

The Effectiveness of Surfactant Replacement Therapy for Preterm Infants with Respiratory Distress Syndrome

W L Lim, MRCP, C T Lim, FRCP, J K Chye, FRACP, Department of Paediatrics, University of Malaya, 50603, Kuala Lumpur

Summary

Thirty preterm infants weighing ≥ 800 g with clinical and radiological evidence of respiratory distress syndrome (RDS) requiring mechanical ventilation with FiO_2 of $\geq 40\%$ were given modified bovine surfactant (Survanta). They were compared with equal number of historical controls. Infants who received surfactant showed prompt and highly significant improvement in FiO_2 , mean airway pressure, arterial/alveolar oxygen tension ratio and ventilatory index. There was significant improvement in mortality rate (10% vs 33%; $p=0.03$). Among the survivors, surfactant-treated infants required shorter duration of continuous positive airway pressure (CPAP) (3.4 vs 9.6 days; $p=0.04$). For survivors with birthweight of >1000 g, surfactant-treated infants required shorter duration of ventilatory support (intermittent positive pressure ventilation + CPAP) (7.5 vs 18.9 days, $p=0.02$). Overall, surfactant-treated infants achieved full enteral feeds sooner (15.7 days vs 24.6 days; $p=0.03$) and required shorter duration of total parenteral nutrition (13.9 days vs 25.6 days; $p=0.02$). We concluded that surfactant replacement therapy was effective in the treatment of preterm infants with RDS.

Key Words: Surfactant, Respiratory distress syndrome, Prematurity

Introduction

In 1980, Fujiwara et al first reported the successful trial of surfactant replacement therapy in preterm infants with respiratory distress syndrome (RDS)¹. Since then, more than 40 clinical trials involving over 6,000 infants have been reported. Meta-analyses based on these trials showed that by decreasing the need for oxygen and ventilatory support, the mortality rates and complications such as pneumothorax were reduced. With the odds ratio for neonatal mortality of about 0.6, a 30-40% reduction in mortality is expected^{2,3}. The efficacy of surfactant therapy demonstrated in randomised clinical trials has been translated into effective clinical use. An observational study involving about 4,400 infants weighing 601-1,300g in eight centres in the USA over a 3-year period reported a

reduction in mortality from 28% to 20% after surfactant was introduced⁴. It was suggested that up to half of the decline in national infant mortality reported between 1989 and 1990 (from 9.7 to 9.1 per 1,000 births) in the United States might have resulted from the use of surfactant therapy.

In Malaysia, surfactant replacement therapy is still a relatively new form of therapy. So far, there has only been one small study published regarding the use of surfactant in Malaysia⁵. As a developing country, there are important obstetric and neonatal factors in which Malaysia is different from the more developed countries. The perinatal services in Malaysia work under constant restraint of lack of personnel and equipment⁶. Exogenous surfactant is expensive and its introduction nationwide has important economic implications. There is thus an

urgent need to provide good local data on surfactant therapy to serve as a rational basis for future guidelines and decision-making concerning priorities in neonatal care.

The objective of this study is to determine the effectiveness of surfactant replacement therapy for preterm infants with RDS in local clinical practice. Specifically, we aim to determine if it would reduce mortality and major morbidities among preterm infants.

Materials and Methods

All preterm infants satisfying the following criteria were enrolled into the study following informed consent from the parents:

1. Clinical and radiological evidence of RDS.
2. Ventilation with intermittent positive pressure ventilation.
3. Fraction of inspired oxygen (FiO_2) requirement of 40% producing a PaO_2 of <11 kPa.
4. No major congenital malformation.

Because of limitation of resources, aggressive resuscitation for preterm infants below 800g has not been practised consistently. Thus, even though some infants below 800g were given exogenous surfactant, for uniformity of analysis, they were excluded from this study.

The records of all preterm infants who required ventilation for RDS during a comparable period prior to the introduction of surfactant in the neonatal unit were reviewed and all infants who fulfilled the same eligibility criteria as outlined above were selected as historical controls.

The surfactant preparation used was Survanta (Ross Laboratories Division of Abbott Laboratories, Columbus, OH), a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant associated proteins. Prior to administration of Survanta, the clinical stability of the infants were ensured. The infant must be normotensive and have no pulmonary air leaks. The infant must be on continuous

cardiopulmonary monitoring and pulse oximetry. An arterial-line (central or peripheral) must be in place for arterial blood sampling and continuous blood pressure monitoring.

