The selection of infants for surfactant replacement therapy under conditions of limited financial resources

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The cost of surfactant replacement therapy (SRT) will restrict its use under conditions of limited health resources. Before the local advent of SRT, infants ventilated for hyaline membrane disease (HMD) had an overall survival rate of 87% and an incidence of bronchopulmonary dysplasia of 6,4%. This, together with the cost of SRT, prompted a study to identify those infants who would benefit the most from SRT. Twenty-two infants assessed as having severe HMD were randomised to receive SRT at 3 - 4 hours (9) or at 6 - 8 hours (13) after birth. Two infants (15%) in the latter group did not require SRT. The outcome of these two groups was the same. Of 56 infants assessed as having moderate HMD, only 24 (43%) qualified for SRT from 6 hours of age. The outcome of the SRT and non-SRT infants was comparable. The group of infants with moderate HMD had a significantly better outcome than those with severe HMD. A limited period of observation to assess the severity of illness did not compromise outcome in this group of 78 infants with moderate to severe HMD.

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Surfactant replacement therapy (SRT) is now well established as a treatment for infants with hyaline membrane disease (HMD).[1-4] However, in developing countries with restricted health budgets the use of an expensive drug such as surfactant is largely determined by cost. Similarly, attempts are made to limit expensive tertiary care, e.g. neonatal intensive care, to those patients with the best prognosis. In accordance with this policy, in our institution infants weighing < 1 000 g are not routinely ventilated. Hence the overall prognosis for ventilated infants with HMD would be expected to be good even in the absence of SRT.

This study addresses a question of great importance where the practice of neonatology is subject to severe financial limitations, i.e. if SRT is to be rationed and rationalised, which infants will benefit the most from SRT? Our hypothesis is that while infants with severe HMD will probably benefit from SRT, most of those ventilated for less severe forms of the disease will have a good outcome without SRT.

Subjects and methods

This study consisted of two parts. The first part involved a review which included all infants weighing between 1 000 and 2 500 g ventilated in our NICU for HMD between 1 January 1989 and 30 June 1991. This corresponds to the period just before the advent of artificial surfactant in South Africa. The second phase involved a prospective study to determine criteria for the administration of surfactant. All infants admitted between 1 November 1991 and 1 November 1992 weighing 1 000 - 2 500 g and ventilated for HMD were eligible for inclusion. The diagnosis of HMD was made on the basis of history, clinical findings and chest radiographic changes. Infants with major congenital anomalies, respiratory distress unrelated to HMD, suspected sepsis and/or persistent hypoxaemia out of keeping with the chest radiograph were excluded if these diagnoses were apparent on admission.

Informed consent was obtained from the parents. Before registration of the product consent was asked for entry of the child into the study. Refusal by the parent at that stage denied the baby access to the product. After registration of the product, consent was asked for the purpose of randomisation (see below). Refusal by the parent resulted in either early or non-administration on clinical grounds. Ethical approval for the study was obtained from the University of the Witwatersrand Committee for Research on Human Subjects.

The study protocol is summarised in Fig. 1. To identify those infants with severe HMD we chose an arbitrary cut-off of the fractional inspired oxygen concentration of 75% (Fio_2 > 0,75) at 3 - 4 hours of age to maintain a partial arterial oxygen pressure (Pao_2) between 50 and 80 mmHg (corresponding A-aDo_2 > 300 mmHg or a/A ratio < 0,2, noting that Johannesburg is at 1 763 m above sea level). These infants were randomised to receive SRT immediately (group 1) or to wait until 6 - 8 hours (group 2). SRT could be given at 6 - 8 hours if the Fio_2 was > 0,6. Infants not qualifying for SRT at 6 - 8 hours could be treated at any of the stages listed below for group 3.

