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The introduction of surfactant replacement therapy into South Africa

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

Within the context of limited financial and physical resources in South Africa, academic neonatologists have established strict criteria for ventilation of neonates with hyaline membrane disease (HMD). In the private sector neonatal care is less structured. Following the introduction of the artificial surfactant (Survanta) in November 1991 it was considered important to monitor its use in the public and private sectors. In collaboration with the marketing company a data sheet containing demographic information and clinical details was drawn up to be completed in each case where Survanta was administered to babies with HMD. Data from 155 babies treated at 10 hospitals were included in the final analysis (70 babies from 4 State-funded academic hospitals and 85 from 6 privately funded hospitals). Within the group of private hospitals there were some which treated large numbers of babies weighing > 2 000 g, while in a few others there was a relative excess of babies weighing < 1 000 g. There was a higher incidence of patent ductus arteriosus and intraventricular haemorrhage, and a higher mortality rate at the academic hospitals. Poor outcome at these institutions may largely have been due to poor antenatal care.

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In November 1991 artificial surfactant (Survanta) became commercially available in South Africa and surfactant replacement therapy (SRT) was introduced into the country against a background of rising costs, restricted health budgets and limited neonatal intensive care (NICU) facilities. In 1987 South Africa spent a total of R9,2 billion on health care, which amounted to 5,8% of the gross national product (GNP) for that year, or R284 per person. Health services in South Africa are provided either by the state-funded public sector or by the private sector. In 1987 the private sector accounted for 44% of total expenditure but supplied health care to only 20% of the population, the remaining 80% being dependent on the public sector. The public sector is unable to provide comprehensive care for this 80% for various reasons, including inefficient use of resources, administrative waste due to fragmentation of health services and duplication of facilities under the apartheid system, and underfunding of the public sector. In 1987 3,3% of the GNP was spent on public sector health, below the 5% target set by the World Health Organisation as a minimum standard. Thus the majority of South Africans do not have access to comprehensive health services.[1-3]

NICU facilities are severely restricted in South Africa. In a previous study which assessed the availability of special care beds in the Johannesburg referral area over a 2-year period (1983 - 1984), it was calculated that 25 beds were required for mechanical ventilation of white neonates. Results showed that only half of this number were available during the period of the study. Facilities for black neonates from the urban and peri-urban areas were even less adequate.[4]

When it was introduced into South Africa it was recognised that SRT could not be advocated for every ventilated newborn infant with hyaline membrane disease (HMD), and that it was necessary to define criteria for SRT. This is a consequence of the limited resources, the escalating costs of neonatal intensive care[5] and the high cost of artificial surfactant (despite its proven efficacy and demonstrated cost-effectiveness[6-9]). In defining criteria for SRT, since most academic NICUs only offer ventilation to infants of birth weight > 1 000 g, delegates to the 10th Conference on Priorities in Perinatal Care in South Africa (March 1991) recommended consideration of SRT only for babies > 1 000 g birth weight and only as rescue therapy (versus prophylaxis). Exceptions to this rule included babies of < 1 000 g born as a result of *in vitro* fertilisation (IVF) programmes and preterm infants of women with medical problems treated aggressively during pregnancy, e.g. for rhesus disease, renal failure and diabetes. In the private sector there is no birth weight cut-off point for ventilation and it was anticipated that SRT would be used in neonates across the full weight spectrum.

With a view to standardisation of national criteria for administration of artificial surfactant, the academic perinatal group went further than simply recommending guidelines for SRT. The group suggested to the two multinational companies which were about to market their respective surfactants that a product launch should include the following: (*i*) an initial meeting with academics to educate the company in terms of the local context; (*ii*) the opportunity to moderate the promotion in the private sector by sharing the platform in each major centre; (*iii*) ongoing collaboration between the company and academics and collection of data on product usage; and (*iv*) a review of the situation after 1 year to evaluate the use and/or abuse of the product. One of the two companies concerned had no hesitation in accepting these suggestions and welcomed the opportunity to work with the group of academic neonatologists in launching its product (Survanta; Abbott).

