The late administration of surfactant

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Current recommendations for surfactant replacement therapy (SRT) in the treatment of hyaline membrane disease (HMD) are to administer the drug as soon as possible after starting ventilation in order to prevent ventilator lung damage. We present a review of 18 infants (gestational age 32,4 ± 1,9 weeks and birth weight 1 795 ± 427 g) who received the initial dose of SRT after they were 12 hours old. Fourteen infants were assessed as having HMD and 4 as having congenital pneumonia. Overall there was a significant and sustained improvement in oxygenation as measured by arterial/alveolar oxygen ratios. The outcome of these infants was good, with a duration of ventilation of 7,9 ± 4,3 days and a duration of hospitalisation of 26,2 ± 12,6 days. No infant developed bronchopulmonary dysplasia. Of particular interest is that 3 infants weighing > 2 400 g with congenital pneumonia responded to a single delayed dose of SRT. Late SRT is effective and there may be a place for SRT in the treatment of conditions other than HMD.

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Surfactant replacement therapy (SRT) has proved to be beneficial in the treatment of premature infants with hyaline membrane disease (HMD).[1-4] However, there are still several unanswered questions regarding SRT, including the optimal dosage, differences between available SRT preparations, the best method of administration and indications for repeated doses.[1-4] SRT may also have a role in the management of conditions other than HMD.[5-7]

Surfactant may be given prophylactically to all premature infants considered to be at risk or it may be used in the treatment of established respiratory distress syndrome (RDS). There does not seem to be any advantage to the prophylactic use of SRT except in extremely premature infants.[8-10] The use of SRT for the treatment of established RDS reduces the number of infants to be treated and hence lowers cost and potential risks.[1] However, treatment early in the course of RDS may have advantages over later treatment;[4] SRT given as soon as possible after the onset of RDS, probably between 2 and 4 hours of age, may prevent significant ventilator lung damage.[10]

The present study addresses the question of whether SRT given relatively late in the course of moderate to severe neonatal lung disease improves oxygenation.

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Subjects and methods

This is a retrospective review of infants who received an initial dose of SRT at > 12 hours of age. All infants had been admitted to the neonatal intensive care unit (NICU) and all were intubated and ventilated. Thirteen of these infants form part of a larger, ongoing prospective study to establish selection criteria for SRT under conditions of severely limited financial resources.[11] According to that protocol, infants assessed as having less severe HMD (as defined by a fractional inspired oxygen concentration (Fio_2) requirement of < 0,75 to maintain the partial arterial oxygen pressure (Pao_2) at between 50 and 80 mmHg at 3 - 4 hours of age) are observed but may receive SRT subsequently if the Fio_2 is > 0,6 at 6 - 8 hours, > 0,5 at 9 - 12 hours, or > 0,4 at 12 - 36 hours.

Three infants not included in the prospective study were initially assessed as having congenital pneumonia on the basis of history and radiographic findings.[11] In these cases SRT was given once infection had been treated and weaning from the ventilator had reached a plateau. One infant with severe HMD had delayed SRT owing to initial parental refusal to administer the product. The last infant had mild HMD and was weaned rapidly initially, but then developed a large patent ductus arteriosus which was closed successfully with indomethacin. Despite this, she remained static on maximum ventilation and SRT was given in an attempt to induce weaning. All infants were eligible for up to 3 repeat doses of SRT at not less than 6-hourly intervals.

To determine the efficacy of SRT, the arterial/alveolar oxygen ratio (a/A ratio) was calculated as follows:

alveolar oxygen (mmHg) = $Fio_2 \times (P_{atm} - PH_2O) - Paco_2/R$, where $Paco_2$ is the partial pressure of CO_2 in arterial blood; PAo_2 is the partial pressure of oxygen in alveolar air; Pao_2 is the partial pressure of oxygen in arterial blood; P_{atm} is atmospheric pressure (627 mmHg at 1 763 m above sea level); PH_2O is saturated water vapour pressure (47 mmHg); R = CO_2 consumption/O_2 consumption and is approximated to 0,8.

