REVIEW ARTICLE

Pharmacoeconomics of Surfactant Therapy

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Surfactant therapy has become an integral part of the standard of care for treating premature infants with respiratory distress syndrome (RDS). Institutions that routinely treat this patient population have to select a surfactant based upon clinical and pharmacoeconomic considerations. Pharmacoeconomic studies have established the cost-effectiveness of individual agents based on a variety of factors, including length of hospitalization, mortality odds ratio, and other direct medical costs. These studies evaluated infants with weights between 600 and 2000 grams and survival periods between 28 days and 1 year. With the cost-effectiveness of surfactants already established as being far superior to no treatment, trials have evolved to compare the available surfactants. Two studies have supported the cost-effectiveness of beractant compared to colfosceril or calfactant. Two others demonstrated lower resource utilization associated with poractant alfa as compared to beractant or calfactant. Evolving treatment approaches in the management of neonatal RDS, such as recent data suggesting continuous positive airway pressure as an alternative to mechanical ventilation for respiratory support, have defined the need to further evaluate the impact of such strategies upon surfactant and resource utilization.

KEYWORDS continuous positive airway pressure, cost-effectiveness, pharmacoeconomic, respiratory distress syndrome, surfactant

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INTRODUCTION

Surfactant therapy has demonstrated clinical benefit through reduced mortality rates.[1] Despite the benefits, the increased expenditure associated with advancing care of high risk subpopulations such as premature neonates has led to concerns regarding the economics of surfactant therapy. The cost of care for this population has consumed significant healthcare resources. Before the introduction of surfactant therapy, the cost per neonate survivor weighing less than 900 grams was estimated to exceed twice the survivor's projected lifetime earnings.[2] Expected hospitalization costs associated with caring for infants with uncomplicated clinical courses of respiratory distress syndrome (RDS) have ranged from $27,224 to $101, 867[3] (Table 1), with the highest costs associated with the most premature and lowest birth weight infants. The average annual hospital expenditure for surfactants has been

ABBREVIATIONS AWP, average wholesale price; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; FDA, Food and Drug Administration; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; RT, respiratory therapists; UK, United Kingdom

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Table 1. Expected per patient costs (USD) associated with Respiratory Distress Syndrome

Birth weight (grams)	Expected cost of initial hospitalization (survivors, uncomplicated course)	Incremental cost of complications	Expected cost of initial hospitalization (all patients)
500 to 1000	$101,867	$22,155	$100,603
1001 to 1500	$64,524	$11,041	$72,353
> 1500	$27,224	$2,448	$28,756

USD, United States dollars

reported to be approximately $113,000, and some institutions with large neonatal units or specialty pediatric hospitals have spent more than $300,000 per annum.[4]

Many factors beyond the simple acquisition cost of the agents influence which surfactant product is most economical for an institution. Agents expected to decrease overall healthcare resource utilization are those that reduce or avoid days of mechanical ventilation and/or increase the survival rate. The avoidance or abbreviation of time during which mechanical ventilation is required is correlated with fewer complications, thus avoiding additional resource utilization. Also, the length of hospital stay must be considered, especially time spent in the neonatal intensive care unit (NICU) as compared to less intensive areas. The number of doses required and amount of waste incurred based on product packaging also impact overall costs. Since cost of care greatly outweighs the cost of the agents,[4] evaluations that do not consider all of these aspects are incomplete.

This article describes published studies that define the cost-effectiveness of surfactant treatment, evaluates comparative studies among various agents, and explores the potential implications of new treatment strategies (e.g., use of continuous positive airway pressure) on surfactant and resource utilization. Furthermore, this article will help clinicians better define a framework for evaluating surfactant preparations and will offer suggestions for further consideration.

Economic Evaluations of Individual Agents

Cost-effectiveness analyses have compared surfactant therapies to traditional non-surfactant-based approaches to treating RDS (Table 2). The 3 natural preparations that are commercially available are beractant (Survanta, Ross Labs, Columbus, OH), calfactant (Infasurf, Forrest Labs, New York, NY), and poractant alfa (Curosurf, Dey L.P., Napa, CA).

