

## Surfactant Therapy for Neonatal Respiratory Distress Syndrome: A Review of Korean Experiences over 17 Years

We undertook a multi-hospital collective study to evaluate outcomes of neonatal respiratory distress syndrome (RDS) patients treated with pulmonary surfactant (PS) over 17 yr in Korea (Group I; 1990/91, Group II; 1996, Group III; 2002, and Group IV; 2007). There were 60 neonates in Group I (16 hospitals), 1,179 in Group II (64), 1,595 in Group III (62), and 1,921 in Group IV (57). We adopted Bomsel's classification to evaluate initial chest radiographic findings, categorized RDS severities, and classified response types to PS therapy. Almost all cases were treated using a single dose in Groups I and II, but 19.5% received multiple-dose therapy in Group IV. In Group IV, Bomsel's stages III and IV composed 62.9% and initial severities of mild, moderate, and severe RDS were 23.0%, 42.0%, and 35.0%. More infants showed good response in Groups II, III, and IV than in Group I (71.7%, 66.8%, and 69.2% vs. 58.3%). Complications and mortality rate were lower in Group IV than in Groups I, II, and III (mortality rate: 14.3% vs. 40.0%, 30.0%, and 18.7%). We conclude that PS therapy in neonates with RDS had a remarkable impact on improving clinical course and outcomes over 17 yr in Korea.

**Key Words :** *Respiratory Distress Syndrome, Newborn; Premature; Complications; Epidemiology; Mortality; Pulmonary Surfactants; Analysis; Therapeutic Use; Data Collection*

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## INTRODUCTION

Neonatal respiratory distress syndrome (RDS) is a progressive respiratory failure that is caused primarily by a deficiency of pulmonary surfactants (PS). In 1959, Avery and Mead (1) showed that PS deficiency is a major factor in the pathophysiology of RDS. The first successful treatment was reported in 1980, when Fujiwara et al. (2) successfully administered exogenous PS to preterm infants with RDS. PS replacement therapy is now the routine method of treatment for infants with RDS, and since its introduction, morbidity and mortality due to RDS in preterm infants has decreased remarkably.

In Korea, Surfacten® (Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan), the first artificial PS, was available in 1991. Thereafter, Exosurf® (Burroughs Wellcome Co., Research Triangle Park, NC, U.S.A.) was available from 1991 to 1997, Newfactan® (Yuhan Pharm Corporation, Seoul, Korea) from 1996, and Curosurf® (Chiesi Farmaceutici, Parma, Italy) from 2003 (Table 1).

In Korea, PS was first used to treat 8 RDS cases in 1990 by Namgung et al. (3), and this was followed by a report on 6 cases by Park et al. (4) in 1991. Subsequently, Bae et al. (5) reported PS therapy outcomes in neonatal RDS on a national basis for 1990 and 1991. Bae et al. published again a report

on the clinical outcomes of PS therapy in Korea in 1996 and 2002, respectively (6, 7).

In the present study, we investigated improvements of clinical outcome achieved by PS therapy for the treatment of RDS on national data basis for the year of 2007 and compared these findings with those of the three previous reports.

## MATERIALS AND METHODS

### Subjects

In March 2008, we sent 57 hospitals in Korea questionnaires that addressed the clinical outcomes of PS replacement therapy in 2007. Details of the 57 participating hospitals and the individuals that participated in this study are included in the list of contributors.

Patients treated in the individual report periods are referred to as groups for convenience, as follows. 1) Group I-patients enrolled in a 1990 to 1991 (24 months) national survey conducted by Bae et al. (5); 2) Group II-patients enrolled in a national survey performed in 1996 (12 months) by Bae et al. (6); 3) Group III-patients enrolled in a national survey performed in 2002 (12 months) by Bae and Kim (7); and 4) Group IV-patients enrolled in a national survey performed

in 2007 (12 months). Approval to use previous data (5-7) was obtained from each publisher of the journals.

Details of the four study groups, numbers of cases, and the hospitals that participated in this survey are shown in Table 2. In Group I, there were 60 patients at 16 hospitals for the year of 1990 and 1991. For Group II, 1,179 cases were recruited nationally at 64 hospitals for 1996, and for Group III, 1,595 cases were recruited nationally at 62 hospitals for 2002. Finally, for Group IV, 1,921 cases were recruited from 57 hospitals for 2007.

