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Economic Outcomes of Colfosceril Palmitate Rescue Therapy in Infants Weighing 1250g or More with Respiratory Distress Syndrome

Results from a Randomised Trial

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Summary

An analysis of the economic data from a multicentre, randomised, placebo-controlled clinical trial of colfosceril palmitate in infants with neonatal respiratory distress syndrome (NRDS) and birthweights of 1250g or more is presented.

Two 5 ml/kg (67.5 mg/kg) doses of a synthetic surfactant (colfosceril palmitate) or air placebo were administered to 1237 infants who were receiving mechanical ventilation and had an arterial/alveolar oxygen tension ratio of less than 0.22. In addition to the clinical end-points for safety and efficacy, data were collected on length of hospital stay, days in the neonatal intensive care unit, days on mechanical ventilation, days on oxygen, and hospital charges until the child reached 1-year adjusted age. One-year adjusted age is attained when the time elapsed since birth is equal to 365 days plus the number of days of prematurity.

Rescue treatment with synthetic surfactant therapy has been shown to reduce the incidence of complications of NRDS. Growth and development of infants who received colfosceril palmitate therapy in the study and survived to 1-year adjusted age were equivalent to those of the survivors in the air placebo group. For the cohort of treated infants, colfosceril palmitate reduced the average length of stay at 2 levels of care needed during both the initial hospitalisation (a reduction of 8 days overall and 5 days in intensive care) and all first year hospitalisations (a reduction of 9 days overall and 5 days in intensive care). Total hospital charges for the initial hospitalisation and through 1-year adjusted age for a hypothetical cohort of 100 infants treated with colfosceril palmitate were less than those for a comparable cohort in the air placebo group.

The results would, therefore, suggest that rescue therapy with colfosceril palmitate in infants with NRDS and birthweights over 1250g can result in substantial reductions in hospital resource utilisation and charges in addition to the clinical benefits associated with its use.

A synthetic surfactant has been studied in controlled clinical trials involving more than 12 000 infants.[1-4] These studies have demonstrated that synthetic surfactant improves both survival and morbidity when administered to premature infants either as rescue or prophylactic treatment for respiratory distress syndrome. While the clinical outcomes are well documented, the economic consequences have not, as yet, been thoroughly assessed and reported.

Health policy-makers, regulatory authorities, reimbursement agencies, and clinicians are increasingly requiring information about the economic value of innovative health technologies before sanctioning their widespread funding or use. For example, in the state of Oregon a policy was recently introduced whereby Medicaid will fund only those healthcare interventions which achieve economic benefits surpassing a prespecified cut-off level. Below this level services will not be reimbursed.[5] In Canada, the Ontario provincial government has prepared draft legislation and guidelines stating that the degree of economic value of a new drug will be used to determine its price and reimbursement status.[6] The Federal government is considering adopting this initiative throughout Canada.[7] Similar policies have already been implemented by the Pharmaceutical Benefits Pricing Commission in Australia.[8]

Economists have developed analytical techniques for assessing the 'value for money' of medical technologies and practices. Known collectively as 'economic evaluation', these techniques bring together the empirical evidence about the effectiveness of a technology and its effects on healthcare costs.[9] Such data are important inputs into decision-makers' assessments of the relative value of healthcare programmes competing for a share of limited healthcare budgets. There is now substantial literature on economic evaluation in healthcare.[10]

Several studies have been conducted to evaluate the economic benefits of neonatal healthcare.[11-13] Irrespective of the country in which the studies were conducted, each has generally concluded that the significant funding required for intensive care of premature infants is a relatively good use of healthcare resources. Nevertheless, provision of neonatal intensive care is expensive[14] and the economic effects of new products designed for use in the neonatal intensive care unit will continue to be subject to close scrutiny.

The introduction of surfactant replacement therapy into routine clinical practice in neonatal care raises a number of important economic questions, including: what will be the effects on cost of care in the neonatal intensive care unit (NICU) for survivors, nonsurvivors and all treated infants; and, if it increases the cost of care for all treated infants, what is the incremental cost per year of life saved?

