The cost and effectiveness of surfactant replacement therapy at Johannesburg Hospital, November 1991 - December 1992

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Objective. To assess the impact of surfactant replacement therapy (SRT) on the outcome of hyaline membrane disease (HMD) and to assess the cost implications of a policy of selective administration of artificial surfactant.

Design. The short-term outcome of 103 newborns ventilated for HMD (61 selected for SRT according to initial and/or ongoing oxygen requirements) was compared with that of a historical control group of 173 infants ventilated for HMD before the introduction of SRT.

Main outcome measures. Mortality and morbidity of HMD including death, bronchopulmonary dysplasia, pneumothorax, pulmonary haemorrhage, patent ductus arteriosus and intraventricular haemorrhage.

Results. There were significant demographic differences between the treatment and control groups (black patients 74% v. 28%, $P < 0,0001$; unbooked mothers 72% v. 15%, $P < 0,0001$) as well as evidence of more severe lung disease in the treatment group (pressor support 44% v. 27%, $P < 0,005$; and paralysis during ventilation 38% v. 25%, $P < 0,005$). Pneumothorax was reduced in the SRT group (7% v. 17%, $P < 0,01$). There were no significant differences between the two groups in the incidence of BPD or mortality. The use of SRT added to the total cost of treating a patient ventilated for HMD.

Conclusion. The selective use of SRT had the effect of converting severe disease into moderate disease rather than achieving maximal benefit in all cases of HMD through routine use of the product. A policy of restricting use may result in cost savings where resources are limited.

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In South Africa limited physical and financial resources for neonatal intensive care exclude many newborns of < 1 000 g birth weight from ventilation at many centres and mitigate against the routine use of surfactant replacement therapy (SRT) in newborn infants with hyaline membrane disease (HMD). At Johannesburg Hospital, infants ventilated for HMD are selected to receive surfactant (Survanta; Abbott Laboratories) according to their oxygen requirements. This policy is based on a study by Ballot *et al.*[1] which showed that using the fractional inspired oxygen concentration (Fio_2) as a criterion for SRT in a group of 78 infants with HMD, 28% required immediate SRT, 31% required later SRT, and 41% of these infants (all initially eligible for SRT according to published criteria) did not qualify for SRT. The short-term outcome of the SRT and non-SRT infants was comparable, suggesting that a limited period of observation to assess the severity of illness before SRT is not deleterious and may be an acceptable way of administering SRT where limited facilities and the cost of the drug impose restrictions on its use.[1]

Using historical controls we compared 103 newborns ventilated for HMD (61 selected for SRT according to the above criteria) with 173 infants ventilated for HMD before the introduction of SRT. The objective was to assess the impact of SRT on outcome, and gauge the cost implications of the policy of selective administration of artificial surfactant.

Methods

From November 1991 to December 1992, infants ventilated for HMD at Johannesburg Hospital were selected to receive Survanta according to initial and ongoing oxygen requirements. Infants who required an Fio_2 > 0,75 3 - 4 hours after birth to maintain a partial arterial oxygen pressure (Pao_2) of 50 - 70 mmHg received SRT at that time. Infants with lower oxygen requirements received SRT if their Fio_2 was > 0,62 12 hours after birth or 0,4 18 - 24 hours after birth. Owing to the lower barometric pressure in Johannesburg, which is situated 1 800 metres above sea-level, these Fio_2 values would correspond to lower Fio_2 values at sea level.

Demographic data and details of disease severity, treatment and outcome were collected from computerised hospital records. Data were also collected from a group of infants ventilated for HMD at Johannesburg Hospital from January 1989 to June 1991, before the introduction of SRT.

During the time periods studied, the indications for paralysis and pressor support during ventilation did not change. Patients received pancuronium when the ventilator rate exceeded 40 breaths per minute and the peak inspiratory pressure (PIP) exceeded 30 cm H_2O. Ventilation practices were also similar during the two time periods. Inspired oxygen and/or PIP were adjusted to maintain a Pao_2 of 50 - 70 mmHg, and rate or PIP were adjusted to maintain an arterial $Paco_2$ of 40 - 50 mmHg.

Dopamine was administered at a dose of 5 - 10 µg/kg/min when the systolic blood pressure fell ⩾ 2 SD below the mean for age.

Bronchopulmonary dysplasia (BPD) was defined as an oxygen requirement at 36 weeks postconceptional age in an infant with radiological evidence of chronic lung disease.[2] Intraventricular haemorrhage (IVH) was classified according to Papile *et al.*[3]

The total cost of treating each group was calculated according to the duration of stay in the intensive care unit (ICU) and high-care and general care wards. Based on a study by Malan *et al.*,[4] daily costs in each of these areas were calculated at R530,00, R265,00 and R88,00 respectively.

