohorts paralleled those seen for LOS (Table 3). Mean unadjusted total cost for the overall population was \$63,618 ± \$73,686. Mean cost was significantly lower for BE (\$58,522 ± \$62,936) when compared to both CA (\$66,024 ± \$75,027, $p < 0.0001$; Δ \$7502) and PA (\$65,898 ± \$79,068, $p < 0.0001$; Δ \$7376). No significant difference in unadjusted cost was noted between CA and PA.

Adjusted Analysis. No significant differences were observed between surfactant treatments for mean total costs (data not shown). Mean total costs (all $p > 0.05$) for BE, CA, and PA were \$50,929 (95% CI \$46,092–\$56,274); \$50,785 (95% CI \$45,060–\$57,236); and \$50,212 (95% CI \$45,716–\$55,150), respectively.

Index NICU Mechanical Ventilation on Days 3 and 7. Descriptive Analysis. On day 3, 36.5% of all infants were still receiving MV (Table 3). Mechanical ventilation use at day 3 was significantly different among all 3 cohorts ($p < 0.0001$), with the highest rate seen with BE (42.3%), followed by CA (36.9%) and PA (32.6%). By day 7, the rate of MV for the overall population declined to 18.3%. Infants treated with PA had the lowest rate (16.8%), which was significantly less than that noted for BE (19.5%, $p = 0.0004$) and CA (20.1%, $p = 0.0003$).

Adjusted Analysis. When compared to PA, BE and CA were associated with greater adjusted odds of MV use at day 3 (OR = 1.56 [95% CI 1.32–1.84] and OR = 1.60 [95% CI 1.28–2.00], respectively) as well as at day 7 (OR = 1.39 [95% CI 1.16–1.67] and OR = 1.28 [95% CI 1.01–1.61], respectively) (all $p < 0.05$) (Figure 3).

Index NICU Mortality. Descriptive Analysis. Mortality rate for the overall group was 2.0% (Table 3). Both PA (1.8%, $p = 0.0025$) and BE (2.0%, $p = 0.0265$) were associated with significantly lower rates of mortality compared to CA (2.8%). The rate of mortality was similar between BE and PA.

Adjusted Analysis. Neonatal intensive care unit mortality was significantly higher with CA than with PA (OR = 1.51; 95% CI 1.08–2.11, $p = 0.015$) (Figure 3). No other significant differences were noted between BE and PA (OR = 1.09; 95% CI 0.81–1.48, $p = 0.567$) or BE and CA (OR = 0.72; 95% CI 0.51–1.02, $p = 0.068$).

Discussion

The introduction of surfactant in clinical practice has significantly reduced the perinatal mortality and cost of care of extremely premature infants.^{14,28} Large studies^{29,30} looking at the LOS, mortality, and the cost of care are few as a result of difficulties in performing such studies prospectively. Therefore, retrospective

Table 3. Unadjusted Length of Stay, Costs (in 2013 US Dollars), Rate of Mechanical Ventilation on Days 3 and 7, and Rate of Mortality During NICU Index Visit for Overall Study Population and Surfactant Cohorts

	Overall Study Population (N =13,240)	Beractant (BE) (N = 4136)	Calfactant (CA) (N = 2502)	Poractant Alfa (PA) (N = 6602)	p value		
					BE vs CA	BE vs PA	CA vs PA
Length of stay (Days)					0.0090	0.0002	0.9547
n	13,240	4136	2502	6602			
Mean $\pm$ SD	32.4 $\pm$ 30.3	30.9 $\pm$ 28.9	33.0 $\pm$ 33.3	33.0 $\pm$ 29.8			
Median	23.0	22.0	21.0	24.0			
Total costs (2013 USD)					<0.0001	<0.0001	0.9984
n	13,231	4133	2497	6601			
Mean $\pm$ SD	63,618 $\pm$ 73,686	58,522 $\pm$ 62,936	66,024 $\pm$ 75,027	65,898 $\pm$ 79,068			
Median	40,500	37,858	40,338	41,985			
Mechanical ventilation day 3, n (%)					<0.0001	<0.0001	0.0001
	4,827 (36.5)	1748 (42.3)	924 (36.9)	2155 (32.6)			
Mechanical ventilation day 7, n (%)					0.6003	0.0004	0.0003
	2421 (18.3)	808 (19.5)	502 (20.1)	1111 (16.8)			
Mortality, n (%)					0.0262	0.5224	0.0025
	269 (2)	81 (2)	70 (2.8)	118 (1.8)			

database studies such as this are useful in gathering large amounts of clinical data in order to perform robust statistical analyses and to derive meaningful information from different NICU settings.