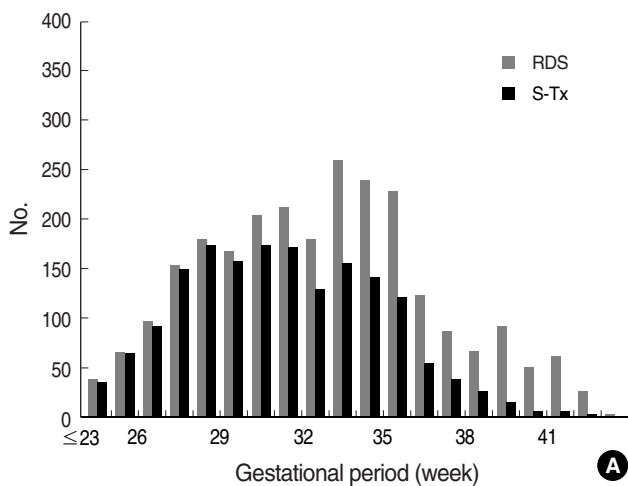
In terms of all RDS births, the proportions of patients who received PS therapy are shown in Table 3 subdivided into in-hospital-born and out-hospital-born patients. For all RDS patients, the percentages that underwent PS replacement therapy increased from 47.3% and 66.2%, in Groups II and III to 77.7%, in Group IV.

Fig. 1 summarizes the proportions of RDS patients in Group IV that underwent PS replacement therapy by birth weight

**Table 1.** Preparations of artificial pulmonary surfactant clinically available in Korea

	Products	Periods
Imported products	Surfacten <sup>®</sup> * (Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan)	1991-present
	Exosurf <sup>®</sup> † (Wellcome Foundation Ltd, London, England)	1991-1997
	Curosurf <sup>®</sup> ‡ (Chiesi Farmaceutici, Parma, Italy)	2003-present
Korean product	Newfactan <sup>®</sup> * (Yuhan Pharm Corporation, Seoul, Korea)	1996-present

\*Lipid extracts of bovine lung mince+DPPC, PG, PA (containing surfactant proteins -B and -C); †Mixture of phospholipid (not contained surfactant proteins -B and -C); ‡Chloroform/methanol extracts of porcine lung mince, purified by liquid gel electrophoresis (also containing surfactant proteins -B and -C).



and gestational period.

**Exogenous PS preparations used for therapy**

In Group I, Surfacten<sup>®</sup> (Japan) was the only available agent in Korea, and was used in all cases. Subsequently, several PS preparations were used, as follows; Surfacten<sup>®</sup> (70.5%) or Exosurf<sup>®</sup> (26.3%) in Group II; Surfacten<sup>®</sup> (35.4%), Newfactan<sup>®</sup>

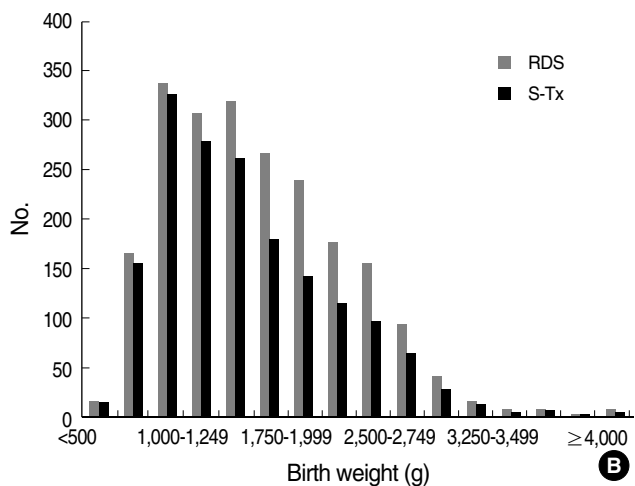
**Table 2.** Data collection for this multi-center study on the clinical use of surfactant therapy in neonatal respiratory distress syndrome in Korea

Groups	Years	Hospitals	No. of surfactant therapies	References
Group I	1990/91	16	60	5
Group II	1996	64	1,179	6
Group III	2002	62	1,595	7
Group IV	2007	57	1,921	This study

**Table 3.** Numbers of respiratory distress syndrome (RDS) patients and surfactant therapy cases

Groups	Total No. of RDS			No. of surfactant therapy		
	Inborn	Out-born	Total	Inborn	Out-born	Total
I	-	-	-	43	17	60
II	1,999	495	2,494	947 (47.4)	205 (41.4)	1,179 (47.3)
III	2,014	396	2,410	1,361 (67.6)	234 (59.1)	1,595 (66.2)
IV	2,154	319	2,473	1,694 (78.6)	216 (67.7)	1,921 (77.7)

(%), No. of surfactant therapy cases/total No. of respiratory distress syndrome cases.



**Fig. 1.** Total number of respiratory distress syndrome (RDS) cases and of pulmonary surfactant therapy cases (S-Tx) in Group IV (2007), by gestational period (A) and birth weight (B).

(64.1%), or a mixture (0.5%) in Group III; and Surfacten® (51.3%), Newfactan® (39.3%), Curosurf® (8.3%), or a mixture (1.1%) in Group IV (Fig. 2).

