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Clinical Investigation

A Pharmacoeconomic Analysis of In-Hospital Costs Resulting from Reintubation in Preterm Infants Treated with Lucinactant, Beractant, or Poractant Alfa

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OBJECTIVES Reintubation and subsequent mechanical ventilation (MV) in preterm infants after surfactant replacement therapy are associated with excess morbidity and mortality and likely increase in-hospital costs. Specific surfactant therapy selection for prevention of respiratory distress syndrome (RDS) in preterm infants receiving conventional MV may impact not only clinical outcomes but also pharmacoeconomic outcomes.
METHODS We conducted a pharmacoeconomic analysis of the impact of surfactant selection and reintubation and subsequent MV of preterm infants on health care resource utilization. Rates of reintubation and duration of MV after reintubation were determined from 1546 preterm infants enrolled in two surfactant trials comparing lucinactant to beractant and poractant alfa. Hospital costs were obtained from a 2010 US database from 1564 preterm infants with RDS, with a direct cost of $2637 per day for MV in the neonatal intensive care unit. Cost of reintubation by study and treatment was estimated as the incidence of reintubation multiplied by days on MV therapy after reintubation multiplied by cost per day for direct MV costs, standardized per 100 surfactant-treated infants.
RESULTS There were no differences between studies or treatment groups in the overall extubation rate. Average MV duration following reintubation was similar between groups in both trials; however, reintubation rates were significantly lower ($p<0.05$) for infants treated with lucinactant than for those receiving beractant or poractant alfa. The observed differences in reintubation rates resulted in a projected cost saving of $160,013 to $252,203 per 100 infants treated with lucinactant versus animal-derived surfactants.
CONCLUSIONS In this analysis, higher reintubation rates following successful extubation in preterm infants receiving animal-derived surfactant preparations significantly increased estimated in-hospital costs, primarily due to excess costs associated with MV. This analysis suggests that surfactant selection may have a significant pharmacoeconomic impact on cost of patient care. Additional cost assessment of potential reduction in reintubation-associated morbidity is warranted.

INDEX TERMS cost analysis, lucinactant, mechanical ventilation, respiratory distress syndrome, surfactant

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INTRODUCTION

Respiratory distress syndrome (RDS) is the most common respiratory disorder among preterm infants and is an important cause of infant mortality.[1] Exogenous surfactant administration has significantly reduced mortality and morbidity in premature newborns with RDS,[2] and intratracheal instillation of surfactant has become the standard of care in this population.[3] Until recently, exogenous surfactants approved for use in the United States for the treatment and prevention of RDS were of animal origin. Lucinactant (Surfaxin; Discovery Laboratories, Inc., Warrington, PA), a non-animal-derived, synthetic surfactant, has recently been approved by the United States Food and Drug Administration for the prevention of RDS in infants at high

risk for RDS following successful completion of two phase 3 clinical trials. Lucinactant contains phospholipids and sinapultide (KL_4), a 21-amino acid synthetic peptide consisting of lysines (K) and leucines (L) arranged in the sequence KLLLLKLLLLKLLLLK, which mimics the action of human surfactant protein B (SP-B).[4,5] Of the four known SPs, the hydrophobic SP-B and SP-C proteins are known to act in a critical manner to stabilize the phospholipid monolayer and enhance the ability of phospholipids to lower surface tension. Of the two, SP-B appears to play the main role, as infants who are congenitally deficient in SP-B develop a fatal form of respiratory failure shortly after birth,[6,7] whereas those deficient in SP-C tend to develop chronic lung disease in early adulthood.[8] Lucinactant has been studied in multiple clinical trials, including two phase 3 studies in infants at risk for RDS[9,10] and phase 2 studies in preterm infants with bronchopulmonary dysplasia (BPD)[11] and in adults with acute respiratory distress syndrome.[12]