Methods

In collaboration with the authors a data sheet was drawn up for distribution by the manufacturer's product representative. The data sheet included demographic information and data regarding dose of Survanta, the number of doses given and dosing interval, severity and complications of HMD, and short-term outcome. Bronchopulmonary dysplasia (BPD)

Department of Paediatrics and Child Health, Johannesburg Hospital and University of the Witwatersrand, Johannesburg

V. A. Davies, F.C.P. (S.A.)

A. D. Rothberg, F.C.P. (S.A.), PH.D.

D. E. Ballot, F.C.P. (S.A.), PH.D.

was defined as a requirement for supplemental oxygen beyond 28 days of age or 36 weeks' adjusted gestational age with abnormalities on a chest radiograph.[10] HMD was graded radiologically.[11] Intraventricular haemorrhage (IVH) was graded according to Papile *et al.*[12] Cranial ultrasound examinations were performed routinely at the academic hospitals but were not always available at private hospitals. For each case in which Survanta was administered a data sheet was completed by the attending paediatrician or nurse. Completed data sheets were collected by the product representative. The data were analysed by the authors using Kruskal-Wallis and Mann-Whitney tests for continuous data and contingency tables for categorical data. The study was approved by the University Committee for Research on Human Subjects.

At the start of the study it was agreed that a follow-up workshop would be held approximately 1 year after the introduction of SRT into South Africa and that the results of this study would be made known to all participating paediatricians and centres. The workshop took place in September 1992.

Results

This analysis covers the period from the introduction of Survanta in November 1991 to the end of July 1992. During this time 223 data sheets were collected from 34 hospitals. Only hospitals in which more than 5 babies were treated were included in the final analysis; consequently the final study population consisted of 155 babies treated at 10 hospitals (70 from 4 state-funded academic hospitals and 85 from 6 privately funded hospitals).

The data from 4 of the private clinics were grouped together (private group 1) as there was an obvious tendency to use SRT in large babies in these facilities; at each of these hospitals at least 33% of the babies treated had a birth weight > 2 000 g. The data from the remaining 2 private clinics were grouped together (private group 2) as there was a relatively large proportion of extremely low-birth weight (< 1 000 g) babies treated at these institutions. Data from the academic hospitals were not pooled as each serves a unique population with its own characteristics and problems.

Formal analysis revealed that there were indeed more babies in the > 2 000 g birth weight range in private group 1 (22 babies, 41%; $P < 0,0001$) than in the other groups, and in private group 2 there were significantly more babies < 1 000 g birth weight (9 babies, 28%; $P < 0,0001$) (Table I). The mean gestational age of babies in private group 2 (29,2 ± 2,9 weeks) was also significantly lower than that of babies at Johannesburg Hospital ($P < 0,01$), and the OFS hospitals ($P < 0,05$) (Table II).

The male/female ratio in private group 2 was significantly higher than in the other groups (78:22, $P < 0,05$). Significantly more black patients were treated at Johannesburg Hospital (68%) and Baragwanath Hospital (94%) that at the other hospitals ($P < 0,0001$). At all the hospitals more than 80% of patients treated were inborn. A high proportion of patients (77%) treated at Johannesburg Hospital were born to mothers who had received no antenatal care. These and other demographic data are summarised in Table II.

Table I. Infants of birth weight < 1 000 g and birth weight > 2 000 g

	JH	Bara	MMH	OFS	Priv 1	Priv 2
No.	31	16	6	17	53	32
< 1 000 g	0	0	1	1	7	9
(%)			(17)	(5)	(14)	(28)[a]
> 2 000 g	1	2	0	3	22	3
(%)	(3)	(13)		(18)	(41)[a]	(10)

Academic hospitals (State-funded): JH = Johannesburg Hospital; Bara = Baragwanath; MMH = Mowbray Maternity Hospital; OFS = Orange Free State (Universitas and Pelonomi Hospitals).
Privately funded institutions: Priv 1 = private group 1 (4 hospitals); Priv 2 = private group 2 (2 hospitals)
[a] $P < 0,0001$.

