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Changes of Neonatal Mortality Rate between 'Pre' and 'Post' Surfactant Period

The objective of this study was to determine how the neonatal mortality rate has changed since surfactant (S) therapy was introduced in our Neonatal Intensive Care Unit (NICU), and to evaluate the efficacy of surfactant therapy in respiratory distress syndrome (RDS) patients. Incidences of risk babies such as outborns, prematurity, low birth weight infants and RDS, and neonatal mortality rates were compared between 'pre' (control, 1988 to 1991, n=4,861) and 'post' S period (study, 1993 to 1996, n=5,430). In RDS patients of 'post' S period, neonatal mortality rate was compared between S-treated and non-treated patients, and chest X-ray and ventilatory parameters were compared between pre- and post-72 hr of surfactant treatment. Surfactant therapy showed short term effects, judging by the decrease of early neonatal deaths and improvement of chest X-ray and ventilatory parameters in RDS patients. The overall neonatal mortality rate had a tendency to decrease in spite of increased incidences of risk babies in 'post' S period but it was less than expected. The reasons were thought to be that we had a high proportion of risk babies, and there was some bias in patient selection for surfactant therapy and its use. In conclusion, with the active prevention of risk baby delivery and appropriate use of surfactant, better results could be expected.

Key Words : *Infant mortality; Surface-active agents; Respiratory distress syndrome*

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INTRODUCTION

Avery and Mead (1) in 1959 suggested that the major pathogenesis of respiratory distress syndrome (RDS) is a deficiency in alveolar surfactant (S). Fujiwara et al. (2) first reported that a single dose of surfactant instilled into the endotracheal tubes resulted in a dramatic decrease in artificial ventilation in ten premature infants with severe RDS who did not improve despite artificial ventilation.

As a result of collaborative multicenter trials of surfactant replacement therapy, it is effective in the prevention and treatment of RDS and ultimately decrease neonatal mortality rate (3-10). In 1990, surfactant was first imported into Korea, and since then many studies regarding surfactant replacement therapy have been reported, popularizing its use in Neonatal Intensive Care Unit (NICU) (11-15).

In this study, we compared the neonatal mortality rate between 'pre' and 'post' S period to see how the mortality rate has changed since surfactant therapy was introduced to our NICU. In RDS patients of 'post' S period, we compared the neonatal mortality between S-treated and non-treated patients and also compared chest X-ray and ventilatory parameters between pre- and post-72 hours of surfactant treatment to evaluate its efficacy.

POPULATION and METHODS

Study Design and Sample Size

Babies who admitted to Chonnam National University Hospital from January 1988 to December 1996 were categorized into two groups, 'pre' (control) and 'post' (study) S period. The control group (n=4,861) consisted of the babies between 1988 and 1991 before the application of surfactant therapy, and the study group (n=5,430) consisted of the babies between 1993 and 1996 after the application of surfactant. Males were more than female with similar ratio in both groups (control 1.23:1 vs study 1.14:1). We reviewed the charts of both groups, respectively. The babies admitted in 1992 were excluded from this study because surfactant had been used inconsistently at that period.

Data Collection and Analysis

In both groups ('pre' and 'post' period), we compared the baby distribution according to sex, birth place, incidence of low birth weight infants, prematurity and RDS, and neonatal mortality rate to see the changing pattern since surfactant therapy was introduced to our NICU. Risk babies included outborns, prematurity, low birth weight infants and RDS patients. In study group, we compared neonatal mortality rate and cause of death between S-treated and non-treated RDS babies, and chest X-ray and several ventilatory parameters between pre- and post-72 hours of surfactant treatment to evaluate its efficacy. We included the patients discharged against medical advice into the death.

We used Surfacten TA (Tokyo Tanabe Co., Japan) for replacement. Original directions recommend that prescribe 120 mg per kg of weight and retreat when the patients require FiO_2 over 0.4 and show no change or even aggravation of chest radiologic findings after replacement. Indications for surfactant therapy followed the guidelines of the 'Korean Medical Insurance Union Regulation' include (1) clinically apparent respiratory distress symptoms; (2) diffuse, very finely granular or reticular appearance and air bronchogram on chest X-ray (more than Bomsel grade III); (3) more than 40% of inspired oxygen (FiO_2) is required to maintain appropriate arterial oxygen pressure (50-80 mm Hg) or oxygen saturation (SaO_2>90%); (4) negative shake test or less than medium (<11-20/mm^3) on stable microbubble rating or less than 2:1 on L/S ratio in maternal amniotic fluid or baby's gastric juice; (5) preterm infant more than 28 weeks of gestation (recently it was changed to 26 weeks) or low birth weight infant. When three or more criteria among the above criteria are met, surfactant is administered but the first four criteria are needed in case of fullterm baby.