Alveolar oxygen (mmHg) = Fio_2 x (627 mmHg - 47 mmHg) – $Paco_2/0,8$.

a/A ratio = Pao_2/PAo_2.

The a/A ratio was calculated just before SRT and 2, 6 and 12 hours afterwards.

Statistical analysis which included paired *t*-tests and descriptive statistics was done on a personal computer using STATPAK version 4.1 (Northwest Analytical, Portland, Oregon).

Results

Eighteen infants of gestational age 32,4 ± 1,9 weeks and birth weight 1 795 ± 427 g received an initial dose of SRT at a mean age of 26,8 ± 24,0 hours (all values mean ± SD). Individual demographic characteristics are shown in Table I. Fourteen of the infants were initially assessed as having HMD and 4 were thought to have congenital pneumonia on the basis of history and chest radiographs. Eleven mothers (61%) had received antenatal care and 2 had been given antenatal corticosteroids (11,1%). Fifteen infants (83%) were inborn and 8 (44%) were delivered by caesarean section. Six infants received an additional dose of SRT at a mean age of 26,3 ± 9,9 hours.

Table I. Demographic characteristics of subjects

	Birth weight (g)	Gestation (wks)	Age at 1st dose (h)	Duration of ventilation* (d)	Duration of oxygen* (d)	Duration* of hospitalisation (d)
	1 160	30	100	Died at 1 month		
	1 165	30	14	15	8	40
	1 385	31	13,5	13	9	36
	1 460	31	25,5	11	13	41
	1 525	32	12	16	1	40
	1 600	33	20	9	10	28
	1 620	32	13	13	3	50‡
	1 710	32	12	4	1	16
	1 720	32	28	5	7	15‡
	1 790	30	13	Died on day 9		
	1 815	33	17	5	5	17
	1 830	34	13,5	4	3	14
	1 835¶	31	19	5	14	21
	1 930	34	18	4	3	19
	2 120	32	15	7	1	14
	2 440¶	36	25	4	2	14
	2 600¶	36	72	5	Transferred out†	
	2 620¶	35	52	6	Transferred out†	
Mean	1 795	32,4	26,8	7,9	5,7	26,3
SD	427	1,9	24	4,3	4,5	12,7

* Survivors only,
† Transferred from NICU to another hospital while still on oxygen.
‡ Prolonged hospitalisation due to social problems.
¶ Initially diagnosed as congenital pneumonia.

Overall, there was a significant and sustained increase in oxygenation in response to late SRT (Fig. 1 and Table II). There appeared to be three types of response to SRT — type a was an initial decline in oxygenation followed by an improvement, type b a sustained response and type c an initial response followed by a decline. Most infants of < 1 750 g exhibited type b (3) and c (5) responses (1 showed type a), whereas those of > 1 750 g showed types a (4) and b (5) (see Table II). This was statistically significant on frequency analysis ($P = 0,026$). These responses were not dependent on the time of dosing and were not related to birth weight within each broad birth weight category.

Table II. Arterial/alveolar oxygen ratio

	Birth weight (g)	Immediately before SRT	2 h post-SRT	6 h post-SRT	12 h post-SRT	Type of response
	1 160	0,08	0,23	0,21	0,28	b
	1 165*	0,27	0,41	0,56	0,24	c
	1 385	0,18	0,50	0,68	0,66	b
	1 460	0,12	0,51	0,38	0,76	c
	1 525*	0,17	0,18	0,20	0,27	b
	1 600	0,20	0,60	0,52	0,35	c
	1 620*	0,11	0,63	0,20	0,11	c
	1 710*	0,35	0,22	0,32	0,40	a
	1 720	0,21	0,37	0,50	0,31	c
	1 790	0,10	0,08	0,35	0,37	a
	1 815	0,22	0,42	0,45	0,45	b
	1 830	0,14	0,27	0,35	0,32	b
	1 835*	0,14	0,09	0,42	0,63	a
	1 930	0,21	0,45	0,5	0,63	b
	2 120*	0,28	0,27	0,27	0,40	a
	2 440	0,14	0,24	0,35	0,48	b
	2 600	0,21	0,17	0,37	0,40	a
	2 620	0,20	0,29	0,38	0,37	b
Mean	1 795	0,18	0,33	0,39	0,41[a]	
SD	427	0,07	0,17	0,13	0,17	

* Two doses of SRT.
[a] Significantly different from baseline ($P < 0,005$).