**Classifications for clinical interpretation**

Initial chest radiograph findings before PS replacement therapy were classified as Stage I, II, III, or IV using Bomsel's classification (8). The classification of Fujiwara et al. (9) uses ventilatory index as a respiratory index. Ventilatory index is calculated using  $FiO_2 \times \text{mean airway pressure (MAP)}/\text{arterial oxygen pressure (PaO}_2)$ . Using ventilatory index values, respiratory distress was classified into 3 groups in the present study, namely, mild respiratory distress  $<0.047$ ; moderate respiratory distress  $\geq 0.047$  and  $<0.133$ ; and severe respiratory distress  $\geq 0.133$ .

We classified the early response to PS therapy using the classification of Fujiwara et al. (10), which utilizes fraction of inspired oxygen ( $FiO_2$ ), MAP, and arterial-alveolar oxygen tension ratio ( $a/A PO_2$ ). Patients were classified into good response, relapse, and poor response groups. The good response group was composed of patients that showed clinical improvements in  $FiO_2$ , MAP, and  $a/A PO_2$  after PS administration. The relapse group was composed of patients that experienced a recurrence of respiratory distress after an initial good response, as determined using respiratory markers. Poor response group members showed no respiratory marker improvement and continued respiratory distress.

**RESULTS**

**Epidemiology**

The incidences of in-hospital-born RDS by birth weight and gestational period in Group IV are shown in Fig. 3. This data shows that RDS incidence increased with decreasing

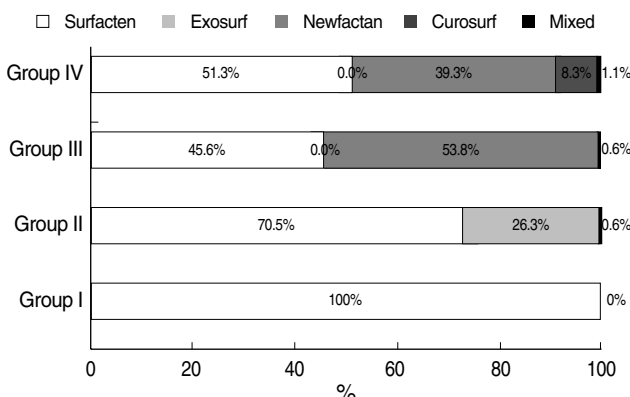


Fig. 2. Preparations of PS used to treat RDS patients in the four study Groups. Surfacten® (51.3%), Newfactan® (39.3%), Curosurf® (8.3%), and mixtures of these (1.1%) were administrated in Group IV.

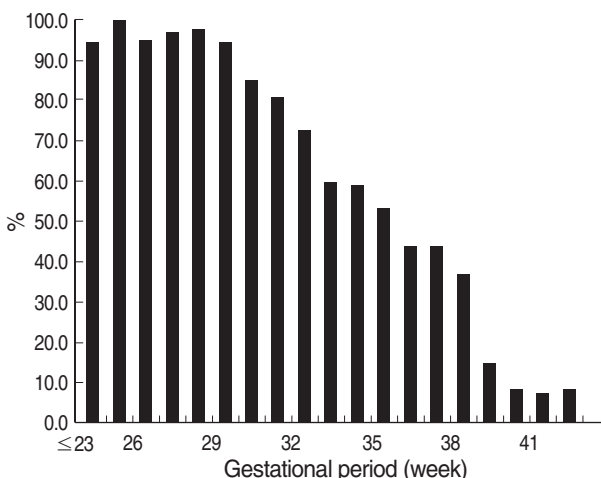


Fig. 4. Proportions of RDS patients in Group IV who received PS replacement therapy by gestational period. The figure shows that use of pulmonary surfactant therapy increased as gestational age is short.