Interpretation of chest X-ray was based on Bomsel grading system (16). Ventilatory parameters included FiO_2, mean airway pressure (MAP), ventilatory index (VI), alveolar arterial oxygen tension gradient (A-a DO_2). The value for MAP was calculated by the formula {frequency x (PIP-PEEP)}/60 x Ti+PEEP, and for A-a DO_2 by the formula (713 x FiO_2-PCO_2/0.8)/PaO_2. Statistical analysis included chi-square, Fisher's exact test and STATA program. Results were considered statistically significant if $p<0.05$.

RESULTS

Incidence Rates of Risk Babies

Of the babies enrolled in the study, more than ninety percent were inborns (control 97.1% vs study 90.1%) with a significant increase of outborns in this study group (control 2.9% vs study 9.9%, $p<0.01$). In terms of risk babies, there was a significantly increased incidence of prematurity (control 18.6% vs study 27.6%, $p<0.01$), low birth weight infants (control 19.9% vs study 29.7%, $p<0.01$) and RDS patients (control 4.2% vs study 7.6%, $p<0.01$) (Table 1).

Table 1. Subject characteristics

		Control	Study
Sex	Male	2,688 (55.3%)	2,900 (53.4%)
	Female	2,173 (44.7%)	2,530 (46.6%)
Place	Inborn	4,720 (97.1%)	4,894 (90.1%)
	Outborn	141 (2.9%)	536 (9.9%)**
Gestational age (week)	< 37	904 (18.6%)	1,497 (27.6%)**
	over 37	3,957 (81.4%)	3,933 (72.4%)
Birth weight (g)	2,500 or less	969 (19.9%)	1,612 (29.7%)**
	over 2,500	3,892 (80.1%)	3,818 (70.3%)
RDS	Yes	204 (4.2%)	414 (7.6%)**
	No	4,657 (95.8%)	5,016 (92.4%)
Total		4,861 (100%)	5,430 (100%)

Significance of the difference between 'control' vs 'study' surfactant era. ** $p<0.01$

Mortality Rates

We compared the mortality rates according to sex, birth place, gestational age, birth weight and presence of RDS between the control and study group. Mortality rates of male and female babies were the same for each group (control 5.0% vs 5.0%, study 4.5% vs 4.5%). Mortality rates were higher in outborns ($p<0.01$), premature ($p<0.01$), and low birth weight infants ($p<0.01$) compared to that of inborns, fullterms or posterms and babies over 2,500 g, respectively. Mortality rate of RDS babies was absolutely higher than non-RDS babies in both groups (control 61.3% vs 2.5%, $p<0.01$, study 28.7% vs 2.5%, $p<0.01$).

We also compared the mortality rates according to these factors between control and study group. Mortality rates of both sex were the same in each group (control 5.0% vs study 4.5%). Mortality rates of outborns (10.6% vs 7.8%, $p<0.05$), premature babies (15.5% vs 11.0%, $p<0.01$), low birth weight infants (14.7% vs 8.9%, $p<0.01$) and RDS babies (61.3% vs 28.7%, $p<0.01$) showed significant decrease, but in inborns, the babies over 37 gestational weeks or over 2,500 g and non-RDS babies were not significantly changed. The overall mortality rate showed little tendency to decrease (5.0% vs 4.5%) (Table 2).