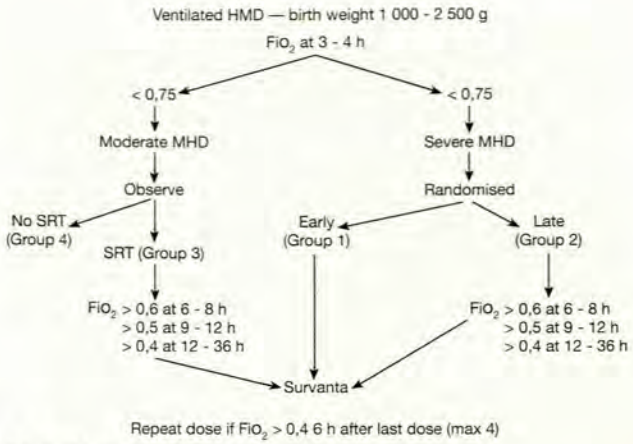

Fig. 1. Study protocol.

Babies with an Fio_2 < 0,75 at 3 - 4 hours were considered to have moderate HMD. These infants were not randomised and were observed. SRT could be administered at any of the following stages; if the Fio_2 was > 0,6 at 6 - 9 hours, > 0,5 at 9 - 12 hours or > 0,4 at 12 - 36 hours to maintain a Pao_2 between 50 and 80 mmHg. Corresponding A-aDo_2 cut-offs would be 250, 190 and 130 mmHg respectively, while a/A ratios would be 0,27, 0,33 and 0,44.

Infants with moderate disease who received SRT comprise group 3 and those that did not, group 4. All study infants were eligible for three additional doses of SRT at a minimum of 6-hourly intervals if the Fio_2 was > 0,4 to maintain a Pao_2 between 50 and 80 mmHg (maximum of four doses in any infant).

Statistical analysis including 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

Phase 1

One hundred and fifty-six infants were ventilated for HMD between January 1991 and June 1992, before the availability of SRT in South Africa. Demographic characteristics and outcome of these infants are shown in Table I. The outcome of these babies was good, with an overall survival rate of 87% and an incidence of bronchopulmonary dysplasia (BPD) (defined as oxygen requirement at > 36 weeks postconceptional age) of 6,4%.

Table I. Characteristics of infants ventilated for HMD prior to the local advent of SRT (total 156 infants)

Gestational age (wks)	31,8 ± 2,5
Birth weight (g)	1 551 ± 392
5-min Apgar	8,0 ± 1,8
Deaths	21 (13%)
BPD at 36 weeks postconceptional age	10 (6,4%)
IVH grade > 3	16 (10%)
Pneumothorax	27 (17%)
Duration of ventilation (d)*	10,3 ± 10,6
Duration of oxygen post ventilation (d)*	3,1 ± 3,1
Duration of hospitalisation (d)*	31,5 ± 17,3

*Survivors only.

Phase 2

A total of 83 babies with birth weight between 1 000 and 2 500 g were ventilated for HMD between November 1991 and November 1992; 78 were included in the prospective study. There were 5 exclusions; 3 babies did not receive SRT according to the stated protocol, 1 set of records was mislaid and 1 infant was admitted from an outlying hospital at > 24 hours of age. Of the study infants, 22 were assessed as having severe HMD and were randomised at 3 - 4 hours (Table II). Nine received SRT immediately (group 1) and 13 were observed for a further 3 - 4 hours (group 2). Two of the latter infants did not qualify for SRT at 6 - 8 hours; 1 (29 weeks, 1 010 g) was ventilated for 30 days and discharged, off oxygen therapy, at 61 days. The other (34 weeks, 1 700 g) was ventilated for 5 days and discharged at 16 days. Thus a delay of 3 - 4 hours in infants with severe HMD resulted in a 15% reduction in the use of SRT. The outcome of infants in groups 1 and 2 was comparable (Table III). BPD was uncommon in both groups.

Table II. Comparison of infants according to severity of illness

	Severe HMD (N = 22)	Mild to moderate HMD (N = 56)	P-value
Birth weight (g)	1 403 ± 307	1 579 ± 379	NS
Gestational age (wks)	30,6 ± 2,1	32,1 ± 2,1	0,006
5-min Apgar	7,4 ± 2,0	8,5 ± 1,4	0,015
Sex ratio (M/F)	13:9	26:30	NS
Inborn	17 (77%)	43 (76%)	NS
Booked*	8 (36%)	19 (34%)	NS
BPD at > 36 weeks	2 (9%)	0	NS
IVH ⩾ 3	6 (27%)	4 (7%)	NS
Pneumothorax	1 (4,5%)	4 (7%)	NS
Pulmonary haemorrhage	1 (4,5%)	0	NS
Deaths	7 (32%)	2 (3,6%)	0,003
Duration ventilation (d)†	16,5 ± 11,4	7,2 ± 7,8	0,0005
Oxygen post ventilation (d)†	16,4 ± 14,0	5,9 ± 5,7	0,00001
Duration hospitalisation (d)†	48 ± 24,6	30,8 ± 18,9	0,01

* Booked patients are those who received antenatal care.
† Survivors only.