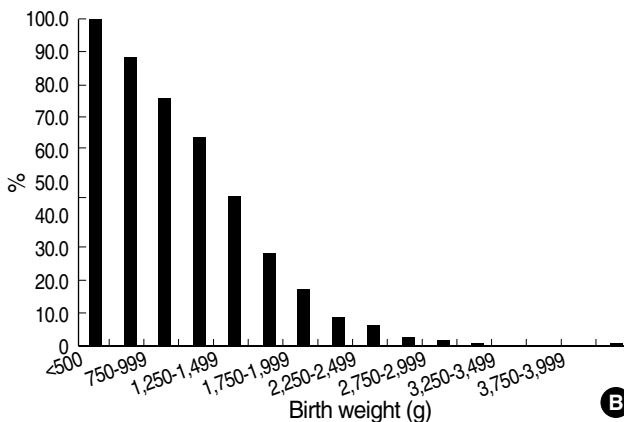
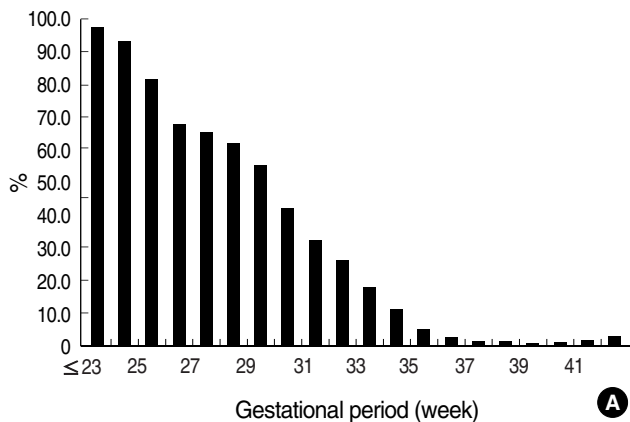


Fig. 3. Overall incidence of RDS by gestational period (A) and birth weight (B) among in-born neonates in Group IV. Gestational age and birth weight were found to be inversely proportional to the incidence of RDS.

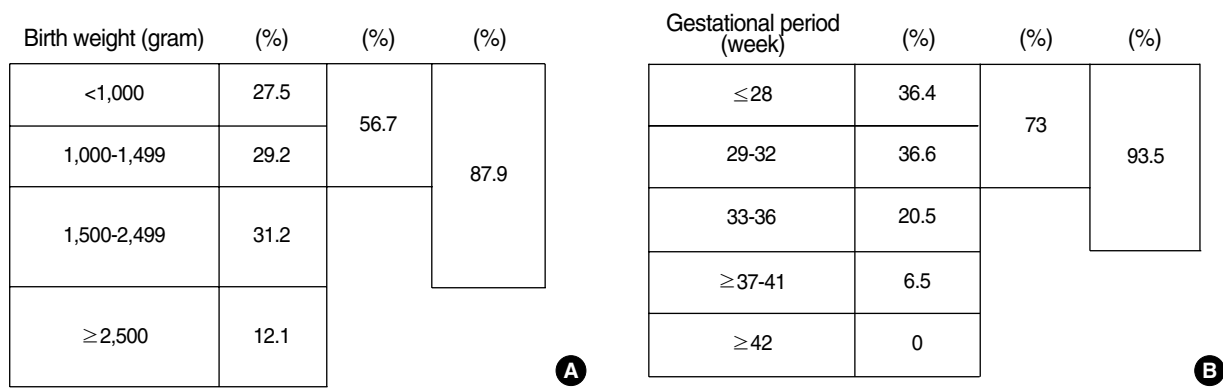


Fig. 5. Birth weight (A) and gestational period (B) distributions in RDS patients that received PS therapy. Low birth weight infants (<2,500 grams), very low birth weight infants (<1,500 grams), and extremely low birth weight infants (<1,000 grams) constituted 87.9%, 56.7%, and 27.5% of total RDS patients, respectively (A) and prematurity (gestational period <37 weeks) was 93% of total RDS patients (B).

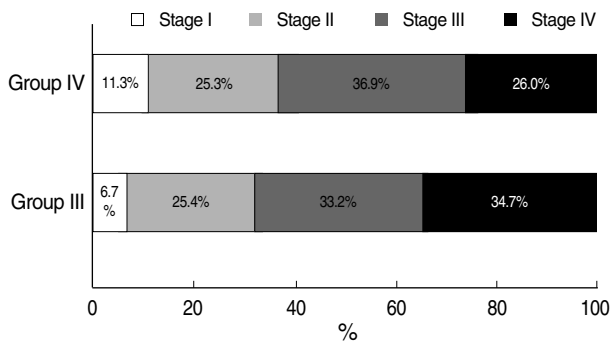


Fig. 6. Initial chest radiographic findings in Groups III (2002) and IV (2007). Initial chest radiographic findings before pulmonary surfactant therapy were classified using Bomsel's Classification. Patients with relatively severe RDS (stages III and IV) composed 67.7% and 62.9% of patients in Groups III and IV, respectively.