Because the most common causes of neonatal death are prematurity, low birth weight and its related problems such as RDS, we investigated the changing pattern of their incidence rates and mortality rates between 'pre' and 'post' S period. Although the incidence rates of risk babies were

Table 2. Mortality rates according to subject characteristics and group

		Control		Study	
		No.	Mortality(%)	No.	Mortality(%)
Sex	Male	2,688	135 (5.0%)	2,900	130 (4.5%)
	Female	2,173	108 (5.0%)	2,530	115 (4.5%)
Place	Inborn	4,720	228 (4.8%)	4,894	203 (4.1%)
	Outborn	141	15 (10.6%)[1]**	536	42 (7.8%)
Gestational age	< 37	904	140 (15.5%)[1]**	1,497	164 (11.0%)[1]**, [2]**
(week)	over 37	3,957	103 (2.6%)	3,933	81 (2.1%)
Birth weight	2500 or less	969	142 (14.7%)[1]**	1,612	144 (8.9%)[1]**, [2]*
(gm)	over 2500	3,892	101 (2.6%)	3,818	101 (2.6%)
RDS	Yes	204	125 (61.3%)[1]**	414	119 (28.7%)[1]**, [2]**
	No	4,657	118 (2.5%)	5,016	126 (2.5%)
T otal		4,861	243 (5.0%)	5,430	245 (4.5%)

[1]Significance of the difference between each subject characteristics, [2]significance of the difference between 'control' vs 'study' group. *p<0.05, **p<0.01

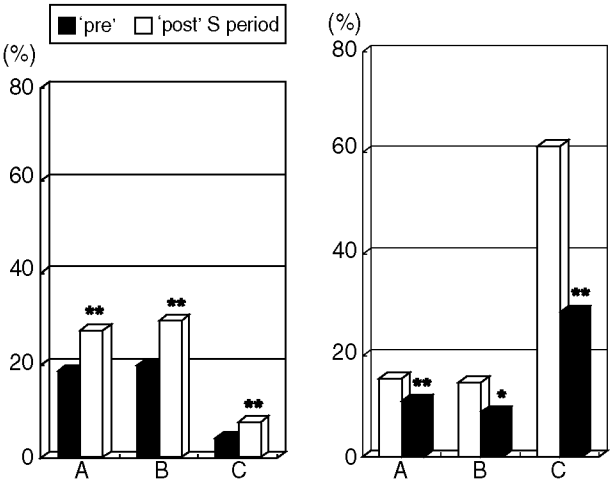

Fig. 1. Incidence (left) and mortality rates (right) of prematurity (A), low birth weight (B) and respiratory distress syndrome (C) babies between 'pre' vs 'post' surfactant period. (*p<0.05, **p<0.01)

increased, mortality rates for each risk category were significantly decreased in 'post' S period (Fig. 1).

RDS Patients in 'Post' S Period

Of 414 RDS patients in the 'post' S period, 128 (30.9%) were treated with surfactant. The mortality rates and causes of death of S-treated and non-treated RDS patients were compared. Early neonatal mortality within one week of age was significantly lower in S-treated RDS patients (8.6% vs 19.9%, p<0.01) but there was no significant difference of total neonatal mortality rate between S-treated and non-treated patients (29.7% vs 27.6%, p>0.5) (Table 3).

We observed the causes of death in RDS patients of post S period (Table 4). Irrespective of surfactant therapy, the most common cause of death was sepsis (over two thirds). Others were intraventricular hemorrhage (IVH), air leak syndrome, renal failure and patent ductus arteriosus (PDA) with congestive heart failure. But when we compared it according to the time of death, IVH and air leak syndrome were the main causes in early neonatal period, and sepsis was the most common in late neonatal period. But it was not significant between surfactant treated and non-treated RDS patients.

Table 3. Mortality rate of RDS patients in study group

	S-treated (N=128) No. of death	S-nontreated (N=286) No. of death
< day 8	11 (8.6%)**	57 (19.9%)
day 8-28	24 (18.8%)	15 (5.2%)
> day 28	3 (2.3%)	7 (2.4%)
Total	38 (29.7%)	79 (27.6%)

**p<0.01

IVH was diagnosed by ultrasonography through anterior fontanelle and graded by Papile classfication (17). Renal failure was defined as sudden decrease in renal function resulting in progressive retention of nitrogenous waste products associated with reduced urine output (18). Diagnostic criteria for PDA include (1) persistent apnea for unexplained reasons in an infant recovering from RDS; (2) an active heaving precordium, bounding peripheral pulse, wide pulse pressure, and a systolic or to-and-fro murmur; (3) carbon dioxide retention; (4) increasing oxygen dependency; (5) roentgenographic evidence of cardiomegaly and increased pulmonary vascular markings; and (6) hepatomegaly, and it was confirmed by echocardiography with Doppler (19).