A recent retrospective study[15] has demonstrated overall cost savings in several US hospitals since the introduction of surfactant therapy for treatment of neonatal respiratory distress syndrome (NRDS) in premature infants. While there are several prospective studies that attempt to address these issues, these studies have been based on data from a small number of patients[16-21] and thus have not produced definitive experimental data about the economic value of this innovative therapy.

The purpose of this paper is to present the results of the analysis of the economic data that were collected prospectively as secondary end-points in a large double-blind, randomised placebo-controlled trial of rescue (i.e. initiated only after the infant has developed symptoms of NRDS) synthetic surfactant replacement therapy. These data are used in conjunction with evidence of clinical effectiveness to assess the economic effect of synthetic surfactant therapy from the perspective of a third-party payer that reimburses hospital charges and from the perspective of the hospital in terms of resource use.

Methods

Economic evaluation of innovative therapies requires assessments of and/or assumptions about clinical effectiveness, medical resource utilisation, and the associated costs.[9] All data used in this

study were collected prospectively in a multicentre, randomised, double-blind, placebo-controlled trial in the US and Canada comparing 2 rescue doses of either synthetic surfactant (colfosceril palmitate) or air placebo in infants with NRDS and birthweights of 1250g or more.

A total of 1237 infants who were receiving mechanical ventilation, had a ratio of arterial to alveolar oxygen tension below 0.22, and were less than 24 hours old, were randomised to receive colfosceril palmitate (n = 614) or air placebo (n = 623). Infants assigned to the colfosceril palmitate group received the initial dose [5ml (67.5mg) per kilogram of bodyweight] within 24 hours of birth, and the second dose 12 hours later. Infants were stratified at birth by birthweight and gender. The economic outcomes, like the clinical outcomes, were evaluated for a period of 1 year following entry into the clinical trial.

Clinical Effectiveness

The trial design and clinical findings of the trial have previously been reported in detail.[2] Significant improvements in measures of efficacy- and safety-related outcomes were observed in the surfactant-treated infants. Mortality was reduced by colfosceril palmitate therapy versus placebo in the neonatal period, 4 *vs* 7%, and at 1 year adjusted age, 7 *vs* 9%. The reduction in mortality was primarily attributable to a reduction in death from NRDS. Reported improvements in perinatal morbidity with colfosceril palmitate versus placebo therapy included a lower incidence of bronchopulmonary dysplasia (3 *vs* 5%; $p = 0.021$), a reduction in the frequency of intraventricular haemorrhage (18 *vs* 23%; $p = 0.036$), patent ductus arteriosus (45 *vs* 54%; $p = 0.004$), pulmonary hypertension (2 *vs* 6%; $p < 0.001$), and a reduction in pulmonary air leaks (18 *vs* 30%; $p < 0.001$).

Results from a follow-up study to determine whether improvements in perinatal morbidity are associated with changes in long term developmental outcomes were reported separately.[22] At 1 year of age, developmental outcomes in the infants randomised to receive colfosceril palmitate were equivalent to those in the air placebo group. Furthermore, chronic lung disease was less common in the colfosceril palmitate recipients. Significantly fewer children in the surfactant treated group were receiving medication for chronic lung disease or respiratory support at 1 year of age.

The findings on clinical effectiveness were used in the analysis of the economic outcomes as follows. Differential survival rates at 1 year of age were computed and used in conjunction with life tables to calculate the additional years of life saved due to colfosceril palmitate treatment.[23] Life tables list the probabilities of being alive at each age. The proportion of females in the trial was approximately 36%. Discounted additional years of life saved were calculated from the life tables using a discount rate of 5%, a rate commonly used in cost-effectiveness studies.[24] Discounting of the benefits (i.e. life-years gained) accounts for the greater value generally assigned to immediate gains compared with those further in the future. Based on the 1-year morbidity data summarised above, we assumed that colfosceril palmitate use did not increase long term medical care resource use and costs associated with residual physical and mental impairment in the treated cohort compared with controls.