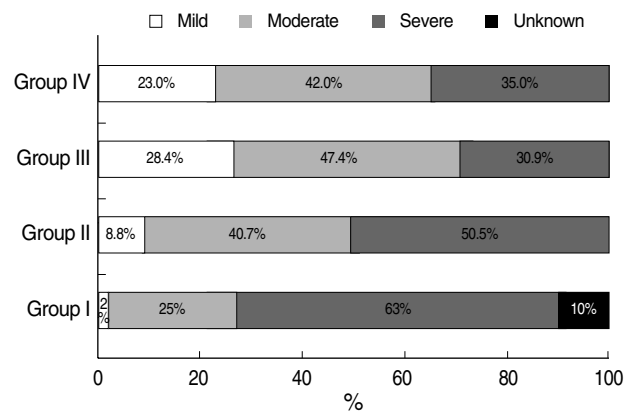


Fig. 7. Initial ventilatory indices of each study Group according to the classification of Fujiwara et al. (8). Ventilatory index is a recognized respiratory index. Mild respiratory distress patients were 23.0% of total RDS patients, moderately affected patients were 42.0%, and severe respiratory distress patients were 35.0% in Group IV.

birth weight and gestational period.

The proportions of patients in Group IV who received PS replacement therapy among all RDS births by gestational period are illustrated in Fig. 4. The data show that the need for PS replacement therapy increased with decreasing gestational period. Interestingly, PS replacement therapy was less used in patients with a birth weight of <500 g, presumably due to the abandonment of rescue therapy due to a perceived low likelihood of survival.

The distributions of birth weights and gestational periods among RDS patients in Group IV who received PS therapy are shown in Fig. 5. PS therapy was performed in 87.9% of low birth weight infants (<2,500 g) with RDS, in 56.7% of very low birth weight infants (<1,500 g), and in 27.5% of extremely low birth weight infants (<1,000 g).

Fig. 5 shows the distribution of RDS patients in Group IV who received PS replacement therapy by gestational period. In the Group III study, PS replacement therapy was conducted in 93.5% of preterm patients with RDS (gestational period <37 weeks), 6.4% of term patients with RDS (gesta-

tional period 37-42 weeks), and in no post-term patient with RDS (gestational period ≥42 weeks). When preterm patients were sub-grouped by gestational period, 20.5% of the gestational period 33-36 weeks subgroup underwent PS replacement therapy, 36.4% of the gestational period 29-32 weeks subgroup, and 36.4% of the gestational period <28 weeks subgroup.

### Clinical findings

In the surfactant treated RDS patients in Group IV, initial chest radiograph findings (before PS therapy) showed that 11.3%, 25.3%, 36.9%, and 26.0% of patients were of Stages I, II, III, and IV, respectively, according to Bomsel's classification. In Groups III and IV the rates of those with relatively severe RDS (Stage III and IV) were high at 67.7% and 62.9%, respectively (Fig. 6).

Distributions of severity according to ventilatory index in each Group before PS replacement therapy are shown in Fig. 7. In Group IV, 23.0%, 42.0%, and 35.0%, of patients had mild, moderate, or severe respiratory distress, respectively.

In Groups I and II, all cases received a single dose of PS, probably because repeated administrations were limited by medical insurance policies at that time. However, because repeated PS administration was approved in part prior to 2002, in Groups III and IV second and third administrations were reported in some cases. Single and multiple uses were reported in 79.9% and 20.1% of cases in Group III, and these were similar to those reported in Group IV (80.5% and 19.5%, respectively). Summarizing, multiple PS was used in about 20% of all RDS patients in Groups III and IV (Table 4).

In terms of early response to PS therapy, using the Fujiwara et al. classification, i.e., good response, relapse, and poor response, responses in Group IV were 69.2%, 14.4%, and 16.4%, respectively. Response results for Groups I, II, III, and IV are shown in Fig. 8.

Complications frequently developed during the management of RDS patients and preterm babies (Table 5). The occurrence rates of infections (including disseminated intravascular coagulopathy [DIC]) were high in Groups I, II, and III at 55.4%, 42.6%, and 47.4%, but the rate was appreciably lower in Group IV (25.3%). These changes were accompanied by decreases in pneumothorax and intraventricular hemorrhage. Furthermore, the frequencies of bronchopulmo-

Table 4. Surfactant doses (single vs. multiple doses)

Groups	Single dose (%)	Multiple doses (%)
I	100*	-
II	100*	-
III	79.9	20.1 <sup>†</sup>
IV	80.5	19.5 <sup>†</sup>

\*multiple doses not available due to limited insurance coverage, <sup>†</sup>multiple doses available due to supports of national insurance requirements.