Although appropriate administration of surfactant replacement therapy (SRT) for the prevention and treatment of RDS has improved outcomes and reduced mortality, preterm infants who receive surfactant commonly fail to maintain adequate gas exchange following extubation and may require endotracheal reintubation and mechanical ventilation (MV). A recently published study showed that reintubation with MV was administered in 35% to 47% of preterm infants treated with exogenous surfactant and appears to be an independent risk factor predictive of major morbidity and mortality.[13] Several acute and long-term complications have been associated with endotracheal intubation and extended placement of an endotracheal tube, including oxygen desaturation, bradycardia, airway trauma, subglottic stenosis, and tracheomalacia, and morbidities associated with MV, such as air leak, pneumonia, sepsis, and BPD.[14,15]

Reintubation and subsequent MV also has the potential to increase in-hospital costs and consumption of resources available in the neonatal intensive care unit (NICU), including additional nursing and respiratory care hours, as well as increased radiology, laboratory, pharmacy, and other in-hospital costs.

Several studies have evaluated the cost of treating RDS and the cost effectiveness of surfactant replacement,[16–25] but the economic consequences of reintubation in preterm infants have not been previously evaluated. The objectives of this study were to estimate the economic impact and health care resource utilization of reintubation and conventional MV strategies in surviving preterm infants weighing 600 to 1250 grams treated with surfactant for the prevention of RDS. Other strategies, such as endotracheal intubation for surfactant administration with early extubation and continuous positive airway pressure (CPAP) initiation (InSurE method)[26,27] and early initiation of CPAP were not assessed.[28,29]

METHODS AND DESIGN

Model and Data Sources

A pharmacoeconomic analysis was conducted to estimate direct and indirect costs of reintubation by study and treatment. Model inputs for calculation of direct costs included 1) incidence of reintubation, 2) days of MV after reintubation, and 3) cost per day of MV in the NICU. Rates of reintubation and average number of days of MV after reintubation per infant were based on data from two multicenter, masked, randomized, controlled comparative surfactant trials: the Safety and Effectiveness of Lucinactant vs. Exosurf in a Clinical Trial (SELECT) and Surfaxin Therapy Against RDS (STAR) trial. Methods, study design, and maternal and neonatal demographics, as well as results for both RDS prevention trials, have been described in detail.[9,10] Briefly, in SELECT, infants at risk for RDS from North and Central America (Unite States, Mexico, Panama), Europe (Poland, Russia, Hungary), and South America (Brazil, Chile, Ecuador, Uruguay), weighing between 600 and 1250 grams at birth were randomized to receive lucinactant (n=527), colfosceril palmitate (n=509; Exosurf; GlaxoSmithKline, Brentford, UK), or beractant (n=258; Survanta; Abbott Laboratories, Columbus, OH) in a 2:2:1 ratio (study conducted from July 2001 to December 2003). In STAR, infants from North America (United States, Canada) and Europe (France, Hungary, Poland, Portugal, Spain, United Kingdom) were randomized to receive lucinactant (n=124) or poractant alfa (n=128; Curosurf, Chiesi Farmaceutici, Parma, Italy) in a 1:1 ratio (study conducted from August 2001 to May 2003). The average number of surfactant doses ranged from 1.3 to 1.9 doses, and the study populations were generally similar between in-

Table 1. Reintubation Rates for Infants Extubated At Least Once Through 36 Weeks Post Menstrual Age, by Study and Surfactant Preparation

Procedure	SELECT Trial		STAR Trial	
	Lucinactant (n=436)	Beractant (n=208)	Lucinactant (n=104)	Poractant alfa (n=106)
Reintubated n (%)	151 (35%)	89 (43%)*	34 (33%)	50 (47%)*

** Significant versus lucinactant (p=0.021)*

fants enrolled in the two trials.[30]

From birth to 36 weeks postmenstrual age (PMA), rates of initial extubation and rates of reintubation for infants extubated at least once through 36 weeks PMA were calculated. Together, the trials enrolled a total of 1546 infants, of whom 1272 were extubated at least once through 36 weeks PMA (>80% in all treatment groups), of whom 33% to 47% required reintubation.