This study found that adjusted mean LOS and costs between 2010 and 2013, regardless of surfactant employed, ranged between 26.2 days and 27.8 days and between \$50,212 and \$50,929, respectively. Likewise, HCUP reported an average LOS of 31.3 days and a cost of \$54,900 for RDS in 2011, which is concurrent with the study's time frame, supporting the resource utilization findings of this analysis. Similarly defined data do not appear to be retrievable from other sources in the literature. Poractant alfa was associated with similar resource utilization to BE and CA. This was observed even though there were fewer deaths with PA compared to CA. A possible explanation for this finding is that fewer infants in the PA group were on MV on days 3 and 7, suggesting a balance of the total costs through the reduction of overall resources required to support mechanically ventilated infants.

The clinical outcomes associated with PA found in this retrospective real-world study are comparable to those from a number of prospectively designed trials and a recent retrospective administrative database analysis of animal surfactants.¹ Six randomized trials^{31–36} comparing PA and BE reported faster weaning of oxygen and mean airway pressure, fewer days on MV, reduced mortality in infants of ≤ 32 -week gestation, fewer air leaks, and less patent ductus arteriosus for PA.

Higher rates of survival without development of BPD were also noted for PA.

In a 2015 Cochrane Database systematic review, a meta-analysis¹⁶ of 9 randomized controlled trials evaluated several clinical outcomes between BE and PA, in aspects comparable to those investigated in this study. An increased risk of mortality prior to discharge, death or oxygen requirement at 36-weeks postmenstrual age, patent ductus arteriosus requiring treatment, and receiving >1 dose of surfactant were noted for BE compared to PA. However, the differences were found only among studies using larger initial doses of PA (200 mg/kg), which is the only approved initial dose of PA in the United States. Significant differences in the evaluated outcomes between BE and CA were not found in the meta-analysis, and meaningful comparisons between CA and PA were not possible because of a lack of adequate studies.

The recent comparative effectiveness retrospective US study by Trembath et al¹⁸ of 51,282 RDS infants from 322 NICUs managed by the Pediatrix Medical Group and treated with BE, CA, or PA showed no clear advantage of one surfactant with respect to preventing air leaks, developing BPD, and death. These authors included a site-variation covariate, as well as GA, small-for-GA status, and discharge year, as well as antenatal steroid use. In addition to the center effect, GA, and discharge year, the study presented herein identified and controlled for other confounding hospital and newborn clinical variables and chose a range of GA that

Figure 3. Adjusted clinical outcomes. Forest plot depicts the odds ratio with 95% CI for mechanical ventilation at days 3 and 7 and for mortality. For comparisons that are statistically significant ($p < 0.05$), an OR of <1.0 favors the first surfactant and an OR of >1.0 favors the second comparator.

increased the robustness of the analyses and the utility of the results. The lack of antenatal steroid information for the current study may have contributed to certain results that differed from the study by Trembath et al; however, the choice of backward elimination of potential covariates by Trembath may have introduced bias or increased issues with multiple inference, for which this study accounted. Although Trembath et al focused on a fixed center effect model over the random effect approach of this study, they did not find significant differences in results between fixed and random effects approaches.

Study findings of reduced likelihood of MV associated with PA treatment of RDS when compared to BE and CA may have clinical implications for reducing risk for developing BPD. Although this study did not formally capture ICD-9 diagnosis codes to determine the rate of BPD in each of the surfactant cohorts, RDS in preterm infants is a risk factor for its development, and the need for prolonged ventilator support could be used as a determinant for BPD.³⁷ Prior studies^{25,26} have assessed the predictive nature of GA and respiratory support on BPD at a number of time intervals, including postnatal days 3 and 7, among others, suggesting that there is utility in choosing such intervals for assessment of clinical status of patients, as was done in the current study.