Soll and colleagues evaluated the costs associated with producing care for patients who had survived 28 days and who had been given beractant.[5] In this study, 210 infants between 26 and 29 weeks gestation and weighing 600 to 1250 grams were included; 103 received beractant, and 107 were controls. This study considered costs including drug therapy (excluding beractant), intravenous therapy and nutrition support, respiratory care, diagnostic procedures, physician treatments and consultations, and radiological examinations. Since the economic perspective for this study was that of society, normative costs were utilized. Price lists from 6 major teaching hospitals in the United States provided the data to derive the normalized costs.

No significant differences existed between study groups at baseline. No differences in the length of hospital stay or accommodation charges were found between groups, and all patients remained in the NICU throughout the evaluation period. Costs for radiological and diagnostic procedures, respiratory care, and drug therapy (other than beractant) were significantly lower in the beractant-treated infants ($P < .01$). Expenditures for both narcotics and central nervous system-active drugs were significantly lower ($P = .01$) for beractant-treated patients. Antibiotics accounted for approximately 40% of drug costs for both groups. Beractant-treated patients exhibited a significant survival benefit (26.2% mortality for placebo and 8.7% for beractant, $P = .001$). Overall, a cost savings of $3,119 (after inclusion of the cost of beractant) was shown for 28-day survivors receiving therapy with beractant.

A small study of 33 infants between 700 and 2000 grams with severe RDS per clinical and radiological criteria evaluated the cost-effectiveness of poractant alfa in the United Kingdom (UK).[6] Medical and nursing care were similar for poractant alfa-treated infants and control infants. Costs were calculated based

Table 2. Pharmacoeconomic evaluations of individual natural agents

Ref	Surfactant	Patients	Endpoints	Key Observations
5	beractant	210 newborns (103 beractant, 107 control) 26 and 29 wk gestational age and 600 and 1250 g	Costs associated with 28-day survival	No differences in length of stay or accommodation costs revealed; Costs (radiology, diagnostic, respiratory care, & drugs) lower in beractant-treated infants ($P < .01$); Antibiotic expenditure similar between groups; Costs associated with narcotics and CNS agents lower in beractant-treated infants ($P = .01$); Incremental cost savings of $3119 demonstrated for 28-day survivor with beractant
6	poractant alfa	33 newborns (19 poractant, 14 control) between 700 and 2000 g	Total direct cost associated with therapy	Cost effectiveness of poractant alfa supported
7	poractant alfa	Cohort of 1000 newborns between 26 and 30 wk gestational age	Mortality; periods of care; hospitalization costs	Extra survivors: 4 (late rescue therapy), 51 (single dose treatment, between 17 and 101 (multiple dose therapy); Increased survival resulted in a 0.8 to 16% increase in hospitalization costs; Early treatment was most cost-effective Poractant alfa accounted for 0.3 and 1.2% of all costs
8	Not specified	118 newborns (62 surfactant, 56 control)	Direct costs of care	Costs associated with surfactant treatment were 39.03% less than non-surfactant treated newborns

on a detailed survey modified from a previous NICU cost study in the UK. Medical and nursing salaries, laboratory and radiology charges, and hospital maintenance, overhead, and equipment expenses were included. Of the total costs included, medical and nursing salaries accounted for 70%. Cost per bed day included consideration for level of care.

Nineteen infants received poractant alfa, while 14 served as controls. Baseline characteristics were similar between groups. While this study was relatively small, it demonstrated that the cost of producing a surviving infant was similar to data in the region, supporting the cost-effectiveness of surfactant administration.

The cost-effectiveness of poractant alfa was further supported in a study by Egberts and colleagues.[7] Costs associated with hospitalization for newborns receiving poractant alfa in the Netherlands were evaluated. Since many prior studies included small numbers of patients, the investigators developed a model to evaluate odds ratios of completed trials with poractant alfa, applying mortality rates for different grades of RDS and standardized hospitalization costs. Outcomes were based on 1,000 newborns between 26 and 30 weeks gestation. The analysis assumed a 55% incidence rate of RDS, and a mean mortality of 35% for newborns with RDS and 19% for those without RDS based on data from the Working Group of Neonatal Pulmonology of the Dutch Society of Pediatrics.[7] Data for newborns with fatal congenital abnormalities were excluded. Further assumptions included that 60% had severe disease, 30% had moderate disease, and 10% had mild disease with 50%, 15%, and 6% mortality, respectively.[7]

The mortality odds ratios for infants with and without RDS were 0.44 in the normalized population treated with poractant alfa. Based on published data, the model further accounted for differences in the days of hospitalization, varying between 56 and 78 days for mean non-intensive care and 16.1 and 21 days for mean intensive care. Costs were corrected for the mean number of doses needed for the type of treatment applied compared to late rescue treatment.