The economic input, cost per day for direct ventilation costs, was obtained from a hospital-based data set (Premiere Hospital Database, 2010; Charlotte, NC), which included 1564 preterm infants with RDS with a birth weight of 500 to 1249 grams from over 500 hospitals in the United States and was based on an average direct cost of $2637 per day of MV in the NICU. Cost inputs for indirect in-hospital charges associated with reintubation included room and board, laboratory, pharmacy, respiratory care, and radiology were also obtained using this database. Costs included in this analysis may not be inclusive of all services received during the days of MV, and pharmacy costs were not assumed to include surfactant costs.

Study Design and Methods

The primary outcome, direct cost of reintubation and subsequent MV, was defined as the actual costs associated with MV in the NICU based on data from the Premier Hospital Database. Total direct cost of reintubation by study and treatment was estimated as the incidence of reintubation multiplied by days of MV after reintubation multiplied by cost per day for direct MV costs, standardized for 100 surfactant-treated infants.

Indirect costs associated with reintubation, including hospital charges related to monitoring and support needed for clinical care of infants receiving MV, were also estimated. Indirect costs were obtained from average in-hospital costs derived with the Premiere Hospital Database. Unlike direct costs of reintubation, it was not possible to calculate total indirect costs of reintubation by study and treatment as not every hospital department charge would occur every day. Therefore, we identified per-patient costs for infants receiving or not receiving MV by hospital reporting department, without considering other costs associated with potentially different morbidity profiles across groups.

RESULTS

Initial extubation rates were similar among patients receiving surfactant treatments in both trials [80%-84%; p=not significant (NS)]. The reintubation rate following initial extubation was significantly lower for infants treated with lucinactant (range, 33%-35%) than that for infants receiving animal-derived surfactants (range, 43%-47%; p=0.021).[13] Table 1 displays rates of reintubation by study and surfactant preparation.

Patient characteristics (birth weight, gender, gestational age) and comorbidities (incidences of sepsis, pneumonia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia) for reintubated infants are presented in Table 2. Generally, patient characteristics were similar among the different surfactant treatment groups; however, more male than female infants were reintubated in the poractant alfa group. In addition, comorbidities were similar between treatment groups in both trials.

Average duration of days of MV per infant following reintubation was similar between treatment groups in each trial; however, as reintubation rates were significantly lower for lucinactant-treated infants, this analysis resulted in fewer total days of MV after reintubation. Table 3 displays the average duration of MV following reintubation per infant and the total duration of MV after reintubation per study and treatment group standardized per 100 infants.

The estimated direct costs of reintubation

Table 2. Demographics and Complications of Prematurity for Reintubated Infants by Study and Surfactant Preparation

Patient Characteristics	SELECT Trial		STAR Trial	
	Lucinactant (n=151)	Beractant (n=89)	Lucinactant (n=34)	Poractant alfa (n=50)
Demographics				
Birth weight (g)*	928 ± 178	969 ± 185	895 ± 172	951 ± 159
Gestational age (wk)*	27.7 ± 1.8	28.0 ± 1.9	27.0 ± 1.1	27.1 ± 1.3
Sex (M/F)	75/76	48/41	17/17	32/18
Complications of Prematurity				
Pneumonia†	54 (36%)	39 (44%)	7 (21%)	14 (28%)
Sepsis†	94 (62%)	51 (57%)	21 (62%)	30 (60%)
NEC†	46 (31%)	25 (28%)	3 (9%)	6 (12%)
IVH†	91 (60%)	58 (65%)	3 (9%)	6 (12%)
PVL†	21 (14%)	17 (19%)	0 (0%)	4 (8%)

IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia
** mean ± standard deviation*
† n (%)

per infant were approximately $6700 to $7900 for lucinactant and between $8400 and $10,500 for animal-derived surfactants in the SELECT and the STAR trial, respectively, suggesting a potential savings per infant ranging from $1600 to $2500 per infant for infants treated with lucinactant. When standardized per 100 reintubated infants, the lower reintubation rate and fewer overall days of MV suggest a potential savings of approximately $160,000 to $252,000 for infants treated with lucinactant (Table 3).