Medical Care Resource Utilisation

Data were collected prospectively on key items of medical care resource utilisation for the treatment of the 2 groups of infants. Previous economic studies in neonatal care have highlighted the resource utilisation parameters which are the main determinants of cost.[12,25] These studies provided the basis for selecting the medical resource use variables to evaluate. Data were collected by a study coordinator and neonatologist for the following variables: days on intermittent mandatory ventilation; days on supplementary oxygen; days in NICU prior to first discharge; days in hospital prior to first discharge; days in NICU to 1 year of age, including readmission days; and days in hospital to 1 year of age, including readmission days. Discharge from the NICU and from the hospital depended on

factors such as weight, adjusted age and health status, and was decided by each investigator.

Conventional methods were used to calculate the summary statistics (mean, standard error, median) for all variables for infants with complete 1-year follow-up, and subdivided by survivors at 1 year and nonsurvivors. 95% confidence intervals (CIs) were calculated for differences in the mean resource use, assuming a standard normal distribution to define plausible ranges for the resource use variables.

Hospital Charges

Economic evaluation requires a monetary value to be placed on the medical care resource used in the provision of the treatments being compared. For this reason, data on total charges were collected for each infant during the trial. The totals included charges for room, laboratory and physician services, and for medications administered. Investigators were instructed to assign to the room charges category all other categories of charges not collected separately. Total charges were counted as missing if all categories of charges were not available. Charge data were collected in the US only [number of infants was 759 (387 in the colfosceril palmitate group, 372 in the placebo group)]. Charge data were obtained from patient bills, and are expressed in terms of $US for the time period of the trial, 1987 to 1990. The database was not finalised until approximately 18 months after the end of the trial to allow for more complete capture of the charge data.

Conventional methods were used to calculate the summary statistics (mean, standard error, median) for the charges for the initial hospitalisation and first year for infants with complete 1-year follow-up, and subdivided by survivors and nonsurvivors. 95% CIs were calculated for differences in the mean charges based on a standard normal statistic to define plausible ranges for the charge data. Results from the analysis of charges were also used in conjunction with the findings on clinical effectiveness to assess ratios of incremental charges to effectiveness of the surfactant.

Ratio of Incremental Charges to Effectiveness

While the key purpose of this analysis was to report the outcomes of the economic variables observed in the trial, it is also possible to use the results to assess the ratio of incremental charges to effectiveness of colfosceril palmitate treatment. This analysis involves weighing the survival benefits of therapy against the charges associated with achieving them. The effectiveness and total charges data were, therefore, combined in 2 ways. First, total charges for a cohort of 100 infants were divided by the number of survivors in that cohort to calculate a 'charge per survivor' for each group. This calculation is in keeping with the reporting of results from other studies in neonatal care.[16] Secondly, and more appropriately for decision-making, incremental analysis was performed, whereby the differences in charges were compared with the differences in survival outcomes, measured in terms of both additional number of survivors and number of life-years gained (additional number of survivors multiplied by life expectancy per survivor). Results reported in this way permit comparisons to be made with findings from other healthcare evaluations.

Sensitivity Analysis

It is standard practice in economic evaluations to examine the extent to which the results are sensitive to changes in the values of key parameters and/or assumptions made.[9] Because of significant loss to follow-up for both resource use (NICU days and hospital days) and charge data at 1 year, the Kaplan-Meier product-limit method was used in a sensitivity analysis to calculate the summary statistics, thus adjusting for missing data for infants who were lost to follow-up after the first hospital discharge.[26] In contrast to the main analysis, Kaplan-Meier estimations include data from infants lost to follow-up, up until the point at which patient records were discontinued. In addition, the charges data collected in the trial were converted to cost estimates using the total cost to charge ratio

Table I. Mortality at 1-year follow-up

Parameter	Air mean (SE)	Surfactant mean (SE)
Birthweight (g)	1911 (21)	1905 (21)
Male patients (%)	63	64
Patients randomised to treatment	623	614
Death by 1 year (%)	9 (1.2)	7 (1.1)
Deaths due to NRDS (%)	33	14

Abbreviations: NRDS = neonatal respiratory distress syndrome; SE = standard error of the mean.

for each study hospital (where available) to determine whether the conclusions from the main analysis changed when costs were used instead of charges. The ratios were available for 19 of 23 US trial study sites. Missing cost to charge ratios were imputed using the median known rates for that type of hospital (children's hospital, state university hospital, and private university hospital). Cost to charge ratios for nonstudy-site hospitals where infants received care during the first year were assumed to be the same as those for the study site where the infant was enrolled and treated with colfosceril palmitate.