We investigated the clinical data of RDS patients to see whether there was any bias in the patient selection of surfactant treatment. Surfactant treated RDS patients showed lower birth weight (1,119±482 vs 1,431±534 g, p<0.01),

Table 4. Causes of death according to the time of death in RDS patients of study group

	surfactant treated			surfactant non-treated		
	early(11)	late(27)	total(38)	early(57)	late(22)	total(79)
Sepsis, DIC	3 (27.3%)	24 (88.9%)	27 (71.1%)	28 (49.1%)	21 (95.5%)	49 (62.0%)
IVH	10 (90.9%)	5 (18.5%)	15 (39.5%)	32 (56.1%)	2 (9.1%)	34 (43.0%)
Air leak syndrome	9 (81.8%)	3 (11.1%)	12 (31.6%)	32 (56.1%)	1 (4.5%)	33 (41.8%)
Renal failure	3 (27.3%)	5 (18.5%)	8 (21.1%)	11 (19.3%)	4 (18.2%)	15 (19.0%)
PDA with CHF	3 (27.3%)	4 (14.8%)	7 (18.4%)	10 (17.5%)	3 (13.6%)	13 (16.5%)
Pulmonary hemorrhage	2 (18.2%)	—	2 (5.3%)	3 (5.3%)	1 (4.5%)	4 (5.1%)
Other	—	1(3.7%)	1 (2.6%)	1 (1.8%)	2 (9.1%)	3 (3.8%)

Parenthesis means number of patients. DIC, disseminated intravascular coagulopathy; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; CHF, congestive heart failure.

shorter gestational weeks (28.1±2.9 vs 30.3±4.1 wk, $p<0.01$) and more severe chest X-ray findings (97.7% vs 58.4%, $p<0.05$) compared to non-treated patients but 1-min Apgar score was similar (Table 5).

We also investigated the treatment profile of 128 RDS patients treated with surfactant to evaluate its adequacy (Table 6). The average postnatal hours of instillation was 18.8±18.9 hours. Only 32 patients (25.0%) received treatment within 6 hours of age and 25 (19.5%) received treatment after 24 hours of age. Only 32 (25.0%) patients received an adequate first dose (120 mg/kg) and three quarter (75.0%) received small dose than presciption described. Surfactant was used once in 93 cases (72.7%) and was used repeatedly in 35 cases (27.3%). We gave surfactant four times in one male patient of 28 gestational weeks, 980 g with severe RDS (Bomsel grade IV). But he showed no response in spite of the mechanical ventilator setting was modified and eventually died on seven days after birth. It was used for rescue therapy in most cases (125 cases, 97.7%). In three cases (2.3%) who showed clinically and radiologically no apparent but negative shake test or less than medium (<11-20/mm^3) on stable microbubble rating in baby's gastric juice it was used for prophylaxis (Table 6).

In the RDS patients treated with surfactant, we compared the chest X-ray and ventilatory parameters between pre- and post-72 hours of surfactant treatment to evaluate its efficacy. One hundred and twenty-five patients (97.7%) showed Bomsel grade III-IV, but decreased to forty-nine (38.3%, $p<0.01$) at post-S 72 hours. And also, several ventilatory parameters indicating ventilatory demand, such as FiO_2, MAP, VI, and A-a PO_2 were significantly improved at 72 hours after treatment with surfactant ($p<0.01$) (Table 7).

DISCUSSION

The prevention and management of RDS is an important topic in newborn medicine because it is a major disease in premature babies and the most common cause of neonatal mortality and morbidity (19). The underlying pathologic

Table 5. Clinical data of RDS patients in study group

		S-treated (N=128)	S-nontreated (N=286)
Birth weight (g)	(M±SD)	1,119±482**	1,431±534
Gestational week	(M±SD)	28.1±2.9**	30.3±4.1
1-min Apgar score	(M±SD)	4.8±2.7	4.9±3.5
No(%) of Bomsel grade III & IV		125(97.7%)*	167(58.4%)

Significance of the difference between S-treated vs non-treated RDS patients. *$p<0.05$, **$p<0.01$

Table 6. Surfactant therapy of RDS patients in study group (N=128)