Table II. Patient characteristics

	JH	Bara	MMH	OFS	Priv 1	Priv 2
No.	31	16	6	17	53	32
Weight (g),	1 466	1 436	1 332	1 409	1 751	1 270[a]
mean (±SD)	(306)	(504)	(262)	(513)	(743)	(520)
GA (wks),	30,6	30,9	30,3	30,6	31,4	29,2[b]
mean (±SD)	(1,8)	(2,9)	(3,3)	(2,4)	(3,6)	(2,9)
Male/female	45:55	60:40	50:50	35:65	48:52	78:22
Black/white	68:32	94:6	—	35:65	12:88	10:90
Inborn (%)	90	81	—	100	83	100
Unbooked (%)	77	—	—	—	—	—

[a] v. JH $P < 0,005$.
[b] v. JH, Priv 1 $P < 0,01$; v. OFS $P = 0,05$.
— = data not available.

There were no differences in the Apgar scores at 1 and 5 minutes or in the radiological grading of HMD between the different groups (Table III). There were no significant differences in the number of doses of Survanta administered between the different groups. The mean age at the first dose was similar for all the hospitals with the exception of one of the academic institutions (Table III). In all patients Survanta was given as rescue therapy, with 97 patients (63%) receiving the first dose within 3 hours of birth and 120 (77%) within 6 hours of birth. In 110 patients (71%) only one dose was given; 32 (20%) received two doses, 9 (6%) three doses and 4 (3%) four doses.

Table III. Apgar scores, grading of HMD, age at first dose and number of doses of Survanta received (mean ± SD)

	JH	Bara	MMH	OFS	Priv 1	Priv 2
Apgar 1 min	5,3	5,5	4,8	4,5	5,6	5,4
	(2,4)	(2,2)	(2,7)	(2)	(2,6)	(2,5)
Apgar 5 min	7,8	6,8	7,4	7,5	6,8	8,1
	(1,7)	(2,3)	(1,9)	(1,3)	(2,1)	(2,4)
Grade HMD	3,0	3,5	4,0	3,1	3,0	3,1
	(0,7)	(0,6)	(0)	(0,6)	(0,9)	(0,8)
No. of doses	1,7	1,3	1,7	1,0	1,2	1,6
	(0,9)	(0,6)	(0,5)	(0)	(0,4)	(1)
Age at dose 1	9,6	9,7	29,3	1,8	7,3	3,2
(h)	(6,4)	(7,4)	(37,2)	(1,03)	(9,8)	(3,1)

Survivors at Johannesburg Hospital were ventilated for a significantly longer period than at the OFS and private group 1 hospitals. The mean peak inspiratory pressure during ventilation at Johannesburg and Baragwanath hospitals (33,6 and 36,3 cm H_2O) was significantly higher than that recorded at the two private groups (21,7 and 23,0 cm H_2O; $P < 0,0001$) and OFS group (22,0 cm H_2O; $P < 0,0001$). More than 70% of babies treated at the academic hospitals required pressor support and paralysis with pancuronium

during ventilation, compared with less than 45% of the babies in the two private groups (Table IV). The indications for ventilation and ventilation practices are considered to be similar at all the hospitals studied.