Results

Clinical Effectiveness

Results from the survival analysis are presented in table I. The survival rate at 1 year of age was higher for the colfosceril palmitate recipients than for the air placebo group (0.93 *vs* 0.91, respectively). Thus, it is estimated that 2 additional lives would be saved for every 100 infants treated with colfosceril palmitate. Based on the 95% CI on the differences between the survival rates (–0.01, 0.05), the plausible range of outcomes is between –1 and 5 additional survivors per 100 infants treated.

Using the provisional US life table for 1992, the actuarial life expectancy for infants aged 1 year, weighted by the ratio of females to males in the study, is 74 years. This life expectancy was discounted at 5% to give 19.0 discounted life-years:

$$\sum_{i=1}^{90} (1.05)^{i-1} \times \text{the probability of being alive at time i}$$

Multiplying the number of survivors in a hypothetical cohort of 100 infants by the undiscounted and discounted life expectancy gives a gain of 148 undiscounted and 38 discounted life-years attributable to the use of colfosceril palmitate treatment [with 95% CIs of (370, –74) undiscounted and (95, –19), discounted].

Medical Care Resource Utilisation

No resource use data were available for approximately 6% of the infants in the trial. Data capture over the 1-year follow-up period was incomplete for 11% of infants for whom some resource use data were available.

Table II. Hospital resource use during the initial hospitalisation only

Parameter	Air		Surfactant		Difference (surfactant – air)	95% CI
	mean (SE)	n	mean (SE)	n		
All infants[a]						
Total days in hospital	45.4 (2.28)	524	37.2 (1.33)	514	–8.2	(–13.4, –3.03)
Days in intensive care	18.6 (1.41)	524	13.8 (0.89)	514	–4.8	(–8.1, –1.5)
One-year survivors						
Total days in hospital	46.1 (2.26)	467	37.6 (1.19)	476	–8.5	(–13.6, –3.4)
Days in intensive care	17.6 (1.36)	466	12.8 (0.61)	474	–4.8	(–7.8, –1.8)
One-year nonsurvivors						
Total days in hospital	39.8 (9.97)	57	31.6 (10.15)	38	–8.2	(–36.7, 20.3)
Days in intensive care	26.4 (6.59)	58	25.4 (8.79)	40	–1.0	(–23.0, 21.0)

a Excluding infants lost to follow-up.

Abbreviations: CI = confidence interval; n = number of infants; SE = standard error of the mean.

Table III. Hospital resource use during first year of life

Parameter	Air		Surfactant		Difference (surfactant – air)	95% CI
	mean (SE)	n	mean (SE)	n		
All infants[a]						
Total days in hospital	49.5 (2.43)	524	40.7 (1.48)	514	–8.8	(–14.4, –3.2)
Days in intensive care	18.9 (1.43)	524	14.0 (0.91)	514	–4.9	(–8.2, –1.6)
Days on mechanical ventilator	11.8 (1.24)	533	7.6 (0.74)	522	–4.2	(–9.4, 1.0)
Days on oxygen	35.9 (3.25)	534	21.9 (2.05)	522	–14.0	(–21.5, –6.5)
One-year survivors						
Total days in hospital	50.5 (2.42)	467	41.4 (1.38)	476	–9.1	(–14.7, –3.5)
Days in intensive care	18.0 (1.38)	466	12.9 (0.61)	474	–5.1	(–8.1, –2.1)
Days on mechanical ventilator	10.1 (1.12)	474	6.2 (0.30)	478	–3.9	(–6.2, –1.6)
Days on oxygen	35.3 (3.38)	475	21.0 (2.07)	478	–14.3	(–22.2, –6.4)
One-year nonsurvivors						
Total days in hospital	41.4 (10.21)	57	32.0 (10.16)	38	–9.4	(–38.2, 19.4)
Days in intensive care	26.4 (6.59)	58	27.6 (9.01)	40	+1.2	(–21.1, 23.5)
Days on mechanical ventilator	26.0 (6.44)	59	23.3 (7.81)	44	–2.7	(–22.9, 17.5)
Days on oxygen	40.7 (11.26)	59	31.8 (9.27)	44	–8.9	(–38.1, 20.3)

a Excluding infants lost to follow-up.