Table III. Severe hyaline membrane disease

	Group 1 (N = 9)	Group 2 (N = 13)
Birth weight (g)	1 389 ± 316	1 414 ± 313
Gestational age (wks)	30,3 ± 2,2	30,8 ± 2
Sex ratio (M/F)	6:3	7:6
5-min Apgar	7,0 ± 2,5	7,7 ± 1,5
Booked	5	3
Inborn	8	9
No. of doses	2,1 ± 0,9	1,4 ± 0,9
Age at 1st dose (h)	3,7 ± 0,5	6,5 ± 0,9
a/A ratio at 1st dose	0,12 ± 0,04	0,15 ± 0,08
Duration ventilation (d)*	18,7 ± 11,8	14,5 ± 11,4
Duration oxygen (d) after ventilation*	24 ± 14,7	10,6 ± 11,1
Duration hospital stay (d)*	56 ± 26,4	42,3 ± 23,6
BPD (> 36 wks)	0	2
IVH ⩾ 3	3	3
Pneumothorax	0	1
PDA	1	6
Deaths	2	5

* Survivors only.
There was no difference between groups 1 and 2 for any of the above parameters.

Fifty-six infants considered to have moderate HMD according to our criteria were not randomised at 3 - 4 hours but were observed for subsequent progress (see Table II). Analysis showed that these infants were less asphyxiated and were of significantly higher gestational age than those with severe HMD. As a group, their outcome was significantly better than for those with severe HMD in terms of duration of ventilation, oxygen therapy and hospitalisation and mortality rate. Twenty-four (43%) of these babies subsequently qualified for SRT (group 3) and the remaining 32 did not (group 4) (Table IV). There was a significantly higher incidence of patent ductus arteriosus in the surfactant-treated group. Otherwise the outcome was the same for both groups.

Table IV. Moderate hyaline membrane disease

	Group 3 (N = 24)	Group 4 (N = 32)
Birth weight (g)	1 627 ± 381	1 543 ± 380
Gestational age (wks)	31,9 ± 2,1	32,2 ± 2,14
Sex ratio (M/F)	9:15	17:15
5-min Apgar	8,6 ± 1,3	8,5 ± 1,5
Booked	11	8
Inborn	20	23
No. of doses	1,4 ± 0,6	—
Age at 1st dose (h)	14,9 ± 6,6	—
a/A ratio at 1st dose	0,19 ± 0,007	—
Duration ventilation (d)*	9,6 ± 7,2	5,5 ± 7,9
Duration oxygen (d) after ventilation*	5,7 ± 4,0	5,9 ± 6,6
Duration hospital stay (d)*	26,9 ± 12,4	33,9 ± 22,4
BPD (> 36 wks)	0	0
IVH ⩾ 3	1	3
Pneumothorax	4	0
PDA	8[a]	2[a]
Deaths	2	0

* Survivors only.
[a] Significantly different at $P < 0,025$.
There was no difference between groups 3 and 4 for any of the above parameters except PDA.

There were 9 deaths in the study group, giving an overall mortality rate of 11,5%. One death may have been related to delayed SRT; this infant received surfactant at 6 hours of age and died of multiple pneumothoraces and severe HMD. One infant with posthaemorrhagic hydrocephalus following a severe interventricular haemorrhage (IVH) died at 55 days of age from staphylococcal meningitis. A further infant died of a complex congenital heart lesion. Four infants died of congenital bacterial infection (group B streptococcus 1; *Escherichia coli* 2; *Acinetobacter* 1) and 2 infants were extremely unstable and did not respond to SRT. The majority of infants who died were extremely ill, asphyxiated, acidotic and shocked in the initial phases and responded poorly to SRT. Four of these infants were delivered preterm as the result of illegal interference with the pregnancy. There were a significantly greater number of deaths in the group of infants with severe HMD.

