An initial inquiry into cost-effectiveness of surfactant in India: a pilot randomized control trial

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Abstract

Background: Exogenous surfactant is used for surfactant deficient lung disease in premature neonates. The cost-effectiveness in terms of cost per life saved by the intervention has not been studied in India.
Aim: The present study was done to evaluate the cost of surfactant therapy per life saved
Setting: Neonatal unit in a tertiary referral hospital.
Design: Prospective randomized controlled trial.
Material & Methods: 20 neonates with gestational age between 27 and 30 weeks with respiratory distress were recruited for the study and randomized for treatment with surfactant or to act as controls. All costs of hospitalization were totaled in both groups and differences in mortality, duration of hospitalization and costs were investigated.
Statistical Analysis: Differences between groups and the standard error of the difference were studied with the 95% confidence intervals.
Results: Odds of death were marginally higher in the surfactant group (OR 1.02 CI 0.39 – 2.7). The duration of hospitalization was significantly lower in the surfactant group. The costs were 20% higher in the surfactant survivors but it did not reach statistical significance.
Conclusion: The study did not show benefit in terms of reduced mortality. This is similar to the conclusion of the Cochrane meta-analysis. The cost per life saved could not therefore be calculated.

Keywords: Surfactant, cost effectiveness, cost per life year gained

1. Introduction

Exogenous surfactant therapy is prescribed for surfactant deficient disease in premature infants. It is not used widely in India because of its prohibitive cost. Over the years the cost of surfactant has steadily come down. It is understood that when cost per life year saved is less than the per capita GNP of the country, the intervention is affordable [1]. We did this small, randomized controlled trial to evaluate the costs and benefits of surfactant use and assess the cost per life year saved.

2. Methods and Materials

This study was conducted in the neonatal intensive care unit of a tertiary level hospital in Delhi between April 2003 and March 2004. Twenty neonates of gestational ages between 27 to 30 weeks, with respiratory distress were recruited for the study. The features of respiratory distress were evidence of increased work of breathing: (respiratory rate 60/min, sub-sternal and supra-sternal retractions and grunting), evidence of increased oxygen requirement: (requiring FiO_2 above 0.40 to maintain saturation above 90%) or chest X ray suggestive of surfactant deficient lung disease. Newborns with congenital anomalies incompatible with life like anencephaly, severe congenital heart disease, and renal agenesis were excluded, as also those with respiratory distress due to other causes like meconium-aspiration syndrome, and congenital diaphragmatic hernia.

The study was done between April 2003 and March 2004. At the time when the protocol was approved, Survanta (surfactant) was not licensed for use in India and it was not hospital policy to use surfactant. The Hospital Research Committee approved the study. Eligible patients were randomized to receive drug or act as controls, by the drawing of lots. Randomization was done in blocks of four. Those randomized not to receive surfactant were treated as per standard unit protocol. Those randomized to receive surfactant were explained the unlicensed status of the drug and its costs and written consent was obtained to use the drug. One parent refused consent. He was managed as per protocol without surfactant. Analysis was done according to intention to treat and also on the basis of the treatment received. Surfactant (Survanta Abbott Laboratories, USA; Dose: 4 ml/kg) was given within four to six hours of life as rescue therapy through endotracheal route via a feeding tube in four standard positions and one fourth of the total dose of surfactant was administered in each position. After giving every aliquot of surfactant, the baby was given positive pressure ventilation with Ambu bag for 30 seconds to ensure homogenous distribution of the drug. They were closely monitored for changes in ventilator settings including their pressure requirements, after receiving surfactant. All babies in the study had chest X ray and blood gas analysis to help guide changes in ventilator settings. The cost of all the drugs and hospital bills were totaled in each patient. Statistical analysis looking at odds ratio and confidence intervals for differences between groups was calculated using Confidence Interval Analysis software (www.som.soton.ac.uk)

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3. Results

Table 1 shows base line characteristics of the babies in both groups. Neonates in both the groups were of similar gestational age and birth weight. Mean gestational age was 28.6 weeks in the surfactant group and 28.45 weeks in the control group while mean birth weight was 1298 grams in the surfactant group and 1122 grams in the control group. On intention to treat analysis mean gestational age was 28.6 weeks in the surfactant group and 28.5 weeks in the control group while mean birth weight was 1268 grams in the surfactant group and 1135 grams in the control group.