The first dose of Survanta was given as soon as possible after the eligibility criteria had been met. The dosage of Survanta used was 4ml/kg/dose. The required dose of Survanta was drawn out from its ampoule into a sterile syringe and allowed to warm to room temperature. The infant is positioned supine on a flat surface with head turned to one side. 2ml/kg of Survanta is then instilled slowly over 10 to 15 minutes into the endotracheal tube via the sideport of an endotracheal tube adapter. The infant remains connected to the ventilator during the instillation procedure. The remaining 2m/kg of Survanta was subsequently given in the same manner but with the head turned to the other side. The total duration of dosing was 20 to 30 minutes. A second dose of Survanta was given 6 hours after the first dose if the infant met the same eligibility criteria. Subsequent doses (3rd and 4th) may be considered 6 hours after the preceding dose if the eligibility criteria for second dose had been met. Infants may receive up to 4 total doses within the first 48 hours of life. The minimum interval between any 2 treatments was 6 hours. Infants were kept in supine position after completion of Survanta instillation. Endotracheal tube suctioning and physiotherapy was not performed for at least 2 hours after each treatment. Arterial blood gases were performed as needed.

All treated infants were evaluated at set intervals during the first 7 days after surfactant therapy. Evaluation were more frequent during the first day with measurements taken every two hours for the first 18 hours. Assessment consisted of physical examination, vital signs, arterial blood gas values, ventilatory settings, mean airway pressure and FiO_2 requirement. Ventilatory index and arterial-alveolar oxygen tension ratio (a/A ratio) were derived from the following formulae:

$$\text{Ventilatory index} = \text{mean airway pressure} \times \text{FiO}_2 / \text{PaO}_2$$

$$\text{a/A PO}_2 \text{ ratio} = \text{PaO}_2 / \text{PAO}_2$$

where $PAO_2 = PIO_2 - PACO_2 [FiO_2 + (1-FiO_2)/R]$, with the assumption that the respiratory quotient $R = 0.8$.

Chest radiographs were performed and after treatment when clinically indicated. The need for other intensive care support was also documented. These included the need for inotropes, duration of intra-arterial monitoring and duration of total parenteral nutrition. Bronchopulmonary dysplasia (BPD) was defined as a need for oxygen at 28 days of age. Each patient was evaluated for the presence of a patent ductus arteriosus (PDA) by clinical, radiographic and, if available, echocardiographic means. Significant patent ductus arteriosus were treated with indomethacin at a dose of 0.1mg/kg daily for 6 days. Where possible, infants had cranial ultrasound performed at 1 to 3 days post-treatment and subsequently as indicated. Examinations were performed through the anterior fontanelle in coronal and sagittal projections. Intraventricular haemorrhage was classified using the standard grading scale. Screening for retinopathy of prematurity was performed by a paediatric ophthalmologist at 35 weeks post-conceptual age.

Statistical analyses for comparisons between the two groups consisted of Mann-Whitney Wilcoxon Rank Sum Test for continuous variables, and the X^2 test and Fisher exact test for categorical data. P values of < 0.05 were considered statistically significant.

Results

From February 1995 to July 1996, 30 infants with birthweight of ≥ 800 g fulfilled the criteria for surfactant replacement therapy and all were treated according to the study protocol. Reviewing the records of all preterm infants with birthweight ≥ 800 g that required ventilation from February 1992 to September 1993, 30 infants would have fulfilled the criteria for surfactant replacement therapy but were not treated because surfactant was still not available. All these 30 infants were selected as historical controls. Infants from October 1993 to January 1995 were excluded from the selection process as this period corresponded to the initial introduction and inconsistent use of surfactant therapy in the unit before uniform guidelines were drawn up. There were no significant difference in their general baseline characteristics such as birthweights, gestation, gender distribution, status at birth and initial ventilatory parameters (Table I). The two groups of infants had similar severity of their RDS as shown by the initial FiO_2 , mean airway pressure, a/A ratio and ventilatory index. In the control group, pre-treatment parameters were taken as that of 4 to 6 hours after intubation; this being the median time of surfactant therapy in the surfactant-treated group.