Statistical analysis, which included descriptive statistics, *t*-tests and Fisher's exact test, was done on a personal computer using Statpak version 4.1 (Northwest Analytical, Portland, Oregon).

Results

From November 1991 to December 1992, 103 infants were ventilated for HMD and 61 qualified to receive Survanta according to their oxygen requirements. The mean age (±SD) at the time of the first dose was 13,8 ± 16,4 hours, and patients received a mean of 1,5 doses. The mean alveolar/arterial oxygen ratio (A/aDo_2) at the time of the first dose was 0,16 ± 0,07.

In Table I demographic features of infants from the present study are compared with a control group of 173 infants ventilated for HMD from January 1989 to June 1991. There were significantly more black patients (74% v. 28%, $P < 0,0001$), and more babies born to unbooked mothers (72% v. 15%, $P < 0,0001$) in the study group. In both groups only 5% of mothers received antenatal steroids.

Table I. Demographics

	Pre-Survanta HMD	Survanta HMD	*P*-value
No.	173	103	
Birth weight (g)	1 694 ± 623	1 522 ± 382	< 0,01
Gestational age (wks)	32 ± 3	32 ± 2	NS
Male/female (%)	60:40	50:50	NS
Black/white (%)	28:72	74:26	< 0,0001
Unbooked (%)	15	72	< 0,0001
Inborn (%)	88	86	NS
Multiple pregnancy (%)	15	7	< 0,05
Antenatal steroids (%)	5	5	NS
Caesarean section (%)	39	32	NS
Apgar 5 min	8 ± 2	8 ± 2	NS
PIP (cm H_2O)	29 ± 7	29 ± 7	NS
Dopamine (%)	27	44	< 0,005
Pancuronium (%)	25	38	< 0,005

Significantly more babies in the study group required pressor support (44% v. 27%, $P < 0,005$) and paralysis during ventilation (38% v. 25%, $P < 0,005$) (Table I).

Table II. Complications and outcome (%)

	Pre-Survanta HMD	Survanta HMD	*P*-value
Pneumothorax	17	7	< 0,01
Pulmonary haemorrhage	1	1	NS
PDA	22	25	NS
All IVH	36	66	< 0,0001
IVH ⩾ grade 3	9	14	NS
BPD	10	17	NS
Death	12	11	NS

IVH = interventricular haemorrhage; PDA = patent ductus arteriosus.

The incidence of pneumothorax was significantly reduced in the study group (7% v. 17%, $P < 0,01$). There were no significant differences between the two groups in the incidence of BPD or mortality (Table II).

The use of Survanta did not significantly alter the time spent at various levels of care but added to the total cost of treating a patient ventilated for HMD (Table III).

Table III. Total cost per patient per group

	Pre-survanta HMD		Survanta HMD	
	Days (mean)	R	Days (mean)	R
ICU	10,5	5 565	10,3	5 459
High care	15,2	4 028	13,9	3 684
General ward	2,05	180	4,6	405
Survanta*				1 777
Total		9 973		11 325

* The cost of Survanta per patient was estimated as follows: 61/103 patients required a mean of 1,5 doses each at R2 000 per dose, i.e. 61 x 1,5/103 doses at R2 000 per dose = R1 777. In other words, the cost is distributed throughout the total group rather than relating only to those who received the product.

Discussion

SRT has been shown to reduce the mortality and morbidity of HMD,[5,6] especially when it is administered early in the course of HMD.[7] The results of the OSIRIS trial suggest that surfactant should be administered within 2 hours of birth to ensure maximal efficacy.[7] However, in South Africa limited resources necessitated the development of some selection criteria for SRT in newborns presenting with HMD. Results of a study by Ballot *et al.*[1] suggest that a limited period of observation to assess the severity of HMD before SRT does not compromise outcome and may be an acceptable way of administering SRT where limited facilities and the cost of the drug impose restrictions on its use. This approach might be regarded as converting severe disease into moderate disease, rather than achieving maximal benefit in all cases of HMD through routine use of the product.