Table 3. Comparative pharmacoeconomic trials of surfactants

Reference	Surfactants Compared	Analysis Type	Key Findings
9	Beractant and colfosceril	CEA	Cost avoidance of $26,000 (USD) annually considering the acquisition cost and number of repeat doses
10	beractant and calfactant	CEA	Beractant more cost-effective due to product waste associated with calfactant
11	calfactant and poractant alfa	CEA	A cost savings of $196.13 (USD) per dose was associated with poractant alfa
12	beractant and poractant alfa	CMA	A cost savings of $180 to $949.57 (USD) (or 20% to 53%) was associated with poractant alfa

CEA, cost effectiveness analysis; CMA, cost minimization analysis; USD, United States dollars

Based upon these criteria, Egberts and colleagues' analysis found that 4 to 51 additional survivors per 1,000 patients resulted from late rescue therapy with poractant alfa (i.e., those receiving surfactant 2 to 15 hours after birth with severe RDS and a FiO_2 of ≥ 0.6).[7] Thirty-eight, 17, and 19 extra survivors resulted from early treatment, low (i.e., 100 mg/kg) multiple-dose, and high (i.e., 200 mg/kg) multiple-dose treatment with poractant alfa, respectively. Mortality rates were up to 11% lower for surfactant-treated patients regardless of regimen as compared to no treatment. Correlating to this decreased mortality, RDS patients receiving surfactant also had longer hospitalization rates (between 0.8% and 16%). Poractant alfa cost accounted for 0.3% and 1.2% of all hospitalization costs. Early intervention was found to be the most effective treatment strategy.

A study conducted in Saudi Arabia compared treatment for RDS with and without surfactant administration. Similar to the studies previously discussed, all inpatient hospital costs associated with the treatment of premature infants were considered.[8] In addition to the positive therapeutic outcomes (lower length of hospital stay, increased survival, and decreased ventilation days), the costs associated with surfactant treatment were found to be 39% lower than the control group.

These studies demonstrate that surfactant therapy, regardless of the agent, is a cost-effective management strategy for treating respiratory diseases. Thus, it is not only clinically sound, but also advantageous from a pharmacoeconomic vantage point. Considering the efficacy of surfactants in general, institutions then face the question of which surfactant is the most economical choice.

COMPARATIVE ECONOMIC ANALYSES AMONG SURFACTANT THERAPIES

With the economic benefits of surfactant therapy established, studies began to focus on comparing the pharmacoeconomics of the various agents in an attempt to determine which should be included on an institution's formulary (Table 3).

Natural versus Synthetic Surfactants

Wyble and colleagues described a comparison of the costs and outcomes associated with colfosceril compared to beractant.[9] A retrospective chart review included all newborns treated for RDS with surfactant therapy. A 16-month period was evaluated; colfosceril was the formulary agent the first 8 months and beractant the formulary agent for the next 8. Dosing and administration of both agents were based on manufacturer recommendations. The necessity of dosing was based on arterial-alveolar oxygen tension (a-A) ratio and chest x-ray findings consistent with RDS. Data collected included days of oxygen support whether through mechanical ventilation or oxygen supplementation, initial surfactant dose, number of doses required, and length of stay.

Colfosceril was used in 36 newborns, and beractant was used in 46. Demographics of the newborns were similar (i.e., birthweight, gestational age, gender, race, birth by cesarean section, Apgar scores). Characteristics of the mothers also were similar in regard to gender, race, multiple births, prenatal care provided, and antenatal corticosteroids. Baseline and post-treatment alveolar oxygen tension ratios were similar. Newborns receiving colfosceril required additional doses as compared to berac-

tant-treated newborns, and the number requiring only a single dose was significantly higher among beractant-treated newborns than in the colfosceril group. To ensure proper application of surfactant therapy, the a-A ratios of newborns requiring a single dose of colfosceril were evaluated and found to be higher than those receiving multiple doses.