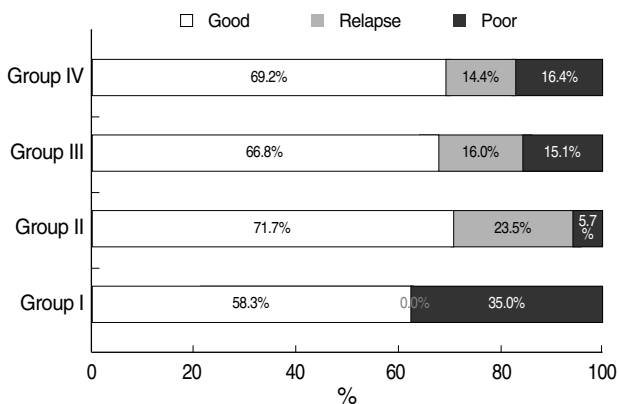


Fig. 8. Early response rates to pulmonary surfactant therapy in the four study groups. In Group IV, 69.2% responded well, 14.4% relapsed, and 16.4% responded poorly.

nary dysplasia (BPD) and retinopathy of prematurity (ROP) were found to be higher in Group IV, in parallel with the improved survival of extremely premature infants in 2007.

## Mortality

As shown in Fig. 9, mortality rates (defined as the percentage of neonates who died within 28 days of birth) dramatically decreased over the study period (40% in Group I, 30% in Group II, 18.7% in Group III, and 14.3% in Group IV).

Mortality rates of surfactant treated patients by birth weight and gestational period in Group IV are illustrated in Fig. 10. In term babies, mortality rates were found to be high, which appears to be due to some co-morbidities other than RDS

Table 5. Associated diseases and complications (%)

Diseases	Groups			
	I	II	III	IV
Sepsis, DIC	55.4	42.6	47.4	25.3
PDA	37.5	59.9	32.4	38.2
PTX & Pneumomediastinum	28.6	11.7	8.6	6.8
IVH (grade>2)	23.2	-	20.4	11.9
PIE	17.9	9.6	2.2	3.1
BPD (CLD)	15.4	17.8	17.0	23.1
PPHN	10.7	6.1	3.2	3.1
ROP	5.6	11.2	16.5	15.6
NEC	2.5	4.6	9	6.8
PH	-	12.7	-	7.8
Pneumonia	-	-	11.7	10.5
Cholestasis	-	-	7.7	9.7

DIC, disseminated intravascular coagulation; PDA, patent ductus arteriosus; PTX, pneumothorax; IVH, intraventricular hemorrhage; PIE, pulmonary interstitial emphysema; BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; PPHN, persistent pulmonary hypertension; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; PH, pulmonary hemorrhage.

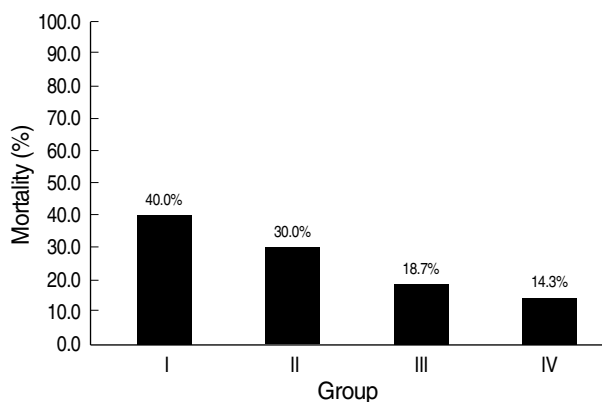


Fig. 9. Changes in RDS mortality rates over the past 17 yr among those that received PS replacement therapy. Mortality rates were found to have reduced dramatically, that is, from 40%, 30%, 18.7%, to 14.3% in Groups I (1990/1), II (1996), III (2002), and IV (2007), respectively.

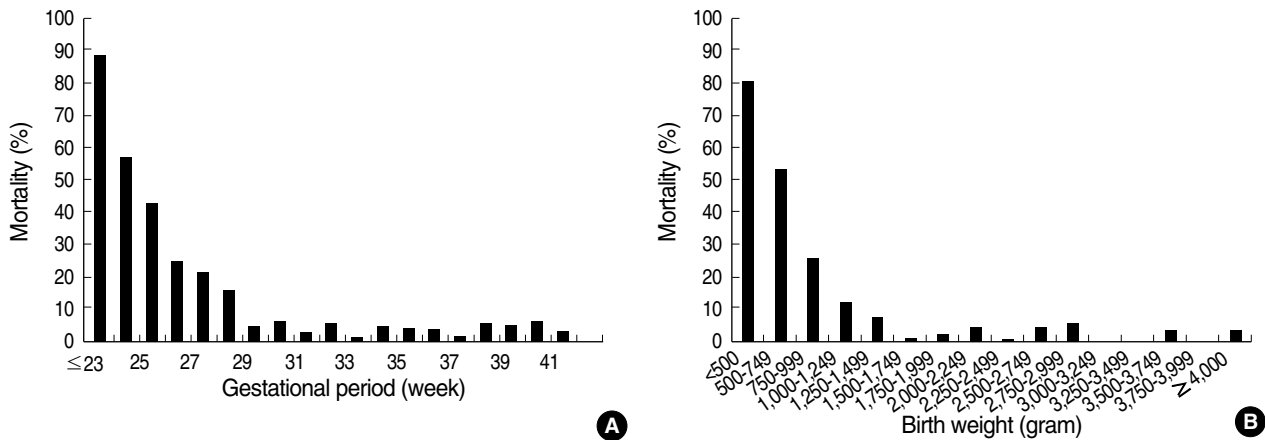


Fig. 10. The mortality rates of RDS patients in Group IV who received PS replacement therapy by gestational period (A) and birth weight (B). The figure shows that mortality rates were found to be inversely related to gestational age and birth weight.