Table 4 displays the average per-patient indirect costs for infants receiving or not receiving MV by hospital department. In general, MV was associated with higher radiology, laboratory, and other indirect costs, reflecting a greater impact on medical resource use.

DISCUSSION

We conducted a pharmacoeconomic analysis of the impact of surfactant selection and reintubation and subsequent MV of preterm infants on health care resource use. As a follow-up to our published observations of increased morbidity and mortality associated with reintubation and MV in preterm infants receiving surfactant preparations,[13] this analysis evaluated the pharmacoeconomic impact of reintubation and MV by examining costs associated with in-patient health care resource use in this population, which is becoming an increasingly important concept in the practice of neonatology.[31] This study demonstrates the potential financial impact of therapeutic choices and also adds increasing evidence of the need to evaluate the impact of therapies designed to prevent RDS in preterm infants.

Reintubation has been associated with increased mortality and morbidity in adults with acute distress respiratory syndrome[32,33] but has not been previously evaluated in preterm infants. In preterm infants at risk for RDS, who were treated with surfactant, we previously reported that reintubation was a predictive independent risk factor for death. Similarly, major complications of prematurity such as BPD, air leakage, sepsis, necrotizing enterocolitis, and intraventricular hemorrhage were also significantly higher in preterm infants who required reintubation, showing a strong association between reintubation and poor clinical outcomes.[13]

More than 80% of infants in the STAR trial and SELECT were successfully extubated during the early hospital course following surfactant administration, reflecting a clinical improvement in pulmonary function following surfactant administration. However, between 35% and 47% of those infants required reintubation for multiple causes, including poor respiratory effort, apnea, and acidosis, among others. Although initial extubation rates were similar across treatment groups in both trials, rates of subsequent reintubation were significantly lower for infants treated with synthetic lucinactant than for those treated with the commercially available animal-derived surfactants beractant and poractant alfa.[13] There are several potential factors that may have led to the relatively lower rate of reintubation observed

Table 3. Cost Component and Cost Comparison

Component	Cost per Day	Incidence of Reintubation	Average No. of MV Days Following Reintubation per Patient	Total No. of MV Days Following Reintubation per 100 Patients	Total Cost* (USD)
SELECT Trial					
Lucinactant	$2637	35%	7.4	256	$6752
Beractant	$2637	43%	7.4	317	$8352
Cost difference per patient					$1600
Cost difference per 100 patients					$160,013
STAR Trial					
Lucinactant	$2637	33%	9.2	300	$7933
Poractant	$2637	47%	8.4	396	$10,455
Cost difference per patient					$2522
Cost difference per 100 patients					$252,203

MV, mechanical ventilation; USD, United States dollars
** cost per day × days of MV × reintubation rate*

in infants treated with lucinactant. Compared with the amount of SP-B protein found in animal-derived surfactants, the concentration of sinapultide in lucinactant is consistently much higher than the SP-B concentration in beractant.[34] In addition, lucinactant appears to be more resistant to inactivation by plasma proteins and oxidant species than other exogenous surfactants[35–38] and has also been shown to reduce plasma protein and neutrophil influx into the alveolar space in vivo and to modulate the inflammatory processes in vitro.[39,40] These factors may have resulted in improved overall lung function, potentially leading to lower rates of reintubation.

Preterm infants at risk for RDS who survive typically require substantially more resources over the course of their hospitalization.[25,41] We hypothesized that the need for reintubation would increase in-patient hospital costs. Consistent with what has been observed in other critical care populations,[33,42] our analysis suggests that higher reintubation rates following successful extubation in preterm infants receiving surfactant preparations significantly increases in-hospital costs primarily because of excess costs associated with MV. The use of MV is associated with direct costs, consisting of expenses directly related to the use of MV, and indirect costs, which are those charges associated with additional medical, imaging, laboratory analyses, supplies, and other miscellaneous costs needed for an adequate clinical management of patients on MV. This analysis provides an assessment of otherwise unavailable data describing the economic impact and increased resource utilization of reintubation and MV.