This analysis revealed that the formulary change to beractant resulted in a cost avoidance of $26,000 annually when acquisition cost and number of repeat doses were considered. This study did not include the costs associated with the time on ventilator, which was quoted by the authors at $800 per day. The colfosceril group was reported as using a mean of 24 ± 28 ventilator days, and the beractant group was reported as using a mean of 16 ± 20. Although the sample size was small, it is likely that additional cost savings might have been realized had these data also been evaluated. Although colfosceril is no longer commercially available, this trial established the existence of pharmacoeconomic differences between agents and supported the need for further trials comparing the natural surfactants.

Natural Product Comparisons

Natural surfactants appear to be superior to synthetic products,[1] and at present, only natural products are available to practitioners. Of these, calfactant and beractant are derived of bovine sources, while poractant alfa is derived from porcine sources. Several pharmacoeconomic studies have evaluated these natural agents.

In a study in a 760-bed private not-for-profit teaching hospital, neonates younger than 36 weeks gestational age and weighing between approximately 800 and 2000 grams received either beractant or calfactant for RDS.[10] Rescue therapy with beractant was administered in 22 infants, while 33 received calfactant. The institution had both agents on formulary, so their goal was to evaluate clinical and economical differences between groups to determine if 1 agent could be deleted from the formulary. No differences existed in demographics, number of doses required, fraction of inspired oxygen (FiO_2), or complications between groups. The study found a cost difference favoring beractant over calfactant due to the higher quantity of waste associated with calfactant dosing rather than differences due to acquisition costs.

The mean cost of drug waste per patient in the study was $81.20 ± $81.93 for beractant and $167.80 ± $101.90 for calfactant. The cost difference was based upon the fact that calfactant is commercially available as a 35 mg/mL preservative-free solution in 3 mL and 6 mL vials with a recommended endotracheally administered dose of 3 mL/kg/dose. Given the recommended doses, a higher amount of unused agent remained in the vial for calfactant as compared to beractant. (FDA approved labeling recommends single entry of vials.)

An open label trial compared poractant alfa and calfactant in 277 mechanically ventilated infants requiring surfactant treatment for RDS.[11] Very low birth weight infants were enrolled in a sequential, non-randomized, open label fashion at a major teaching hospital. In the 31-month study period, poractant alfa was used for the first 23 months, and calfactant was used for the latter 8 months. Poractant alfa was used at the manufacturer-recommended dosing of 2.5 mL/kg initially with 1.25 mL/kg for additional doses. Calfactant was dosed at 3 mL/kg for all doses. All doses were administered intratracheally by respiratory therapists (RT) in 2 aliquots per manufacturer guidelines. A standard data collection tool was completed by the RT to gather data concerning time required for drug preparation and administration, as well as for defined clinical data such as pulse oximetry and heart rate.

Primary outcomes for the study included time of drug preparation and administration, number of surfactant doses required, reflux up the endotracheal tube or into the pharynx, oxygen desaturation, and bradycardia. Secondary outcomes included the number of single-dose vials used and the amount of waste for each dose administered. The cost of surfactant administration was calculated by multiplying the RT wage by the time required to prepare and administer the dose. The cost of wasted drug was calculated on a per milliliter basis based on average wholesale price (AWP), taking the total vial volume minus the volume administered.

