2 - 4 hours of birth to minimise ventilator lung damage. We are not suggesting that SRT should be delayed as a routine; our policy is to treat those infants with severe HMD as early as possible. However, we are proposing that infants with less severe HMD may not require immediate or even early SRT. These infants can be observed safely for a period of time and will still respond to later SRT. The adoption of this policy is in response to a situation in which neonatology is practised under severe financial constraints and we are therefore attempting to limit SRT to those infants who will benefit the most.

An interesting aspect of this study was the use of SRT in bigger infants. There were 3 infants weighing more than 2400 g in this study; all were initially assessed as having congenital pneumonia on the basis of history and chest radiographs. As initial sepsis work-up did not show evidence of infection, the initial diagnosis may well have been HMD, although surfactant deficiency is an unusual cause of RDS in infants of this birth weight. These 3 infants initially weaned well, but then had increasing ventilatory requirements. SRT was given in an attempt to induce weaning and to treat any surfactant deficiency present, whether primary or secondary. All 3 responded very well to the SRT and weaning was accomplished. A further infant was static on maximum ventilation following a large PDA which had been successfully closed with indomethacin. Once again, a single delayed dose of SRT initiated weaning. Secondary surfactant deficiency or inactivation has been implicated in ventilator lung damage and may account for the response to SRT in these cases. SRT may also have a role in conditions other than HMD. A recent study has demonstrated surfactant deficiency in infants with pneumonia and meconium aspiration syndrome.

It does not appear that late SRT compromised the outcome of these babies. The duration of ventilation and hospitalisation was short and none of the subjects developed BPD. One of the deaths may have been preventable by the early administration of SRT; this infant would normally have received early treatment, but SRT was delayed because of initial parental refusal. The second infant died of complications unrelated to HMD and ventilation. The risk of pneumothorax is reduced by SRT and the relatively high incidence of pneumothorax in this study may be related to delayed SRT.

This small review has obvious limitations; it is retrospective and uncontrolled and involves small numbers. However, the observation that late SRT is effective in moderate HMD and can initiate weaning in ventilator-dependent infants is important and has not been reported previously.

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Accepted 5 April 1994
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The cost and effectiveness of surfactant replacement therapy at Johannesburg Hospital, November 1991 - December 1992

V. A. Davies, D. E. Ballot, A. D. Rothberg

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 < 0.001; unbooked mothers 72% v. 15%, P < 0.001) 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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A. D. Rothberg, F.C.P (S.A.), M.D.
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. which showed that using the fractional inspired oxygen concentration (FiO₂) 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 FiO₂ > 0.75 3 - 4 hours after birth to maintain a partial arterial oxygen pressure (PaO₂) of 50 - 70 mmHg received SRT at that time. Infants with lower oxygen requirements received SRT if their FiO₂ 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 FiO₂ values would correspond to lower FiO₂ 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 H₂O. Ventilation practices were also similar during the two time periods. Inspired oxygen and/or PIP were adjusted to maintain a PaO₂ of 50 - 70 mmHg, and rate or PIP were adjusted to maintain an arterial PaCO₂ 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 (AaDO₂) 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

<table>
<thead>
<tr>
<th></th>
<th>Pre-Survanta</th>
<th>Survanta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>173</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1 694 ± 623</td>
<td>1 522 ± 382</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>32 ± 3</td>
<td>32 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>60:40</td>
<td>50:50</td>
<td>NS</td>
</tr>
<tr>
<td>Black/white (%)</td>
<td>28:72</td>
<td>74:26</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Unbooked (%)</td>
<td>15</td>
<td>72</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Inborn (%)</td>
<td>88</td>
<td>86</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple pregnancy (%)</td>
<td>15</td>
<td>7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Antenatal steroids (%)</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Caesarean section (%)</td>
<td>39</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>PIP (cm H₂O)</td>
<td>29 ± 7</td>
<td>29 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Dopamine (%)</td>
<td>27</td>
<td>44</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Pancuronium (%)</td>
<td>26</td>
<td>38</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

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 (%)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Survanta</th>
<th>Survanta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>17</td>
<td>7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>PDA</td>
<td>22</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>All IVH</td>
<td>36</td>
<td>66</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>IVH &gt; grade 3</td>
<td>9</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>BPD</td>
<td>10</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>11</td>
<td>NS</td>
</tr>
</tbody>
</table>

IVH = intraventricular 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**

<table>
<thead>
<tr>
<th></th>
<th>Pre-survanta HMD</th>
<th>Survanta HMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days (mean)  R</td>
<td>Days (mean)  R</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>10.5 5655</td>
<td>10.3 5499</td>
</tr>
<tr>
<td>High care</td>
<td>15.2 4028</td>
<td>13.9 3684</td>
</tr>
<tr>
<td>General ward</td>
<td>2.05 180</td>
<td>4.6 405</td>
</tr>
<tr>
<td>Survanta*</td>
<td>-</td>
<td>1777</td>
</tr>
<tr>
<td>Total</td>
<td>9 973</td>
<td>11 325</td>
</tr>
</tbody>
</table>

* 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, especially when it is administered early in the course of HMD. The results of the OSIRIS trial suggest that surfactant should be administered within 2 hours of birth to ensure maximal efficacy. 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. 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. 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.

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. 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 which had been considered.

Taking indirect costs into account, in a study by Mamel et al. 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. 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.

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 very-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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Accepted 4 May 1995.

The outcome at 12 months of very-low-birth-weight infants ventilated at Tygerberg Hospital

G. F. Kirsten, J. I. van Zyl, M. le Grange, E. Ancker, F. van Zyl

Objective. To determine the outcome at 1 year of age of a group of very-low-birth-weight (VLBW) infants, from urban and rural communities, ventilated at Tygerberg Hospital, W. Cape.

Study design. Prospective descriptive study in which the prevalence of bronchopulmonary dysplasia (BPD), sensorineural deafness, intra-ventricular haemorrhage (IVH), retinopathy of prematurity (ROP) and abnormal motor development outcomes were determined in 153 ventilated VLBW infants from rural and urban areas. Of these, 69% were from lower socio-economic backgrounds.

Main outcome measures. Attrition rates for rural and urban babies, BPD, ROP, IVH and abnormal motor development.

Study population and setting. All ventilated VLBW infants discharged from the neonatal intensive care unit at Tygerberg Hospital over a 1-year period were followed up at 3-monthly intervals for 12 months.

Results. BPD was diagnosed in 19% of the babies, with significantly more babies with birth weights under 1 000 g and gestational ages under 28 weeks having BPD. Of the babies with BPD, 25% had abnormal motor development at 1 year of age. Seven per cent of the babies had grade 3 or 4 ROP and 2.6% had sensorineural hearing loss. One hundred and seventeen (79%) of the infants attended the follow-up clinic until 12 months of age (corrected for prematurity). There were no significant differences in the number of babies followed up from rural or urban areas. Seventeen (11.9%) of the babies had abnormal motor development. A disturbing finding was that so many babies had spastic quadriplegia (8.57%) versus diplegia (6.43%).

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Accepted 4 May 1995.

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