Table 2 shows the number of complications in the two groups. The numbers are too small for drawing statistical inferences but there were 9 instances of complications in the surfactant group compared to 6 in the control group.

Table 3 shows the outcome in the two groups according to the treatment received. The mortality in the surfactant group was marginally higher (OR = 1.02, C.I. 0.39 to 2.7). The duration of hospitalization was lower in the surfactant group. The neonates who died after receiving surfactant died significantly earlier and those that survived, had a shorter stay in the hospital. The cost was not significantly different in the two groups. The early death in the surfactant group would lower costs in that group. We therefore analyzed cost among survivors. The mean cost for survivors who received surfactant was higher than for those who had not received surfactant, but the difference was not statistically significant.

The intention to treat analysis is shown in Table 4. The trend is the same as in the analysis according to treatment received.

4. Discussion

Our study showed increased mortality in the group that received surfactant but the difference did not reach statistical significance. Babies who received Surfactant had a significantly shorter stay in the hospital. Cost of hospitalization was higher in the surfactant group but this was not significant. We have looked at all hospital costs including all drugs used in the child. The perspective is that of the patient. Indirect costs like transport of parents to the hospital were not added.

There are a number of ways in which to calculate cost and benefits and to evaluate if an intervention is affordable. The purpose of the study was to calculate the cost per life saved and further to calculate the cost per life year gained. The study however found that no life was saved for the extra expense incurred – and as such, use of surfactant cannot be recommended using these criteria. We have not studied the 'willingness to pay' for the benefit of shorter hospital stay. This needs to be done only if there is no increase in mortality in the intervention group. (We assume here that the increased probability of mortality will outweigh any benefit afforded by a shorter hospital stay.)

The increase in mortality with surfactant has been seen in some previous studies also [2,3]. We have previously drawn attention to the fact that the Cochrane meta-analysis did not find improved survival in those that received Surfactant [4, 5] and our finding in this study are similar to the Cochrane study.

There is a large incidence of small-for-date babies in India [6]. Small-for-date babies are stressed *in utero* and such babies are less likely to need exogenous Surfactant. The need for Surfactant and its cost implications need to be evaluated separately here. This is arguably the first randomized control trial on Surfactant use in India. A study published previously looked at mortality in a group of patients whose parents could afford the use of surfactant, against controls who could not afford the drug [7]. Given the difference in mortality between socio-economic groups, it is difficult to determine how much of the improved survival was due to the drug intervention.

In our study Surfactant use was associated with shorter hospital stay. Early death in the group that received Surfactant was also seen. This would have helped reduce costs in that group. We therefore analyzed, separately, the cost among survivors in the two groups. Here the mean cost was 20% higher in the intervention group but it was not statistically significant.

The study was done in a Christian charitable hospital. Patients pay for all costs, except the indigent who were treated free of charge. Costs are kept low as overheads are kept to the minimum and there is no need to generate shareholder returns. There is however deep disparity between the availability of advanced medical facilities in private and public sectors as well as between rural areas, smaller town and larger cities. This study done in a charitable hospital in the capital city of Delhi cannot be said to have studied a representative population of preterm neonates in the country.

Another drawback of this study is that sample size is very small so it will be too early to reach to any conclusion regarding effectiveness of surfactant therapy. The sample size of 20 neonates is slightly smaller than another single center study considered in the Cochrane meta-analysis that studied 25 patients [8].

5. Conclusion

The findings of our study justify a larger multi-center study across the country. However the situation with regard Surfactant has changed since the study was started. Surfactant is now licensed for use in the country. Ethically, in future, parents will have to be given the option to choose between use and non-use of Surfactant. The new study can offer them a third option of participating in a randomized trial. The research ethics committee will have to look at the ethics of such a study given the uncertainty about benefit of Surfactant seen in this study and two other studies [2,3] conducted in the West.

Surfactant is used in surfactant deficient disease in preterm babies. The Cochrane meta-analysis shows that it does not improve survival up to discharge. This paper indicates the costs in patients given Surfactant in India is 20% higher than those treated without surfactant. In the absence of improved survival, the cost per life saved could not be carried.