Abbreviations: CI = confidence interval; n = number of infants; SE = standard error of the mean.

Tables II and III show the mean levels of medical care resource utilisation observed in the trial for each treatment group as well as the 95% CI for the initial hospitalisation and first year of life, respectively. During the initial hospitalisation, the use of colfosceril palmitate for all infants with complete 1-year data saved an average of 8.2 days of hospitalisation overall and 4.8 days of intensive care treatment for each infant. During the first year these savings were maintained, 8.8 days overall and 4.9 days in intensive care. In addition, there were 4.2 fewer days on mechanical ventilation and 14 fewer days on oxygen. These differences were all statistically significant except for the difference in days on mechanical ventilation. The resource utilisation differences for the first year are also illustrated in figure 1.

The results for the survivors to 1 year and nonsurvivors analysed separately, for both the initial hospitalisation and the first year, are also worthy of comment. The data for the 1-year survivors show large, statistically significant, reductions in each component of resource use for the colfosceril palmitate group compared with the placebo group. However, the treatment differences for the nonsurvivors were statistically nonsignificant. The results for the nonsurvivors should be considered with caution because of the small number of deaths in each treatment group. The resource use data were subdivided by country, US and Canada, and reanalysed. There were no differences in the results between the 2 countries.

Hospital Charges

Use of colfosceril palmitate resulted in overall savings in mean hospital charges. The mean charges for each treatment group as well as the 95% CIs are shown in table IV. Total charges in the colfosceril palmitate group for the initial hospitalisation were $US46 807 compared with $US59 478 for the air placebo group, a saving of $US12 671 per treated infant. The difference in total charges per treated infant is the same at the end of the first year, $US12 891. These results are consistent with the significant reductions in the levels of medical care resources reported in tables II and III. Figure 2 presents the charge differences between the treatment groups broken down by charge category, room charges, laboratory charges, medication charges (excluding the cost of the colfosceril palmitate),

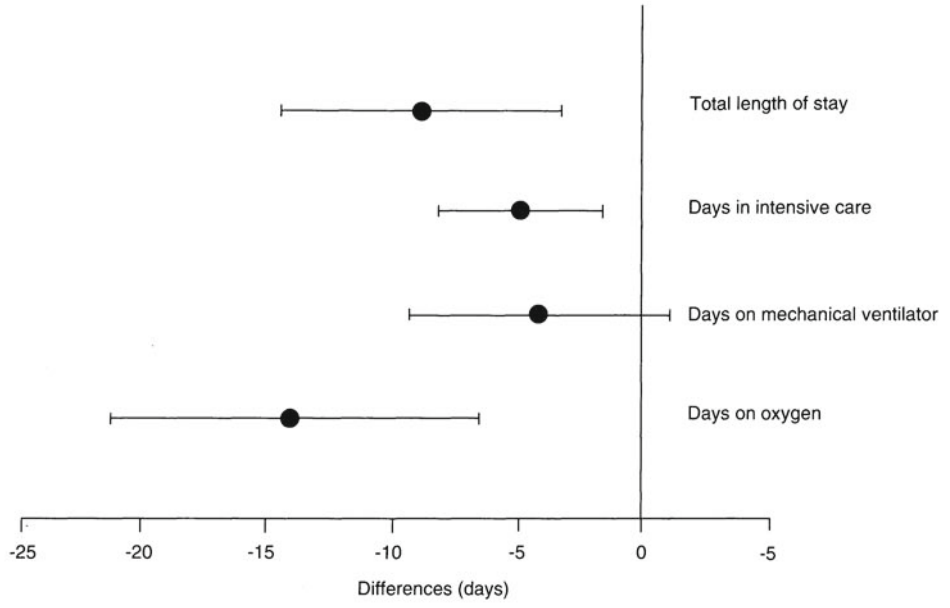

Fig. 1. Mean differences in 1-year resource use (colfosceril palmitate recipients minus air recipients) across all infants enrolled in the clinical trial. The bars indicate 95% confidence intervals.

physician charges, and total charges (including the cost of the colfosceril palmitate). Although reductions in charges are apparent for all categories, the largest effect is through reduced room charges.