Table I
Baseline characteristics and initial ventilatory parameters

Characteristics	Survanta (n=30)	Control (n=30)
Male	18 (60%)	21 (70%)
Mean birthweight \pm SD (grams)	1317 \pm 331	1306 \pm 315
Mean gestational age \pm SD (weeks)	29.7 \pm 2.1	29.7 \pm 2.3
Intubation in labour room	13 (43%)	16 (53%)
Apgar score at 1 min, mean \pm SD	5.0 \pm 2.4	5.3 \pm 2.4
Apgar score at 5 min, mean \pm SD	8.1 \pm 1.6	8.0 \pm 1.6
Antenatal corticosteroids	7 (23%)	2 (7%)
Initial ventilatory parameters		
Fraction of inspired oxygen	0.69 \pm 0.18	0.68 \pm 0.15
Mean airway pressure (cmH ₂ O)	12.8 \pm 1.4	12.2 \pm 1.4
Arterial-alveolar oxygen tension ratio	0.14 \pm 0.06	0.12 \pm 0.05
Ventilatory Index	0.16 \pm 0.08	0.17 \pm 0.07

Differences not statistically significant

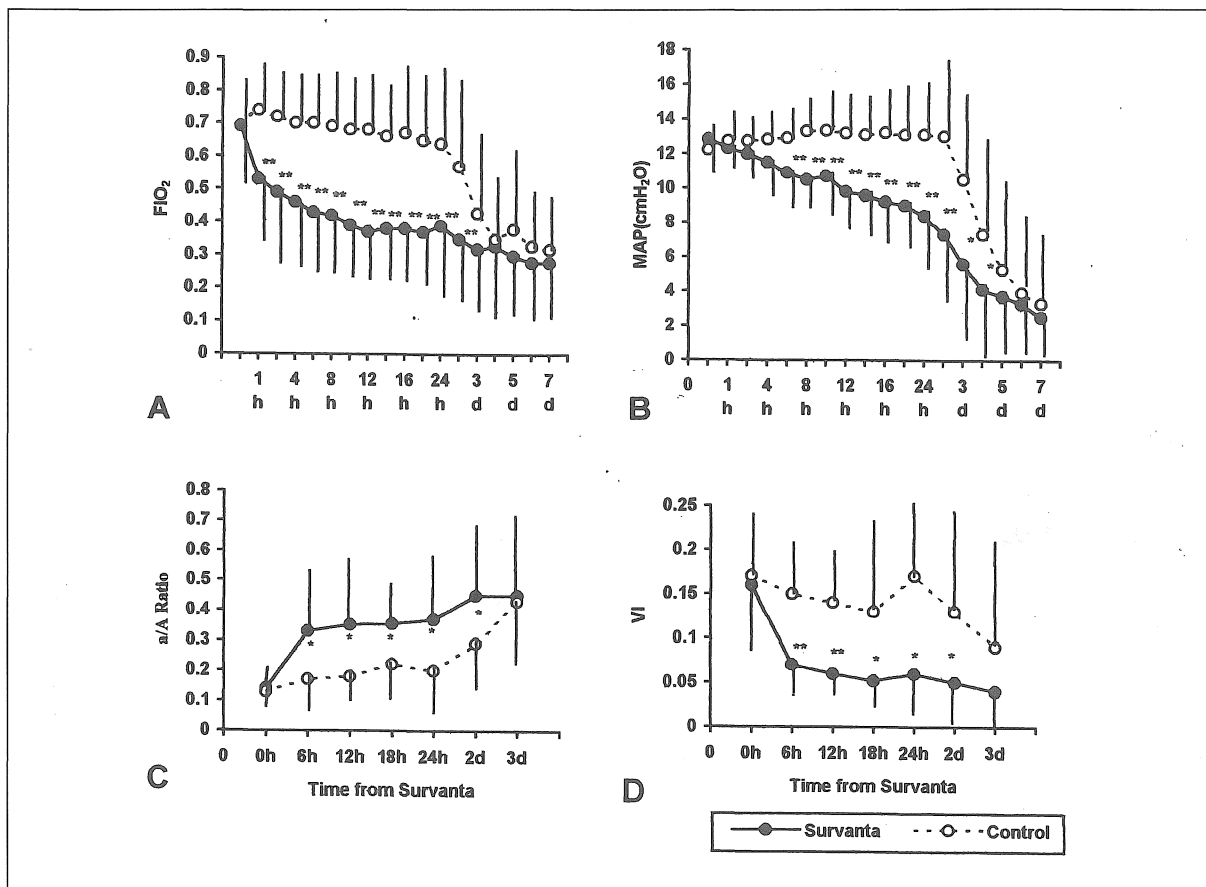


Fig. 1: A-D: Fraction of inspired oxygen (FiO₂), mean airway pressure (MAP), arterial-alveolar oxygen tension ratio (a/A Ratio) and ventilatory index (VI) in study and control infants at various time intervals after surfactant replacement therapy. (h = hour, d = day) Results are mean values ±1SD. (* p < 0.01, ** p < 0.001)