Two hundred thirteen infants received poractant alfa, and 64 received calfactant during the 22-month evaluation period. Significant differences were revealed for mean dosage administration times, administration costs,

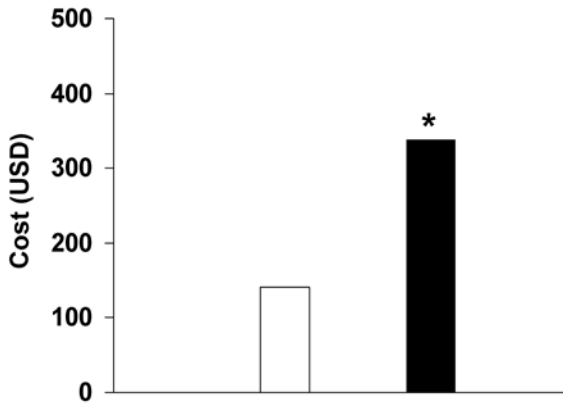

Figure 1. Mean Wastage Cost per Dose Comparing Poractant Alfa (□) and Calfactant (■).
USD, United States dollars
** P < .01*
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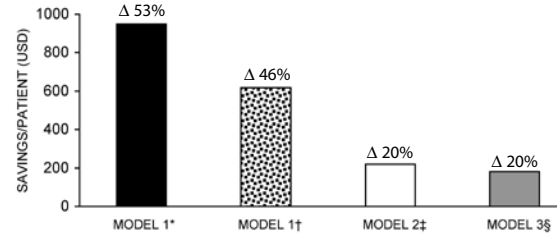

Figure 2. Comparison of cost differences for the three models comparing beracatant and poractant alfa.
USD, United State Dollars
** Speer et al. (mean weight, single-use vial).*[13]
† Ramanathan et al. (mean weight, single-use vial).[14]
‡ Ramanathan (individual weight, single-use vial); P< .01.[14]
§ Ramanathan (individual weight, multiple-use vial); z score = -2.37;[14]
P = .018.
P-values reflect Mann Whitney U tests for difference between groups.
Adapted with permission of Journal of Pediatric Pharmacotherapy and Therapeutics.[12]

and cost of wasted product. The primary driver of cost differences between poractant alfa and calfactant was found to be wasted product, with a mean cost of wasted product for poractant alfa of $141.21 and $337.34 for calfactant (P < .001; Figure 1). This resulted in a cost difference of $196.13 per dose delivered, favoring poractant alfa. In addition to the costs associated with waste, the mean doses administered for calfactant were greater than for poractant alfa (1.72 doses and 1.67, respectively). Mean dosage administration times were 3.8 minutes for poractant alfa and 5.3 minutes for calfactant (P = .006), with 58.9% of poractant alfa and only 4.3% of calfactant doses being administered in less than 5 minutes (P < .001). The total administration cost per dose for poractant alfa was $2.21, while the cost for calfactant was $3.08. While waste was the primary driver in the difference in cost favoring poractant alfa, number of doses and time of administration also contribute to the total cost of surfactant use.

In a cost minimization analysis comparing beractant and poractant alfa, Marsh and colleagues found poractant alfa to be associated with a lower cost than beractant.[12] This analysis developed 3 cost models to comparatively evaluate the agents using data from 2 published clinical trials comparing poractant alfa and beractant.[13,14] The first 2 models assumed single-dose use of the vials as recommended by the manufacturer. Costs for the 2 medications in all 3 models were defined using the average wholesale price (AWP). Results from these models are shown in Figure 2. The first model estimated the costs of the 2 agents based upon the published mean weight of the infants from both trials, while the second model was based on the costs for each infant from the Ramanathan trial.[14] The third model was similar to the second model except it assumed multi-dose use of the vials.

Cost savings with poractant alfa ranged from $180 in Model 3 to $949.57 in Model 1 for the Speer trial.[13] This represented a savings from 20% to 53%, depending on the model used. Contributing significantly to the savings with the use of poractant alfa for Models 1 and 2 were a reduction in actual doses of poractant alfa administered compared to beractant and the commercially available vial sizes that allowed more administration of poractant alfa that required the use of only 1 vial versus multiple vials. In Model 3, where multi-dose use of each vial was assumed, the cost savings were attributed to the reduction in the number of doses given with poractant alfa.