Table IV. Duration of high oxygen therapy, ventilation, ICU and hospital stay (mean ± SD), and percentage of patients requiring pressor support and paralysis during ventilation

	JH	Bara	MMH	OFS	Priv 1	Priv 2
IPPV (d)	13,2[a]	—	5,8	7,7	7,6	9,8
	(9,6)		(3,1)	(8,5)	(8,3)	(9,0)
PIP	33,6[b]	36,3[b]	29,4	22	21,7	23
(cm H_2O)	(7,1)	(7,9)	(1,3)	(5,2)	(5,2)	(4,5)
Dopamine (%)	70[c]	81[c]	0	94[c]	40	15
Pancuronium (%)	73[d]	81[d]	0	88[d]	51	44
Fio_2 > 0,4 (d)	2,7	2,0	1,8	3,1	7,1	3,4
	(2,1)	(1,4)	(1,0)	(7,2)	(14,6)	(5,3)
ICU (d)	14,8	26,5	10,3	10,8	11,3	15,2
	(9,6)	(0,7)	(1,5)	(10,6)	(11,5)	(11,7)
Hospital (d)	36,4	—	—	44,2	33,2	53,7
	(12,9)			(28,5)	(27,8)	(20)

[a] v. OFS $P < 0,01$; v. Priv 1 $P < 0,005$.
[b] v. OFS, Priv 1, Priv 2 $P < 0,0001$.
[c] $P < 0,0001$ v. other groups.
[d] $P = 0,0001$ v. other groups.
— = data inadequate; IPPV = duration of ventilation in survivors; Fio_2 > 0,4 = duration of exposure to Fio_2 > 0,4 in survivors; ICU = duration of stay in ICU of survivors; Hospital = duration of hospital stay of survivors.

There was no significant difference in the length of time that survivors in the different groups were exposed to an oxygen concentration of > 40%, although this tended to be longer in babies in private group 1. The duration of stay in the NICU was similar in all the groups but survivors in private group 2, the group with the higher percentage of < 1 000 g babies, had a longer total hospital stay than survivors in the other groups (Table IV). This difference did not reach statistical significance.

More than 50% of babies treated at Johannesburg and Baragwanath hospitals had an IVH. This was significantly higher than expected for all grades of IVH, but the incidence of IVH ⩾ grade 3 was similar for all groups studied. The inter-hospital difference between the rates of all IVHs v. ⩾ grade 3 is perhaps partly a result of routine screening at Johannesburg and Baragwanath hospitals v. selective ultrasound examination in other centres. There were no differences in the incidence of pneumothorax or pulmonary haemorrhage in the various groups. Bronchopulmonary dysplasia occurred in 46% of the infants in private group 1, a significantly higher incidence than in the other groups. The mortality rate at Baragwanath Hospital was 75%, which was significantly higher than that seen at other centres (Table V).

Table V. Outcome and complications in patients ventilated for HMD who received Survanta (%)

	JH	Bara	MMH	OFS	Priv 1	Priv 2
All IVH	75[a]	57[a]	0	13	26	22
IVH ⩾ grade 3	29	28	0	13	16	11
Pneumothorax	7	27	17	6	12	10
Pulmonary haemorrhage	4	14	0	6	10	25
PDA	35	20	100	35	31	50
BPD	29	14	0	12	46[b]	18
Death	23	75[c]	0	0	13	31

[a] $P < 0,005$
[b] $P < 0,03$
[c] $P < 0,0001$.

Discussion

In a developing country such as South Africa, limited financial and physical resources for medical care in general and intensive care in particular, mitigate against the routine use of SRT for ventilated babies with HMD. This study reviews 8 months of SRT since its introduction into South Africa in November 1991. Data were collected from 155 babies treated with Survanta at 10 hospitals (4 academic and 6 privately funded). The birth weights of the babies covered a wide range (530 - 3 600 g); however, the birth weight and gestational age of most of the babies studied fell within the range associated with a good prognosis in HMD.[13,14]

In a group of the private sector hospitals 41% of babies treated with SRT had a birth weight of > 2 000 g. The diagnosis of HMD and need for SRT in these infants may be questioned. Apparently, as reported at the feedback meeting, factors such as parental and social pressure and pressure from attending obstetricians greatly influence management in such infants, many of whom are born by elective caesarean section and are considered to be at some risk for respiratory distress syndrome. In another group of private sector neonates, 28% were < 1 000 g birth weight; this contrasts with the situation in the academic hospitals where due to limited facilities babies < 1 000 g birth weight are not routinely ventilated or given SRT. In many instances the large number of babies < 1 000 g birth weight treated in the private hospitals was the result of active IVF programmes in which a policy of multiple implantation of embryos was followed. Thus the 1-year feedback meeting served the purpose of exposing various neonatal and obstetric practices to peer review; however, it remains to be seen whether those who are involved in SRT for almost-term neonates or for multiple products of IVF programmes will modify their behaviour simply as a result of the review process.