When SRT was introduced into South Africa in November 1991 its use had already been evaluated in several randomised controlled trials. Consequently, companies marketing the product in South Africa were unwilling to conduct further randomised trials in this country. This was despite the fact that SRT under conditions of limited resources had not been studied. In fact, the introduction of the drug into South Africa was a unique opportunity for such a study, and for subsequent development of selection criteria for SRT. Thus, although the randomised controlled trial remains the gold standard for evaluating any intervention or therapy, it was not justifiable in our situation. In this study, the outcome of a group of 103 infants ventilated for HMD (61 of which were selected to receive Survanta according to the above criteria) is compared with that of a control group of 173 infants ventilated for HMD prior to the introduction of SRT in South Africa. This type of observational study has been shown to be a valuable supplement to the data from randomised controlled trials, provided certain criteria are met. It has been suggested that five criteria should be met in assessing the evidence from observational studies using historical controls.[8] The present study meets these criteria in that: (*i*) SRT was administered with the intention of affecting outcome; (*ii*) the study was planned before the data were generated; (*iii*) based on randomised trials, SRT was expected to reduce mortality; (*iv*) the study results would have been of interest even if they had been different from those that were actually obtained; and (*v*) the results can be generalised, because treatment protocols were similar in the treatment and control groups (except for the use of surfactant).

From November 1991 to December 1992, 61 of 103 (59%) infants with moderate to severe disease qualified to receive SRT after a period of observation. Thus 42 infants (41%), while initially eligible, did not receive SRT. This represents a cost saving if one accepts international criteria which propose that all such infants should be treated with artificial surfactant.

There were significant demographic differences between the treatment and the control groups (a higher proportion of black patients and more unbooked mothers in the treatment group), and in markers of disease severity (more severe disease in the treatment group than in the control group, as evidenced by a higher proportion of patients requiring pressor support and paralysis during ventilation). These factors place infants in the treatment group at risk for more severe disease and a poorer outcome. Despite this, the incidence of pneumothorax was significantly reduced in the treatment group, and there were no significant differences between the two groups in terms of mortality or BPD (although there was a trend towards slightly reduced mortality in the treatment group). Only 14 (23%) of the infants who received Survanta received it within the first 6 hours of life. Earlier administration of SRT as suggested by the OSIRIS trial may have resulted in a more favourable outcome (decrease in BPD, death) in the infants reported on in this study. Therefore we propose that SRT modifies disease severity in infants with severe disease, resulting in an outcome similar to that of a control group with less severe disease.

In this study, even selective use of SRT added to the total cost of treating a patient with HMD. The method of estimating cost of treatment was based on the duration of stay at various levels of care. Selective SRT administration was shown not to result in any differences in the length of time that patients spent in various wards during treatment when compared to historic controls. These findings are similar to those reported elsewhere.[9]

In some studies, patients treated with SRT had longer hospital stays, possibly owing to improved survival in previously unsalvageable infants. However, there are also studies which have shown that SRT decreases the cost of treating HMD by reducing ancillary costs such as treating pneumothorax.[10] Ancillary costs were not taken into account in this study and, as the rate of pneumothorax was significantly reduced, there may well have been a reduction in costs had these been considered.

Taking indirect costs into account, in a study by Mamel *et al.*[11] the true cost of SRT as measured by quality-adjusted life years (QALYs) was approximately $1 500 per year (QALY is defined as the cost per extra survivor divided by the number of years of normal survival). When considering the potential economic contributions of survivors, the initial expense is a cost-effective outcome. In Mamel *et al.*'s study the difference in survival rate between treated and control infants is small — of the order of 1% — as in this study. Their calculations and arguments could thus be extrapolated

to the infants studied here, concluding that, despite the lack of direct cost savings, SRT may well be a cost-effective treatment.

Other studies using the QALY as a measure of cost-effectiveness have shown SRT to be more cost-effective than many other forms of intervention such as coronary bypass surgery and renal dialysis.[12] The validity of such calculations has, however, been questioned, and while SRT may result in an initial decrease in the use of resources for infants with HMD and appear to have long-term cost benefits, it has been shown that SRT will lead to a total increase in the cost of neonatal care resulting from the increased numbers of very-low-birth-weight survivors. Therefore, the increase in total cost for the care of the very-low-birth-weight (< 1 500 g) infant would offset any savings resulting from improved mortality and morbidity rates in the higher weight groups.[13,14]

These considerations are particularly relevant in South Africa, where not only facilities for neonatal intensive care but facilities for caring for the survivors, especially the handicapped, are restricted.

In this study we have shown that delaying the administration of Survanta according to initial and ongoing oxygen requirements meant that 42 of 103 (41%) infants ventilated for HMD and initially eligible for SRT did not receive SRT. Survanta added to the total cost of treating HMD, and a policy of restrictive SRT use may result in cost savings where resources are limited, particularly if SRT is generally promoted as a routine form of therapy for low-birth-weight infants with HMD. More lenient entry criteria would most likely have resulted in earlier administration of SRT, and perhaps improved outcome in some infants. However, relaxation of the criteria would also have resulted in infants with less severe disease being treated with SRT. As discussed in this paper, widespread use and survival of the smallest and sickest are factors which are likely to drive costs up significantly.

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