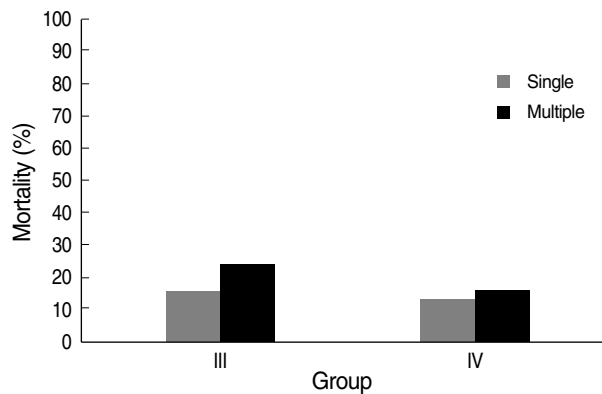


Fig. 11. The mortality rates among RDS patients who received PS therapy according to the number of PS treatments administered. Mortality rates for single use in Groups III and IV were 15.6% and 13.0%, respectively, and for multiple use were 24.1% and 16% in Groups III and IV. Presumably because more severe cases were administered multiple PS.

causing respiratory distress such as, persistent pulmonary hypertension, meconium aspiration, sepsis, and so on, which also influence negatively the function of surfactant. Many of co-morbidities are known to bring their clinical courses severe enough even leading to death.

As shown in Fig. 11, in Groups III and IV, mortality rates of those who underwent PS once were 15.6% and 13.0%, respectively. These rates were lower than mortalities among those who underwent repeated treatment (24.1% in Group III and 16% in Group IV), probably because more severe cases were administered multiple PS.

### DISCUSSION

In 1980, Fujiwara et al. (2) first successfully administered exogenous PS to preterm infants with RDS, and subsequently several PS preparations were developed. These preparations

have since been shown to reduce mortality and morbidity effectively among RDS patients by several double blind, randomized, controlled studies. Today PS replacement therapy has become a routine method of treating infants with RDS.

The PS preparations used today are either animal-sourced or synthesized. Animal-sourced agents, include; 1) Alveofact® (Bovactant, Germany), BLES® (Canada), Infasurf® (Calfactant, U.S.A.), Survanta® (Beractant, U.S.A.), Surfacten® (Surfactant-TA, Japan), and Newfactan® (Korea), which are all extracted from bovine lungs, and 2) Curosurf® (Poractant alfa, Italy) from porcine lungs. Synthetic agents include; ALEC® (Pulmactant, U.K., no longer manufactured), Exosurf® (Colfosceril palmitate, U.S.A.); phospholipid synthetics, and Surfaxin® (Lucinactant, U.S.A., not FDA licensed), a surfactant protein B synthetic (11). Of these, Surfacten®, Newfactan®, and Curosurf® are currently being used, but Exosurf®, which was used for short time, is no longer available in Korea. The PS agents used in Korea are listed in Table 1.

Surfacten® and Newfactan® contain phospholipids extracted from bovine lung, and surfactant proteins -B and -C, which increase surface physical activity and reduce surface tension on the alveolar surface. Curosurf® is produced from porcine lung by chloroform/methanol extraction and liquid gel electrophoresis for purification, and contains surfactant proteins -B and -C. In Group IV, Surfacten® (51.3%) was administered in more than half cases, and Newfactan® (39.3%), Curosurf® (8.3%), and mixtures of these agents (1.1%) were followed. Several meta-analyses concluded that PS replacement therapy reduces mortality in RDS patients. In 1993, Jobe et al. (12) after integrating results from 1985 to 1992, reported that mortality is decreased by PS therapy when used as a prophylactic or rescue therapy with an odds ratio of 0.6. Furthermore, in 1993 Ptamanik et al. (13) reported that PS agents of synthetic or animal origin administered as prophylactic or rescue therapies effectively reduce mortality among RDS patients (odds ratio 0.5-0.6). In a meta-analysis conducted by the Committee on Fetus and Newborn of the American

Academy of Pediatrics (2008) (14), attributed remarkable reductions in the mortalities of RDS patients to these agents (odds ratio of 0.6 for agents of animal origin and of 0.7 for those of synthetic origin when administered with prophylactic intent; and of 0.67 for agents of animal origin PS and 0.73 for those of synthetic origin when administered as rescue therapies).