It is of interest that the male/female ratio was approximately equal in all groups except for the group with the mean birth weight of 1 270 g and gestational age of 29,2 weeks. This finding is in keeping with the results of Ballard *et al.*[15] Their data for HMD showed that males and females were affected equally between 1 251 g and 1 750 g, but males predominated in the group 751 - 1 250 g. In terms of the effect of race on HMD, previous data from the Johannesburg group of academic hospitals have shown that black infants have lower HMD rates than whites, whether compared by weight or by gestational age.[16] However, in the present study the outcome for the black infants at Johannesburg and Baragwanath Hospitals was worse than expected, largely as a result of poor antenatal care, interference with the pregnancy, and/or nosocomial infections. These and other factors were responsible for the severe disease seen at these two academic hospitals, resulting in requirements for higher peak inspiratory pressures, more pressor support and greater use of paralysis for ventilation.

The incidence of complications such as PDA, IVH ⩾ grade 3, pneumothorax and pulmonary haemorrhage was similar for the various groups studied. The overall BPD rate for the 155 infants was 20% and the mortality rate 24%. The highest overall incidence of IVH and higher mortality rate at Johannesburg and Baragwanath Hospitals may in part be due to the high proportion of patients born to mothers with inadequate prenatal care and/or attempted termination of pregnancy. This is not the case in the private sector where

the majority of babies are born to mothers who have received excellent antenatal care. The high mortality rate seen in private group 2 (31%) reflects the high proportion of extremely low birth weight infants in this group.

In considering the data in this study it must be noted that the review includes all infants given Survanta. One must therefore recognise that in several instances at Johannesburg and Baragwanath Hospitals the drug was administered during or shortly after resuscitation in moribund infants, or to shocked septicaemic infants with severe respiratory distress. Clearly the outcome in such circumstances will be less than optimal, irrespective of SRT. These poor results mitigate against the use of SRT as part of resuscitation or as a last resort in a moribund infant. The results are also influenced by subsequent problems, e.g. the high nosocomial infection rate which remains a problem at Baragwanath Hospital as a consequence of overcrowding.

This review of the first 8 months of SRT in South Africa has shown differences in Survanta use between public and private sectors. Some aspects of introducing an effective yet expensive form of treatment such as SRT into a health care system with significant inequalities have been highlighted. Arising from this study is the need to define criteria for SRT clearly in a situation of limited resources (see related article, Ballot *et al.*[17]). The objective is to ensure that SRT is not administered to babies in whom it is not indicated and that it is not withheld from those who would benefit most from its use. This issue is also receiving attention in the USA where health care providers have recognised that advances in care for the smallest infants will result in fewer beds for the bigger babies (who usually have a better prognosis[18]). Further studies are in progress to assess medium- and long-term outcome in the infants included in this analysis and to establish the cost-effectiveness of the policies recommended by academic neonatologists for implementation in South Africa.

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Reprint requests to: Dr V. A. Davies, Dept of Paediatrics and Child Health, Johannesburg Hospital, Private Bag X39, Johannesburg, 2000, RSA.

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

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

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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Department of Paediatrics and Child Health, Johannesburg Hospital and University of the Witwatersrand, Johannesburg

D. E. Ballot, F.C.P. (S.A.), PH.D.

A. D. Rothberg, F.C.P. (S.A.), PH.D.

V. A. Davies, F.C.P. (S.A.)