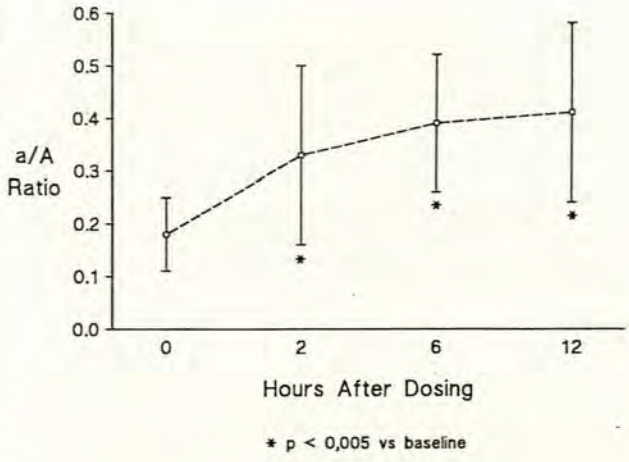

Fig. 1. Arterial/alveolar oxygen ratio following administration of surfactant.

The outcome of infants receiving delayed SRT was good. The mean duration of ventilation of surviving infants was 7,9 ± 4,3 days. Oxygen therapy post ventilation was required for a mean of 5,7 ± 4,5 days and infants were hospitalised for a mean of 26,2 ± 12,6 days. No infant developed bronchopulmonary dysplasia (BPD) as defined by an oxygen requirement at more than 36 weeks post-conceptional age. Four infants developed a pneumothorax (22%); one occurred in an infant on low inspiratory pressures who developed a tension pneumothorax after his second dose of SRT. The administration of SRT was generally well tolerated, apart from in 1 infant who developed sustained, profound hypoxaemia. There were 2 deaths — one was the infant with severe HMD who had delayed SRT due to initial parental refusal; she developed pulmonary interstitial emphysema and died on day 9. The second infant died from septicaemia at 1 month due to contaminated intravenous hyperalimentation solution.

Discussion

We have shown that SRT administered beyond 12 hours of age to infants with moderate HMD results in an improvement in oxygenation and facilitates weaning in ventilator-dependent infants. According to the prospective study protocol,[11] infants assessed as having severe HMD on the basis of oxygen requirement at 3 - 4 hours are given SRT early, whereas those with less severe disease (the majority of subjects in this study) are observed and treated later if necessary. Although these latter infants are considered to be less sick, they nevertheless have significant respiratory disease as reflected by the a/A ratios. It is interesting to note that SRT responses vary according to birth weight categories, although the reason for this is not apparent. The mechanism of the 'type a' response (initial deterioration before improvement) is not clear; it may possibly be related to delayed SRT or to ductal shunting.

Delaying SRT is contrary to current opinion. In the majority of trials of natural surfactant SRT was administered within 8 hours of birth, whereas in those using synthetic surfactant the initial dose was recommended within 24 hours of birth.[1] In practice it is felt that rescue SRT should be given within

2 - 4 hours of birth to minimise ventilator lung damage.[8,12] 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.[11] However, we are proposing that infants with less severe HMD may not require immediate or even early SRT.[11] 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.[11]

An interesting aspect of this study was the use of SRT in bigger infants. There were 3 infants weighing more than 2 400 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.[13] 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[13] and may account for the response to SRT in these cases. SRT may also have a role in conditions other than HMD.[5,6] A recent study has demonstrated surfactant deficiency in infants with pneumonia and meconium aspiration syndrome.[7]

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[1] 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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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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