The observed effectiveness seen with PA compared to BE and CA in this study and those of others^{38,39} may be due in part to its source, preparation, and composition. Surfactant synthesized by the developing human lung is made up of 70% to 80% phospholipids, of which dipalmitoylphosphatidylcholine is the main component, 10% of surfactant proteins A, B, C, and D, and 8% neutral lipids, predominately cholesterol.⁴⁰ The natural

animal-derived surfactant preparations mostly vary in their concentration of phospholipids and surfactant proteins SP-B and SP-C.^{39,41} These components play a significant role in preventing lung collapse during end-expiration.⁴¹ Beractant is a bovine minced lung extract with a phospholipid concentration of 25 mg/mL, modified with added dipalmitoylphosphatidylcholine, palmitic acid, and tripalmitin, containing an unspecified amount of SP-B, and has a recommended dosage of 4 mL/kg birthweight (100 mg/kg).⁴² Calfactant is a lavaged calf lung extract with a higher concentration of phospholipids than beractant, 35 mg/mL, an SP-B content of 0.26 mg/mL, and has a recommended dosage of 3 mL/kg birthweight (105 mg/kg).⁴³ Poractant alfa is a porcine minced lung extract with the highest concentration of phospholipids, 80 mg/mL, an SP-B content of 0.45 mg/mL, and a recommended initial dose of 2.5 mL/kg birthweight (200 mg/kg).⁴⁴ The high concentration of phospholipids in PA permits approximately twice the phospholipid dose of other surfactant preparations at the lowest administration volume.

A retrospective US, 5-year study by Ramanathan et al¹³ analyzed all-cause mortality in 14,173 preterm infants treated with PA, BE, and CA discharged from Premier Health hospitals between 2005 and 2009. In this study, PA was associated with an approximate 50% reduction in odds of mortality compared to CA. No significant difference was seen between BE and CA. The present study extended these mortality observations with additional concomitant healthcare economics measures of LOS and costs as well as clinical outcomes data. This study revealed a lower overall unadjusted rate of mortality compared to other similar analyses.^{13,19} In addition to differences in hospital characteristics and

trends in clinical practice from previous analyses, this result reflects a study design with a focus on evaluating outcomes exclusively within the initial continuous NICU stay (index period) and may not have included infants requiring readmission to the NICU or the entire extended duration of hospitalization for all infants.

Major strengths of this study include findings that are generalizable to the US preterm infant RDS population and are based upon data describing real-world clinical practices. Use of a very large administrative hospital database with detailed hospital and patient characteristics allowed for significant modeling for confounding variables to more accurately represent economic and clinical outcomes data and reduce bias. The models controlled for site variation, which has been linked to unexplained differences in outcomes such as BPD and death.⁴⁵ In addition, the findings of this study are specific to high-level NICU care costs and costs associated with respiratory therapies in order to reduce the possibility that other types of costs drive differences, such as those which cannot be mitigated by choice of surfactant. Unlike the study of Trembath et al, this study also provided economic outcomes data.

Overall study limitations inherent to administrative database studies include imperfect ICD-9 coding as well as non-standard accounting methods and non-standard pricing across hospitals. It is unknown whether mothers at risk for preterm babies with RDS were treated with antenatal steroids to limit the severity of RDS because of limited data capture outside the hospital-based episode of care. Finally, NICU mortality and other study results describe associations and not causal effect, as is appropriate for most retrospective, observational database-derived studies.

Conclusions

This study was designed using real-world hospital data to directly compare healthcare economic outcomes and clinical efficacy associated with the use of the available surfactants. Although LOS in the NICU and costs associated with high-level NICU care were similar among all surfactant groups, preterm infants receiving PA were less likely to need MV support and had lower odds of NICU mortality compared to CA. With US preterm births on the rise, with a societal economic burden of \$26 billion dollars annually,⁴⁶ the findings of this study have important implications for preterm infants who will be born with RDS.

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