Postnatal hours of the first dose	M±SD	18.8±18.9
	<7	32 (25.0%)
	6-24	71 (55.5%)
	>24	25 (19.5%)
First dosage (mg/kg)	<120	96 (75.0%)
	120 or more	32 (25.0%)
Frequency	one	93 (72.7%)
	two	27 (21.1%)
	more than three	8 (6.2%)
Mode	prophylactic	3 (2.3%)
	rescue	125 (97.7%)

Significance of the difference between S-treated vs -nontreated RDS patients. *$p<0.05$, **$p<0.01$

Table 7. Comparisons of parameters between pre- and post-surfactant therapy in RDS patients of study group (N=128)

		Pre No.(%)	Post 72 hr No.(%)
Bomsel grade	I	—	26 (20.3%)
	II	2 (1.6%)	52 (40.6%)
	III	46 (36.0%)	43 (33.6%)
	IV	79 (61.7%)	6 (4.7%)
FiO_2 (%) (M±SD)		0.76±0.24	0.39±0.19**
MAP (cmH_2O) (M±SD)		8.31±2.33	6.81±1.83**
VI (M±SD)		0.134±0.116	0.052±0.058**
A-a DO_2 (mmHg) (M±SD)		436.3±168.1	145.9±135.4**

FiO_2 fraction of inspired oxygen; MAP, mean airway pressure; VI, ventilatory index, A-a DO_2, alveolar arterial oxygen tension gradient. ** $p<0.01$

process of RDS is believed to be a deficiency in alveolar surfactant which is a lipoprotein complex including phospholipid (80%), protein (10%) and neutral lipid (10%), and prevents lung atelectasis by reducing surface tension between air and liquid in the lung.

After the report of Avery and Mead (1) reporting the deficiency of alveolar surfactant as the pathogenesis of RDS for the first time, many investigators have been studying its morphology, biochemistry, physics, and molecular biology. As a result we came to better understand the structure, metabolism, function and action of surfactant. Now, surfactant replacement therapy has been generally accepted in the treatment of RDS in addition to conventional ventilation and it is known as a major contributor in improving neonatal survival (3-10).

In 1980, Fujiwara et al. (2) developed a mixture of both natural extract of minced calf lung and synthetic surface active lipid for use in humans. Since then, there have followed a series of collaborative multicenter trials in which purely natural (from animal lungs or human amniotic fluid), mixture of natural and synthetic, and purely synthetic preparations were employed (3-10).

At present there are many commercialized preparations such as Surfacten®, a reconstituted bovine surfactant (Tokyo Tanabe Co., Japan), Survanta®, a modified bovine surfactant (Ohio Ross Laboratories of Columbus, America), Curosurf®, a minced porcine surfactant phospholipid fraction (Cheisi Co., Italy), Exosurf®, a purely synthetic preparation (North Carolina Burroughs-Wellcome Co., America) etc. Surfactant-TA (Surfacten®) was imported to our country in 1991 but we have been actively using it only since 1993. This preparation is more rapidly spread than other preparations and has excellent hysteresis at surface tension area diagram (20). It maintains very low surface tension in vitro and it also shows excellent improvement in lung compliance, histology, and chest X-ray findings in vivo animal studies with good physical and physiological properties (20, 21).

We investigated how the incidences of risk babies and neonatal mortality rate have been changing since surfactant therapy was introduced in our NICU. Improved socioeconomic, cultural status and medical insurance policy enable many risk babies to have an opportunity to receive therapy. Because our hospital is a tertiary facility, many risk pregnancies and babies are transferred. This was the reason why the proportion of risk babies such as premature and/or low birth weight and RDS was extraordinarily high with a significant increase in 'post' S period than 'pre' S period. In spite of the significant increase of risk babies ($p<0.01$) there was a slight decrease in total mortality rate (control 5.0% vs study 4.5%) and even mortality rates for each risk category were significantly decreased ($p<0.01$ for prematurity and RDS, $p<0.05$ for outborns and LBW). It may possibly mean that the survival of high risk babies has improved.