References

[1] Tyagi V, Singh SK, Sawhney A, Taneja V, Puliyel JM. Using gross national product to calculate acceptable immunisation costs: deploying cost-effectiveness calculations in reverse. Pharmacoeconomics. 2003;21:497-9.

doi: 10.1588/medver.2006.03.00150

[2] Shennan A, Dunn M. Surfactant replacement trials - the need to maintain concurrent placebo controls. Pediatr Res 1989; 25:231A.
[3] Dunn M, Shennan A, Possmayer F. Bovine surfactant prophylaxis in neonates less than 30 weeks' gestation: A Randomized controlled trial of prophylaxis versus treatment. Pediatrics 1991;87:377–86.
[4] Tiwari L, Puliyel J, Upadhyaya P. Truth and evidence based medicine: spin is everything.. BMJ. 2004;329:1043.
[5] Soll RF Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review). In: T*he Cochrane Library*, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.)
[6] Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity: Experience in a large maternity unit with a medium sized level-3 nursery. Indian J Ophthalmol 2001;49:187–8
[7] Narang A, Kumar P, Dutta S, Kumar R. Surfactant therapy for hyaline membrane disease: the Chandigarh experience. Indian Pediatr. 2001 Jun;38(6):640-6.
[8] Kwong MS, Egan EA, Notter RH, Shapiro DL. Double-blind clinical trial of calf lung surfactant for prevention of hyaline membrane disease in extremely premature infants. Pediatrics 1985;76:585–92

Table 1 : Baseline characteristics in two groups according to treatment received

	Surfactant (n=9)	Control (n=11)	SE of difference (95% C.I.)
Mean gestational age weeks (SD)	28.6 (0.74)	28.45 (0.82)	0.222 (-0.32 to 0.62)
Mean birth weight grams (SD)	1298 (466)	1122 (148)	148 (-135 to 487)

Table 2 List of complications in the two groups according to treatment received

Complication	Surfactant group (numbers with complication)	Control (numbers with complication)
Sepsis	3	2
Pneumothorax	1	0
Pulmonary hemorrhage	2	0
Intra-cranial hemorrhage	1	2
Patent ductus arteriosus	2	0
Narcotizing enterocolitis	1	2
Retinopathy of prematurity	0	0
Total	**9**	**6**

Table 3. Outcome in the two groups according to the treatment received

	Surfactant (n=9)	Control (n=11)	SE of difference (95% C.I.)
Mortality	55.5%	54.5%	0.22 (-0.37 to 0.38)
Mean duration of hospital stay	7.1 days (19.6)	26.3 days (16.3)	8.0 (-36 to –2)
Mean duration of hospital stay in babies who died (SD)	2.8 days (1.41)	13.8 days (4.45)	1.55 (-14.3 to –7.7)
Mean duration of hospital stay in survivors (SD)	12.5 days (10.25)	41.5 days (11.67)	5 (-39 to –18.5)
Average cost per patient in Rs.[1] (SD)	32188 (13445)	32423 (12198)	5738 (-12291 to 11821)
Average cost among survivor in Rs.[1] (SD)	43183 (11926)	35359 (15918)	6419 (-5662 to 21310)

[1]1 Rs. = 1 Rupee or 1 India Rupee, INR; 1 USD = 46.136 INR

Table 4 Analysis according to intention to treat

	Surfactant (n=10)	Control (n=10)	SE of difference (95% C.I.)
Mean (SD) Gestational Age (weeks)	28.6 (0.74)	28.45 (0.82)	0.222 (-0.32 to 0.62)
Mean (SD) Birth Weight (g)	1298 (466)	1122 (148)	148 (-135 to 487
Mortality	50%	60%	0.22 (-0.45 to 0.29)
Mean duration of hospital stay	10.3 days (15.7)	24.1 days (15.2)	6.9 (-28 to 0.72)
Mean duration of hospital stay in babies who died (SD)	2.8 days (1.3)	13.3 days (4.45)	1.46 (-13.6 to –7.4)
Mean duration of hospital stay in survivors (SD)	19.8 days (18.6)	39.5 days (11.67)	6.9 (-34.3 to –5.1)
Average cost per patient in Rs.[1] (SD)	34,386 (14,456)	30,249 (10,371)	5,626 (-7,683 to 15,957)
Average cost among survivor in Rs.[1] (SD)	45,380 (11,436)	30,658 (15,918)	6,198 (1,700 to 27,743)

[1]1 Rs. = 1 Rupee or 1 India Rupee, INR; 1 USD = 46.136 INR

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