Ratio of Incremental Charges to Effectiveness

The ratio of incremental charges to effectiveness may be assessed by comparing charge per survivor for the 2 patient groups, or by computing the ratio of the incremental charges with the incremental benefits, measured in lives saved and life-years gained for the 2 patient groups. These computations are presented in table V. The charge per survivor is $US53 526 for the colfosceril palmitate treatment group and $US68 868 for the air placebo group. Since the mean incremental charges for treatment are negative, it is not appropriate to calculate the incremental charge per year of life saved.

Sensitivity Analysis

Table VI presents the results of the product-limit analysis of the 1-year resource use (USA and Canada) and charge (USA only) data, using data from infants with both complete and incomplete follow-up. The results show that although the numerical estimates differ from the estimates using only infants with complete follow-up, the direction and magnitude of the effects are similar. Table VI also presents the cost estimates for the USA infants with complete follow-up. The differences in costs are similar in magnitude to the differences in charges.

Discussion

The results presented in this paper show that treatment of NRDS with colfosceril palmitate in infants with birthweights of at least 1250g results in reduced charges compared with the placebo group in addition to the health benefits. There are 3 likely reasons for these results.

First, for premature infants larger than 1250g, NRDS is likely to prolong their stay in the hospital. For smaller infants, size and gestational age are the major factors in determining when they can be discharged. In smaller infants, even untreated NRDS generally resolves itself before the infant is ready

Table IV. Charges (in 1987-1990 $US) for initial hospitalisation and those incurred during the first year of life (US infants only)

Parameter	Air		Surfactant		Difference (surfactant – air)	95% CI
	mean (SE)	n	mean (SE)	n		
All infants[a]						
Initial hospitalisation	59 478 (5748)	239	46 807 (3878)	216	−12 671	(−26 261, 919)
First year	62 670 (5922)	239	49 799 (4050)	216	−12 891	(−26 953, 1171)
One-year survivors						
Initial hospitalisation	61 330 (6186)	211	43 629 (1927)	194	−17 701	(−30 659, −4742)
First year	64 694 (6377)	211	46 761 (2343)	194	−17 933	(−31 522, −4345)
One-year nonsurvivors						
Initial hospitalisation	45 529 (15 324)	28	74 831 (34 197)	22	+29 302	(−45 645, 104 247)
First year	47 420 (15 645)	28	76 392 (34 154)	22	+28 972	(−46 162, 104 106)

a Excluding infants lost to follow-up.

Abbreviations: CI = confidence interval; n = number of infants; SE = standard error of the mean.

to leave the hospital and, thus, does not in itself prolong hospitalisation unless complications occur. On the other hand, for larger premature infants, successful treatment of NRDS could lead to a reduction in hospitalisation since larger infants may have shorter hospital stays.

Secondly, complications associated with prematurity such as intraventricular haemorrhage and bronchopulmonary dysplasia were reduced in infants receiving synthetic surfactant,[2] as was use of medications in the NICU. Thus, a lower intensity of daily care in the hospital was observed.

Thirdly, treatment of NRDS with synthetic surfactant in larger premature infants has only a small absolute effect on survival largely because survival is excellent without surfactant. In smaller prema-