IMPLICATIONS OF SURFACTANT THERAPY AND CONTINUOUS POSITIVE AIRWAY PRESSURE

As new technologies become available, pharmacoeconomic models must evolve to evaluate

the impact of these changes. While the previously discussed literature assessed surfactant therapy in patients for whom mechanical ventilation was the primary modality of respiratory support, a new method of using continuous positive airway pressure (CPAP) is emerging. As discussed by Kris Sekar, MD, in this issue, of the 3 emerging strategies for treating RDS in low birth weight infants, 2 focus upon CPAP as opposed to traditional mechanical ventilation. Incorporating surfactant, the method involves endotracheal intubation of the infant for surfactant administration followed by respiratory support via CPAP. This strategy may have pharmacoeconomic implications associated with shorter mechanical ventilation and potentially different rates of complications that might be associated with mechanical ventilation, especially if long-term studies are conducted that incorporate the costs of managing chronic lung disease.

A prospective, randomized trial evaluated the hypothesis that the use of nasal CPAP and surfactant administration followed by immediate extubation would result in fewer mechanical ventilation days over the course of hospitalization for preterm infants of less than 30 weeks gestation.[15] Poractant alfa was used at a 200 mg/kg dose and administered at two 100 mg/kg aliquots with manual ventilation for 1 minute after each dose. An additional 100 mg/kg dose was permitted 12 hours later for infants with a FiO_2 greater than 0.50. The need for mechanical ventilation at 7 days of life was evaluated. Secondary endpoints included the need for a second surfactant dose, bronchopulmonary dysplasia (BPD), and length of stay in the NICU.

At 7 days of life, none of the 13 patients in the CPAP group remained on mechanical ventilation, yet 6 of the 14 patients in the mechanical ventilation group did. Mean mechanical ventilation days for the CPAP group were 2 ± 1.4 days and 5.6 ± 3.1 days for the mechanical ventilator group ($P < .001$). Furthermore, no patient in the CPAP group required a second dose of surfactant ($P = .006$), whereas 7 required a second dose in the mechanically ventilated group. Length of stay in the NICU was shorter for CPAP patients (21.7 ± 10.1 days versus 29.9 ± 8 days, $P = .027$). Incidence of BPD and duration of overall hospitalization stay were similar between groups.

This study illustrates the need to design pharmacoeconomic models to assess this newer application of surfactant therapy involving CPAP since quality of NICU stay, costs associated with respiratory support strategies, and number of surfactant doses are expected to be different than those experienced with traditional mechanical ventilator strategies. Future analyses should consider methods of evaluating the long-term cost-effectiveness of surfactant therapy, especially as new, less invasive treatment methods such as CPAP evolve. As clinical care of RDS evolves, pharmacoeconomic models addressing these changes must evolve as well. These data demonstrate that newer strategies may lead to continued optimization of the benefits associated with surfactant therapy. The cost of these agents is partially offset by avoidance of other supportive therapies such as mechanical ventilation, and the avoidance of such therapies might lead to further improved clinical outcomes.

CONCLUSIONS

Surfactant therapy is the mainstay of treatment for high-risk infants of 31 weeks gestation or less, many of whom need to be treated for respiratory diseases. Clinical trials demonstrate that early administration of multiple doses of surfactant is associated with better clinical outcomes, with natural products associated with better outcomes than synthetic products. These agents have increased survival and have become the standard of care.

Many trials have demonstrated the economic benefits of surfactant therapy. These trials analyze direct acute care costs that contribute to the total cost of hospital care. Subsequent trials provide comparative pharmacoeconomic assessments among surfactant agents. Analyses reveal that the choice of medication could result in cost savings for the institution such as the 20% to 53% reduction in institutional costs for poractant alfa as compared to beractant therapy seen in 1 described study.[12] Surfactant therapy can promote shorter durations of invasive management (i.e., mechanical ventilation). Early extubation and maintenance of CPAP allow for equivalent clinical outcomes with fewer long-term complications compared

to mechanical ventilation. This approach is advantageous from both a clinical and pharmacoeconomic perspective, as prolonged intubation is associated with the development of chronic lung disease and BPD. The merging of surfactant therapy with modern management such as CPAP has the potential to aid clinicians in further improving outcomes, survival rates, and costs related to the neonatal population. As these new management strategies are adapted, new agents enter the clinical arena, and surfactant therapy begins to be applied in new therapeutic areas beyond RDS, pharmacoeconomic models will need to evolve to comparatively assess their effectiveness against current standards.

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