There are a few potential limitations pertaining to this analysis. First, the clinical inputs used for this analysis are derived from two phase 3 clinical trials conducted between 2001 and 2003 in study sites in various regions of the world, whereas the cost data used for the analysis is derived from a recent US-based hospital cost database. While services and care may differ between different global regions, the clinical trial protocols followed by all sites included guidelines on the respiratory care and treatment of the preterm infants that reflected standards of care practiced in the United States. Moreover, these standards of care have remained fairly constant over the last 10 years. It is therefore unlikely that the services and care delivered during the clinical trials differs significantly from that practiced in the United States at present. Notably, new respiratory support strategies, such as endotracheal intubation for surfactant administration with early extubation and continuous positive airway pressure (CPAP) initiation (InSurE method)[26,27] or early initiation of CPAP,[28,29] are now used in some care centers in addition to those used in clinical trials, and these new strategies may have health benefits not evaluated in this study. However, these support strategies are not defined as part of the current standard of care and are themselves experimental.

It should be noted that the primary comparison in SELECT was lucinactant compared with colfosceril palmitate, a surfactant that is no lon-

Table 4. Per Patient Cost by Hospital Department

Hospital Reporting Department	Actual Costs (USD)*		Difference
	MV	No MV	
Room and board	$1375	$1204	$171
Laboratory	$144	$68	$76
Pharmacy	$298	$88	$210
Respiratory Care	$414	$80	$334
Radiology	$135	$106	$29
Supply	$244	$64	$180
Therapy	$82	$115	–$33
Totals	$2692	$1725	$967

MV, mechanical ventilation; USD, United States dollars

** Costs shown are daily costs applied when the charge occurred, not average daily costs*

ger commercially available in the United States, with beractant serving only as a reference agent. Furthermore, the STAR trial, which compared lucinactant with poractant alfa in a noninferiority manner, was terminated prior to achieving its enrollment goal. While these are limitations in the clinical studies, the endpoint of reintubation, a prespecified endpoint, was evaluated across a large number of infants included in this analysis, with over 650 preterm infants treated with lucinactant and nearly 400 preterm infants treated with beractant and poractant alfa. This large sample size is sufficient to provide reliable estimates.

Another potential limitation of this analysis is the self-selecting nature of the Premiere Hospital Database dataset that was used to estimate current costs in the United States associated with preterm infants treated in the NICU. However, the large dataset of 1564 infants that was captured in the Premiere Hospital Database represents information from over 500 NICUs in the United States and is, therefore, likely to be a good overall estimate of current costs associated with treating this population in the NICU. Future studies should be conducted to validate the results that we found, inclusive of a more comprehensive assessment of the costs associated with potential differences in morbidity profiles (such as differences in rates of BPD) when selecting a particular surfactant preparation.

CONCLUSIONS

Among preterm infants receiving surfactant therapy for the prevention of RDS, the need for reintubation after successful extubation appears to be a frequent event. Pharmacoeconomic modeling suggests that higher rates of reintubation result in higher direct and indirect costs associated with MV, which in turn leads to higher in-hospital patient cost. In this analysis, the lower reintubation rates observed in infants treated with lucinactant, relative to infants treated with animal-derived surfactants, potentially resulted in lower estimated in-hospital costs. Selection of a specific surfactant for the prevention of RDS may have a significant pharmacoeconomic impact. Additional cost assessment of potential reduction in reintubation-associated morbidity is warranted.

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ABBREVIATIONS BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IVH, intraventricular hemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; ns, not significant; n, number; PMA, post menstrual age; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; SP, surfactant protein; SRT, surfactant replacement therapy; US, United States; SELECT; Safety and Effectiveness of Lucinactant vs. Exosurf in a Clinical Trial; STAR, Surfaxin Therapy Against RDS Trial

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