Of the 30 infants who received Survanta, 15 (50%) had one dose of Survanta, 12 (40%) received 2 doses while 3 (10%) infants received up to 3 doses of Survanta. The median time to first dose of surfactant was 5 hours. Attempts were always made to administer surfactant as soon as possible after an infant had met the criteria for replacement therapy. Nevertheless, time taken for initial stabilization of the babies and radiological confirmation of RDS were a cause of delay of surfactant therapy in some infants.

Most infants tolerated the administration of surfactant well, with majority experiencing only small transient

fluctuations in their oxygen saturation as measured by pulse oximetry. A few infants developed problem of blocked endotracheal tube during administration. In most cases, this could be overcome by manually ventilating the infants, often using a slightly higher peak inspiratory pressure. Blocked endotracheal tube can also occur up to a few hours after the dose of Survanta had been instilled. In 2 infants, the endotracheal tube had to be changed. No major changes in heart rate and blood pressure was observed during and after administration of surfactant.

The early response following surfactant replacement

Table II
Duration of ventilatory support among survivors

	Duration, mean (days)		p value
	Survanta	Control	
All infants	n=27	n=20	
IPPV	8.4	9.4	0.76
CPAP	3.4	9.6	0.04*
IPPV + CPAP	11.8	19.0	0.17
Supplemental oxygen	20.5	31.6	0.20
Hospital stay	50.0	51.3	0.84
Infants > 1,000g	n=23	n=19	
IPPV	5.0	9.2	0.11
CPAP	2.5	9.7	0.03*
IPPV + CPAP	7.5	18.9	0.02*
Supplemental oxygen	14.7	31.6	0.06
Hospital stay	43.3	50.7	0.37

therapy in the two groups are shown in Figure 1. Within the first few hours, infants who received surfactant showed highly significant improvements in all ventilatory parameters (FiO₂, mean airway pressure, a/A ratio and ventilatory index). The improvement in these parameters remained significant for 2 to 4 days after surfactant therapy.

Among the survivors, the mean duration of intermittent positive pressure ventilation (IPPV), continuous positive airway pressure (CPAP), IPPV + CPAP and total duration of oxygen were all lower for the surfactant-treated group (Table II). These differences were statistically significant in relation to duration of CPAP. Infants who had surfactant therapy needed a mean of 3.4 days of CPAP compared to 9.6 days in the controls ($p = 0.04$). This reduction in the duration of ventilatory support was more evident in infants with birthweight >1000g. In this subgroup of infants, the mean duration of CPAP and IPPV+CPAP was

significantly lower (9.7 vs 2.5 days, $p=0.03$; 18.9 vs 7.5 days, $p=0.02$, respectively). The overall duration of hospital stay was not significantly different between the two groups.

Data on mortality and short-term morbidity is summarised in Table III. Infants in the surfactant-treated group had significantly lower mortality rate compared to the controls (10% vs 33%; $p=0.03$). The incidences of bronchopulmonary dysplasia, pulmonary haemorrhage, patent ductus arteriosus, sepsis and necrotizing enterocolitis were not significantly different between the two groups.

The facility for cranial ultrasound was more readily available during the study period than the period of the historical controls. Twenty eight (93%) study infants had cranial ultrasound compared to only 15 (50%) in the control group. This precludes any meaningful statistical comparison between the incidence of

Table III
Mortality and morbidity in study and control infants

	Survanta n=30	Control n=30	p value
Death	3 (10%)	10 (33%)	0.03*
BPD**	11 (37%)	8 (40%)	0.33
Pneumothorax	4 (13%)	7 (23%)	0.25
Pulmonary Haemorrhage	3 (10%)	3 (10%)	1.00
PDA	11 (37%)	13 (43%)	0.40
Sepsis	4 (13%)	3 (10%)	0.68
NEC	0 (0%)	2 (7%)	0.49

** Infants who died before 28 days were excluded from analysis.

BPD = bronchopulmonary dysplasia, PDA = patent ductus arteriosus, NEC = necrotizing enterocolitis

intraventricular haemorrhage in the two groups. Nevertheless, 4% (1 out of 24) of infants in the surfactant group had severe IVH (Grade III to IV) while up to 39% (5 out of 13) of infants in the control group had severe IVH (Grade III to IV).