The use of PS therapy obviously decreased mortality among Korean RDS patients over the 17-yr study period, i.e., from 40.0%, 30.0%, 18.7%, and 14.3% for the periods 1990/91, 1996, 2002, and 2007, respectively. Furthermore, PS therapy reduced mortalities not only among RDS patients, but also among prematurities and neonates in Korea. In the pre-PS era (before 1990), mortality due to RDS was much higher. In addition, several advances in neonatal supportive care, such as, improvements in artificial ventilator strategies, and the prevention and early management of infections and complications, have also undoubtedly contributed to these reductions in mortality (15-17).

A double blind, randomized, controlled study on Surfacten® conducted in Japan found lower mortality among RDS patients (8%, birth weight <1,750 g) than we found in the present study (9). On the other hand, other double blind, randomized, controlled study performed on Survanta®, which has the same composition as Surfacten®, reported a RDS mortality of 18.4% (birth weight <1,750 g) (18).

In the present study, we investigated the frequency of RDS among in-hospital-born patients in 2007 treated at 57 hospitals and found that the frequency of RDS decreases as birth weight is light or gestational period is short.

Furthermore, in the present study, PS was administered to a greater proportion of RDS patients with time, i.e., 47.3%, 66.2%, and 77.7% in Groups II, III, and IV, respectively. This appears to be due to changed attitude of the Korean Medical Insurance Association in terms of PS administration. In terms of our 2007 data, rates of PS use were found to be greater in patients with a smaller gestational period, which implies that RDS is more severe among these patients. Furthermore, PS replacement therapy was used in 87.9% of low birth weight infants (<2,500 g) and in 56.7% of very low birth weight infants (<1,500 g) in terms of birth weight, and in 93.5% of preterm infants in terms of gestational period (especially 73% had a gestational period of <32 weeks). In brief, infants with a gestational period of <32 weeks and a birth weight of <1,500 g were major members.

In terms of the classification of initial chest radiographic findings in RDS patients, stage distributions were similar for Groups III and IV. The proportions of patients with stage III or IV (severely affected) composed about 2/3 of Groups III and IV, which confirms that patients with more severe initial chest findings by radiography require more PS therapy.

Initial respiratory distress classifications using ventilatory index showed that patients who received PS therapy in Groups I and II had milder conditions than those in Groups III and

IV, which appears to be due to the extended indication for PS referred to above. Groups III and IV had similar initial respiratory distress distributions. In Group IV, 23.0% had mild respiratory distress, 42.0% had moderate, and 35.0% had severe respiratory distress. Furthermore, those with moderate or severe respiratory distress constituted as much as 77% of Group IV RDS patients, and thus, more aggressive management is required in these patients.

Korean medical insurance policies did not permit multiple administration of PS in 1990/91 (Group I) or in 1996 (Group II), when only a single dose was administered in all cases. However, the policy was changed to a direction permitting multiple dose in 2001. In Groups III and IV multiple administrations were performed in roughly 1/4 of cases. In Groups III and IV 14.4% and 16.0% of patients relapsed and these patients were treated with multiple doses of PS.

The classification of early response to the PS treatment showed better results in Groups III and IV than in Groups I and II. In Group IV, 69.2% responded well, 14.4% relapsed, and 16.4% responded poorly, which means that about 1/5th of RDS patients relapsed after initial PS treatment. In a Japanese report (10), 79% responded well, 16% relapsed, and 5% responded poorly, which is a substantially better response rate that observed in our 2007 study.

To improve the prognosis of RDS patients early detection and adequate management of co-morbidities, including associated diseases and complications, are as important as general supportive care. We examined data for the past 17 yr in terms of complications and associated diseases that developed during the management of RDS patients and preterm babies (Table 5).

Mortalities of RDS neonates in Korea were found to dramatically improve over the 17-yr study period, i.e., from 40.0%, 30.0%, 18.7%, to 14.3% for 1990/91, 1996, 2002, and 2007, respectively. Furthermore, our study of birth weights and gestational periods showed that both are inversely related to mortality, which means that these high-risk patients require more attention.

In this longitudinal study, we analyzed clinical findings, disease severity, dose schedule of PS administration, response to treatment, associated diseases, complications, and mortalities, with respect to RDS and PS treatment in neonates over a 17-yr period in Korea. We conclude that surfactant treatments in neonates with RDS have had a marked impact on clinical course and outcome, together with substantial reduction of mortality rates among RDS patients over the last 17 yr in Korea.

## LIST OF CONTRIBUTORS

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