We compared the neonatal mortality rate between S-treated and non-treated RDS babies to determine how the surfactant therapy improves survival in RDS patients. In terms of early neonatal death within one week of life, RDS patients treated with surfactant showed significantly lower mortality rates (8.6% vs 19.9%, $p<0.01$) but the total mortality rate showed no difference compared to non-treated patients (29.7% vs 27.6%) which is quite different from other reports (4, 9). Fujiwara et al. (2) reported that the mortality rate was 20% (2/10) in infants who were treated with surfactant and Bae et al. (14) reported 40% in Korea.

The reasons why the neonatal mortality rate in our study was somewhat high was thought to be that we included the patients discharged against medical advice into the death. And the other reasons were as follows. 'Korean Medical Insurance Union' strictly regulates the use of surfactant because of high cost. We could not use it for prevention but only for rescue therapy in severe RDS patients. We administered small dose if the baby's body weight was more than 1 kg and also lost opportunities to administer it at appropriate time. And also we could not retreat even indicated such as the patients required FiO_2 over 0.4 and showed no change or even aggravation of chest rádiologic findings after surfactant replacement. S-treated RDS patients showed lower birth weight ($1,119\pm482$ vs $1,431\pm534$ gm, $p<0.01$), shorter gestational period (28.1 ± 2.9 vs 30.3 ± 4.1 wk, $p<0.01$) and more severe chest X-ray findings (97.7% vs 58.4%, $p<0.05$) than S-nontreated patients. It means that there was some bias in the patient selection for surfactant therapy in our study. In other words, we treated surfactant only in small, less mature and more severe RDS patients in order not to being rejected medical expense by the 'Korean Medical Insurance Union'.

In RDS patients treated with surfactant, we compared the chest X-ray and several ventilatory parameters between pre- and post-72 hours of surfactant treatment to evaluate its efficacy. Chest X-ray finding significantly improved after replacement and this result agreed with those of other studies (13, 16). We used A-a DO_2 to estimate arterial blood oxygenation which reflects gas exchange capacity in the lung as the best parameter for indicates physiologic L-R shunt volume under FiO_2 environment (22). As pulmonary compliance increased, ventilation and perfusion improved which indicates the improvement of pulmonary function. In this study, post-treatment A-a DO_2 was significantly increased compared to pre-treatment and this result was similar to other studies (2, 3, 6, 12, 14). After replacement, FiO_2, which indicates oxygen requirement, was significantly decreased and this result coincided with Fujiwara et al. (7).

We observed MAP changes of pre and post-surfactant replacement to assess the requirement of ventilators. MAP is the mean airway pressure of the respiratory tract during respiration as a parameter of non-compliant lung. Because the

RDS patients require a MAP of more than 10 cmH_2O for several days, many complications such as pneumothorax, pulmonary interstitial emphysema, intraventricular hemorrhage and respiratory failure can occur (6, 7). In this study, MAP was significantly decreased after replacement. It means that respiratory control is possible with a low MAP and eventually it can decrease secondary lung injury due to the improvement of pulmonary function from stiff lung.

We also investigated VI to assess the ventilation status according to Fujiwara et al. (7), when VI is 0.047 and below, it means mild, when from 0.047 to 0.133, means moderate, and when 0.133 or more, indicates severe respiratory failure. We found that VI was significantly decreased after replacement. They also reported that surfactant replacement could maintain MAP and VI in a lower state which reduced the incidence of pneumothorax and intraventricular hemorrhage. But we could not observe significant decrease of air leak syndrome and intraventricular hemorrhage in surfactant treated RDS. In this study, it was clear that oxygenation ratio and ventilation environment improved after surfactant replacement in RDS patients. In 1980, according to Fujiwara (2), the common causes of death were IVH, pneumothorax, interstitial emphysema and PDA but in this study, sepsis with DIC was the most common cause of death. So it was thought that prevention and appropriate management for infection are also important in our country.

In conclusion, although the overall neonatal mortality rate was not significantly decreased as expected in 'post' S period compared to 'pre' S period, there was a tendency to decrease in spite of the increased incidence of risk babies. It could be suggested that the survival of high risk babies has improved. And we observed that surfactant therapy apparently showed a short-term effect, judging from significant decrease of early neonatal death within one week of life and improvement of chest X-ray and ventilatory parameters in RDS patients treated with surfactant. We can expect better results if the incidence of risk babies is decreased with good antenatal care, the patient discharged against medical advice is decreased, and surfactant is used appropriately with experienced skill and management including infection control in RDS patients.

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