Discussion

The practice of tertiary care, including neonatal intensive care/high care, in a developing country with severely limited

financial resources is, of necessity, limited by cost. Artificial surfactant, which is now regarded as standard therapy for HMD in developed countries,[1-4] is expensive. Regimens involving multiple dosing or prophylactic administration may add to the cost. In our neonatal intensive care unit (NICU), owing to financial constraints, infants below 1 000 g birth weight are not routinely ventilated. Hence babies with a better prognosis are selected out and would be expected to have a favourable outcome. This assumption was confirmed in phase 1 of this study which was a review of infants ventilated prior to the local advent of SRT. The overall survival was 87%, the incidence of BPD was 6% and the overall duration of ventilation and hospital stay were short.

The good outcome of infants with HMD admitted to our NICU prior to the use of surfactant and the high cost of the drug prompted this study to objectively identify infants who would benefit most from SRT. Infants with respiratory distress syndrome were observed for a period of time to allow the severity of illness and need for SRT to be evaluated.

In infants defined as having severe HMD, the period of observation of 3 - 4 hours only resulted in a 15% reduction of SRT; this is of questionable benefit in terms of the cost saving. Also, one death in this group was possibly attributable to delayed SRT. Although the numbers are small, it would seem fair to conclude that infants assessed as having severe HMD should be treated as early as possible.

As a group, whether SRT was required or not, infants with moderate HMD had a better outcome than those with severe HMD. The oxygen requirement at 3 - 4 hours proved to be a simple and reliable means of differentiating these two groups of infants. Only 43% of infants with moderate HMD required SRT and their outcome was similar to those who did not receive SRT. Our results suggest that in infants assessed as having moderate HMD, our policy of observing babies and only using SRT in selected cases seems to be justified.

Cost-effectiveness of SRT is receiving attention in developed countries. Factors under consideration include the cost of the drug and the increased demand on NICU and high-care facilities due to improved survival of premature infants. Prophylactic use of SRT has been shown to reduce costs by about 27% per patient by reducing severity of RDS and the length of NICU stay,[5] but the cost of treating large numbers of surfactant-sufficient infants unnecessarily was not discussed. A further study showed a cost reduction of approximately 25% in surfactant-treated infants compared with controls, mainly through reducing the costs of ancillary services such as radiology and laboratory investigations.[6] However, the actual cost of surfactant was not considered as it was obtained free of charge as part of the study. Tubman *et al.*[7] showed an expense of £13 700 per additional survivor when infants were treated with SRT. However, when considered in terms of QALYs (quality-adjusted life years) the cost compared favourably to several standard treatments used in adults, e.g. coronary bypass. This is not surprising since the life expectancy of an infant post-SRT and NICU is around 70 years; this is obviously considerably longer than the life expectancy of an adult who has survived an expensive treatment or procedure.

There have not been any reports on the costs of SRT in a developing country. It was not possible to obtain actual costs of NICU care in our public service institution other than to establish that SRT is regarded as an additional expense and is not written off, for example against shortened ICU stay or improved survival. The hospital administration's frame of reference is important in such a debate; on an individual basis any expense to improve survival is justified, but in circumstances of severely limited resources, the costs and benefits to the whole community take priority. In terms of non-paying indigent patients, the cost of NICU stay to the State is highest in the first 2 days because of the increased number of procedures and investigations. It is therefore cheaper to have one NICU bed occupied for weeks by a stable chronic infant than to have several new admissions in the same time.

The concept of limiting effective treatment on the basis of cost is unfamiliar and even offensive to doctors practising in developed countries. Indeed, in seeking the manufacturer's approval for the present study the view was expressed that it would be unethical initially to withhold SRT from neonates diagnosed as having moderate HMD. The results of this study suggest that in infants with moderate HMD a period of observation does not compromise outcome and that the majority of these babies will do well without SRT.

This study addresses a health issue of importance to neonatologists in Third-World countries where health care is often influenced by cost, rather than determined by ideals. This analysis confirms that a large number of infants with HMD do well without SRT and suggests that, certainly in ventilated infants with moderate HMD, allowing time for the severity of illness to be assessed does not compromise outcome.

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