In the surfactant group, 17 (57%) infants had ophthalmological examination by discharge compared to 8 (27%) in the control group. Infants may have ophthalmological examination on subsequent follow-up; but information regarding such subsequent follow-up was not included in this study. None of the infants in the control group had any retinopathy of prematurity. One infant in the surfactant group developed Grade III retinopathy of prematurity with plus disease and required cryotherapy.

There was no difference between the two groups in relation to requirement for inotropic support, duration of intra-arterial blood pressure monitoring, need for muscle relaxant, blood transfusion and central venous lines (Table IV). In terms of nutritional support, similar proportion of infants in the two groups required total parenteral nutrition at some time during their illness. Infants in the surfactant group, however, were able to

achieve full enteral feeds earlier (15.7 days vs 25.6 days; $p = 0.03$). Similarly, infants in the surfactant group required significantly shorter duration of parenteral nutrition compared to the control group (13.3 days vs 25.6 days; $p = 0.02$). The average weight gain till term or discharge was nevertheless no different in the two groups.

Antenatal corticosteroids was defined as those who had received two doses of dexamethasone 12 hours apart before delivery. In the surfactant-treated group, 7 (23%) had antenatal corticosteroids administered to the mothers compared to 2 (7%) in the control group ($p = 0.15$). To determine if this may be a confounding factor in evaluating the efficacy of surfactant replacement therapy, comparison was made among surfactant-treated infants between those whose mothers received antenatal corticosteroids and those who did not. Infants whose mother received antenatal corticosteroids required a mean of 13.5 days of ventilatory support (IPPV + CPAP) compared to 8.2 days in those whose mother did not ($p = 0.25$). There was also no statistically significant difference between the two groups in terms of the incidences of death, bronchopulmonary dysplasia, pneumothorax, PDA and pulmonary haemorrhage.

Table IV
Intensive care support among study and control infants

Parameters	Survanta n=30	Control n=30	p value
Number needing inotropes	14 (47%)	13 (43%)	0.80
Number needing paralysis	9 (30%)	13 (43%)	0.42
Mean total blood transfusion (ml/kg)	47.4	48.5	0.94
Mean duration of intra-arterial BP (d)	6.2	5.8	0.75
Number needing central venous line	12 (40%)	16 (53%)	0.44
Nutritional support :			
Mean age at first enteral feed (d)	4.9	5.8	0.31
Mean age at first full enteral feed (d)	15.7	24.6	0.03*
Number requiring TPN	18 (60%)	16 (53%)	0.37
Mean duration of TPN (d)	13.3	25.6	0.02*
Average weight gain (gram/week)	85.4	86.3	0.92

TPN = total parenteral nutrition

Discussion

This study has demonstrated that Survanta given early in the course of severe RDS leads to prompt and sustained improvement in oxygenation and a decrease in ventilatory support. All four parameters used in this study (FiO₂, MAP, a/A ratio and VI) showed highly significant improvements, often within one hour of commencement of treatment. This finding is consistent with many other similar studies⁷⁻¹⁰.

A significant improvement in mortality rate among infants treated with exogenous surfactant was also shown (10% versus 33%, p value 0.03). This is also consistent with other studies⁷⁻¹⁰. One large multicentre randomised controlled trial involving infants weighing 600g to 1,750g at birth showed an improvement in overall mortality from 27.3% to 18.4%¹¹. Meta-analysis of surfactant replacement therapy calculated an odds ratio for mortality of 0.6, suggesting a 30-40% reduction of mortality^{2,3}.

In terms of other associated morbidities, it is now generally agreed that surfactant replacement therapy has not significantly altered the incidences of pulmonary haemorrhage, patent ductus arteriosus, intra-ventricular haemorrhage, bronchopulmonary dysplasia and retinopathy of prematurity². However, one of the most prominent beneficial effects of surfactant therapy in most of the randomised control trials has been the reduction in the incidence of pneumothorax. Meta-analysis of trials using natural surfactant for rescue therapy showed a relative risk of 0.43 for pneumothorax in surfactant-treated infants². In this study, we have not been able to demonstrate any significant difference in the incidence of pneumothorax in the surfactant-treated group (p value 0.25). This could have been due to our relatively small sample size. It is also possible that infants in the study group were treated relatively late in the course of their RDS, while earlier treatment may have prevented the escalation of ventilatory pressures that predisposed them to pneumothorax.