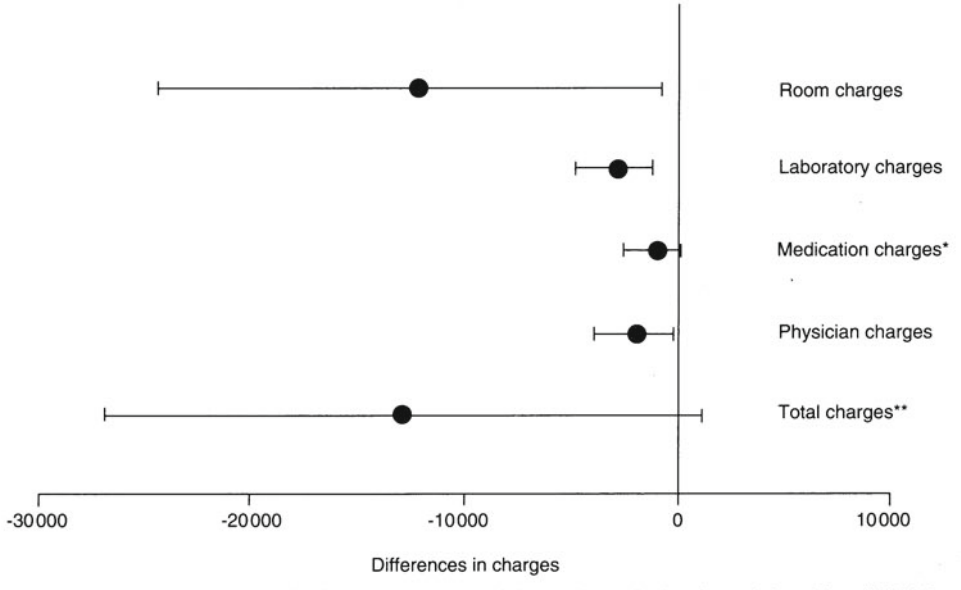

Fig. 2. Mean differences in 1-year charges (colfosceril palmitate recipients minus air placebo recipients) for all US infants enrolled in the clinical trial. The bars indicate 95% confidence intervals. *Symbols:* * denotes not including colfosceril palmitate; ** denotes including colfosceril palmitate. Charges are in 1987-1990 $US for infants treated in the US only.

Table V. Economic value analysis. Charges are in 1987-1990 $US

Parameter	Difference (surfactant – air)	95% CI
Charges per infant	–12 891	(–26 953, 1171)
Additional 1-year survival probability	0.02	(–0.01, 0.05)
Life-years gained (undiscounted) per infant	1.48	(3.70, –0.74)
Life-years gained (5% discount) per infant	0.38	(0.95, –0.19)
Charges per survivor[a]	–15 342	

a Total charges for a cohort of 100 infants divided by the expected number of survivors at 1 year.

Abbreviations: CI = confidence interval.

ture infants, the absolute effect of synthetic surfactant on survival is much greater. Since premature infants who survive the first year generally incur large charges that year, while those who die do not,[20] there are only limited increases in the charges of treating increased survivors to offset the reduction in charges for the infants who would have survived without surfactant treatment.

Resource use data are presented for both the initial hospitalisation as well as the first year of hospital use only for those infants that had complete 1-year resource use data. In general, resource use data were more complete for the initial hospitalisation than for the full first year. In particular, 6% of infants had no resource use data and 11% had incomplete follow-up for the resource use data after the 28-day evaluation. Other studies on the economic value of surfactant therapy have presented only data for the initial hospitalisation.[16] The results indicate that the reductions in resource use continue after the first hospital stay.

Data were not collected for outpatient care during the trial period. At 1 year of life, differences observed between the treatment and placebo groups in the use of medications for chronic lung disease indicate that there may also be reductions in outpatient care during the first year for infants with NRDS treated with synthetic surfactant.

The financial data collected during the trial from the US sites were hospital charges data (the amounts that appear on the patient bill). These data are relevant for third-party payers who reimburse the hospital on the basis of charges and for the hospital in terms of revenue estimation for charged-based patients. Charges are generally higher than costs, because the hospital attempts to generate funds for new programmes and equipment and building replacement, as well as to cover bad debts and costs or charges that are disallowed by selected third-party payers. Economic costs (the prices paid by the hospital for the resources consumed) are more relevant from a societal perspective and accounting costs (economic costs allocated to each unit of service) more relevant for those who reimburse on the basis of costs.[26]

As part of the sensitivity analysis, the total charge data were adjusted by estimated hospital accounting cost to charge ratios, taken from Medicare cost reports. This adjustment was only approximate because total cost to charge ratios were only obtained for a subset of the study sites and were obtained for none of the hospitals that were not listed as a study site. The missing values were imputed from the available data. The results of the sensitivity analysis illustrate that the cost differences between the placebo and treatment groups are somewhat smaller than the charge differences in absolute magnitude, but were in the same direction as the charge differences. Thus, the conclusions from the charge estimates presented in this paper do not change when this adjustment is made. Charges data were collected at the US sites only and were less complete than the resource use data (29% with no data and 15% with incomplete data).

Discounting of the benefits (life-years gained) is generally recommended for economic analyses[9] and has been used in previous economic analyses of neonatal intensive care. For example, Boyle et al.[13] justify their use of discounting for benefits with the argument that new treatments in the NICU require the early expenditures of large sums of money to achieve later gains in numbers of life-years or productivity. Thus, discounted survival benefits are the most appropriate for economic evaluation.

The product-limit survival techniques that we used to estimate the level of hospital care use and

Table VI. Sensitivity analysis

Parameter	Air		Surfactant		Difference (surfactant – air)	95% CI
	mean (SE)	n	mean (SE)	n		
Product-limit estimates[a]						
Total days in hospital	53.6 (2.71)	584	43.3 (1.61)	580	–10.3	(–16.6, –4.0)
Days in intensive care	22.3 (1.78)	584	18.8 (1.52)	579	–3.5	(–8.2, 1.2)
1-year charges ($US)	85 578 (11 885)	280	67 358 (8342)	256	–18 220	(–47 261, 10 821)
Cost estimates[b]						
Initial hospitalisation	46 811 (5427)	239	35 322 (3480)	216	–11 489	(–24 125, 1147)
First year	49 431 (5556)	239	37 846 (3654)	216	–11 585	(–24 615, 1445)

a All infants with resource use data.

b Excluding infants lost to follow-up.

Abbreviations: CI = confidence interval; n = number of infants; SE = standard error of the mean.

charges through 1 year in the sensitivity analysis[27] are similar to those which have been used recently by several researchers in the analyses of the costs of treating patients with AIDS.[28-30] All of these research groups have recognised the value of using statistical techniques that were developed for obtaining the most information possible from incomplete data. In this study, incomplete data were rare for the data obtained during the initial hospitalisation, but were more common for the 1-year data. Use of product-limit techniques allowed us to use all the data that we were able to collect while adjusting for the incompleteness. The results of the main analysis of data from infants with complete follow-up were not significantly different in either direction or magnitude from results obtained using the product-limit method.

The economic value of a new therapy depends both on its effect on healthcare budgets and on lifetime health, including both the quality and duration of life. Eidelman,[31] on the basis of several published studies, has suggested that the total annual cost of surfactant use in the US might be in the range of $US280 million to $US350 million because of the increased number of survivors in the 750 to 1350g birthweight range. The recent study of Schwartz et al.,[15] as well as this study, indicate that the cost savings attributable to surfactant use for larger infants, most of whom would have survived without it, offset increased costs because of increased survival in the smaller infants. In the Schwartz et al.[15] study, hospital costs are estimated to have decreased for all infants weighing between 500 and 1500g after the introduction of surfactants. However, average length of stay remained the same.

The estimates presented in this paper focus on the infants in the upper end and above the birthweight range in the Schwartz et al.[15] paper and show a reduction in total hospital resource utilisation and charges for infants with NRDS and birthweights of at least 1250g who are treated with 2 rescue doses of colfosceril palmitate during their first 24 hours of life. Clinical follow-up data for the infants in this paper show that, although there are a few more total survivors in the colfosceril palmitate group than in the air placebo group, there is no difference in the number of infants with mental or physical developmental impairments. In fact, the absolute number of impaired infants is less in the group treated with colfosceril palmitate.[22] This finding suggests that the charges of care for infants treated with colfosceril palmitate after 1-year adjusted age will be no different from those for an untreated cohort.[32-33] The results would, therefore, suggest that 2 rescue doses of colfosceril palmitate in infants with NRDS and birthweights over 1250g can result in substantial reductions in hospital resource use and substantial savings in hospital charges during the first year of life in addition to the clinical benefits associated with its use.

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