One concern regarding the use of historical controls is that the infants in the two periods may in fact be different. To address this issue, controls were chosen from the period soon before the implementation of routine protocol for surfactant therapy in the neonatal unit to minimise the time lapse between the study and control periods. There has been minimal turn-over of nursing staff during the two to three year period before and after the availability of surfactant. The senior medical staff in the neonatal unit has remained largely unchanged. The obstetric risk factors of the mother and the initial resuscitations of the babies were similar in the two groups. In addition, the initial FiO_2 , mean airway pressures, a/A ratio and ventilatory index were almost identical in the two groups, suggesting similar severity of RDS at the initial stages. The proportion of infants who used intra-arterial blood pressure monitors and central venous catheters were similar in the two groups, suggesting that the quality of intensive care were not significantly different.

The percentage of infants who had antenatal corticosteroids was higher in the surfactant group, although the difference was not statistically significant. Studies have shown that antenatal corticosteroids significantly improve the outcome of preterm infants with RDS¹². In this study, comparison has been made between surfactant-treated infants whose mother had antenatal corticosteroids and surfactant-treated infants whose mother did not have antenatal corticosteroids. It is rather surprising that infants whose mother had antenatal corticosteroids seemed to have a trend towards slightly poorer outcome than those whose mother did not. It is not possible to interpret this further as the numbers involved are small. What is certain though is that the use of antenatal corticosteroids in this particular study did not contribute to the improvement seen in the surfactant-treated group.

One of the important objectives of this study was to assess the impact of surfactant replacement therapy in the Malaysian setting. There were certain indicators that suboptimal neonatal resources had affected the quality of surfactant replacement therapy. The average time taken to first dose of Survanta was 5 hours, a significant delay, attributable to lack of good in-hospital neonatal transport equipment and radiological facilities. Nevertheless, there had not been any significant complications relating directly to the administration of

Survanta. Thus, with careful monitoring, surfactant replacement therapy is a safe procedure. In relation to the optimal number of doses of surfactant, there are evidence to suggest multiple doses is better than single dose, although doses more than two may not confer additional benefit¹³. Due partly to cost consideration, this study has elected not to routinely give multiple doses of Survanta, but rather to rely on specific re-treatment criteria. As a result of this, half of the infants were successfully treated with only a single dose of Survanta.

Despite these limitations, this study has demonstrated that significant reduction of mortality is still achievable. Among the infants who survived, there was also a significant reduction in the duration of ventilation. This reduction is even more significant among infants weighing more than 1,000g. The duration of ventilatory support was cut by 11.4 days from 18.9 to 7.5 days. This has important implication for the practice of neonatology in Malaysia as infants weighing more than 1000g still forms the bulk of preterm infants with RDS offered intensive care support in many centres. In addition to cost savings, shorter duration of ventilation would also make available precious ventilator resources so that more babies can be ventilated and saved. This study has also demonstrated that infants treated with surfactant were able to achieve full enteral feeds earlier and hence require significantly shorter duration of parenteral nutrition. This represented obvious areas of further cost savings.

While this study and many others have demonstrated the unequivocal benefits of surfactant replacement therapy, it is important that overall high quality of neonatal intensive care is maintained. In addition, it is important that the use of antenatal corticosteroids continued to be emphasised. Antenatal corticosteroids significantly reduces the incidences of RDS, the mortality of RDS and other pulmonary as well as non-pulmonary complications of RDS¹². Studies have shown that the combination of antenatal corticosteroids and surfactant therapy provides optimum outcome for preterm infants at risk of RDS¹⁴⁻¹⁶. Antenatal corticosteroids is much cheaper and simpler than surfactant to use. In the setting of developing country like Malaysia, this is certainly a much more cost effective option. With the availability of surfactant, there is more reason we should intensify our use of antenatal corticosteroids.

In conclusion, this study has demonstrated that surfactant replacement therapy in preterm infants with RDS improves survival and reduces need for ventilatory and nutritional support. The routine use of surfactant replacement therapy, following individual unit guidelines, will very likely result in significantly improved outcome for preterm infants in Malaysia.

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