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Comparison of Clinical Efficacy of Newfactan® versus Surfacten® for the Treatment of Respiratory Distress Syndrome in the Newborn Infants

Newfactan® is a domestically developed, bovine lung-derived, semi-synthetic surfactant. The aim of this study was to compare the clinical efficacy of Newfactan® with that of Surfacten® in the treatment of respiratory distress syndrome (RDS). Newfactan® or Surfacten® was randomly allocated to 492 newborn infants who were diagnosed as RDS and required surfactant instillation in four participating hospitals. The comparisons were made individually in two subsets of infants by birth weight (<1,500 g group [n=253] and ≥1,500 g group [n=239]). Short-term responses to surfactant and acute complications, such as the total doses of surfactant instilled, response type, extubation rate, ventilator settings, changes in respiratory parameters, air leak, patent ductus arteriosus, pulmonary hemorrhage, and intraventricular hemorrhage, and mortality during the 96 hr after surfactant instillation were measured. Long-term outcome and complications, such as total duration of intubation, bronchopulmonary dysplasia and periventricular leukomalacia, and ultimate mortality were measured. There were no significant differences in demographic and perinatal variables, short-term responses to surfactant and acute complications, and long-term outcome and complications between Newfactan® and Surfacten® in both birth weight groups. We concluded that Newfactan® was comparable to Surfacten® in the clinical efficacy in the treatment of RDS in both birth weight groups.

Key Words : *Newfactan®; Surfacten®; Pulmonary Surfactants; Respiratory Distress Syndrome, Newborn*

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INTRODUCTION

Pulmonary surfactant is the cornerstone of the treatment of respiratory distress syndrome (RDS) in the newborn infants. A number of pulmonary surfactants have been developed, but only several agents are used in the present days in the world (1). In Korea, Surfacten® and Exosurf® came into the market in 1990, and Curosurf® in 1996. Surfacten® and Curosurf® are modified natural surfactants derived from bovine and porcine lung, respectively. While on the other, Exosurf® is a purely synthetic surfactant. However, Exosurf® has dropped out of the market before long, and Surfacten® imported from Japan has been the most commonly prescribed pulmonary surfactant for the treatment of RDS in the newborn infants in Korea since the first clinical report by Namgung et al. (2) and the following multi-center clinical trial by Bae et al. (3, 4). However, because of the high cost of Surfacten®, the need for less expensive domestic pulmonary surfactant agent has emerged. Thereupon, Newfactan®, a semi-synthetic pulmonary surfactant derived from bovine lung, was co-developed by a domestic pharmaceutical company and a medical college. Both in vitro and in vivo studies confirmed the efficacy of Newfactan® (5, 6). However, the clinical data on the efficacy of Newfactan® are scant (7-9), especially in extremely low birth weight infants whose survival rate has improved remarkably recently. The initial clinical report on its efficacy in RDS was not a comparative study, but a single agent study (7). A single comparative study of Newfactan® with Surfacten® was done so far (8). In that study, a total of 60 newborn infants were enrolled with 30 infants in each surfactant group. There were no differences in the efficacy in the treatment of RDS, the incidence of complications, and mortality between Surfacten® and Newfactan® groups. However, this study has some limitations as the authors mentioned in the discussion. Firstly, the number of the newborn infants enrolled was small because only two centers participated in the study. Secondly, the study lacks the data on the extremely low birth weight infants, especially the infants with birth weight of less than 800 g, whose survival rate has improved dramatically recently. Therefore, further comparative studies with the larger number of newborn infants, especially the extremely low birth weight infants whose birth weight was less than 1,000 g are required to verify

the comparability of Newfactan® to Surfacten® in clinical efficacy in the treatment of RDS. Therefore, we did a multi-center clinical comparative study enrolled a fairly large number of the newborn infants, especially the extremely low birth weight infants. A total of 112 extremely low birth weight infants were included in our subjects.

MATERIALS AND METHODS

Subjects

A total of 492 newborn infants who were admitted to the neonatal intensive care units in four hospitals: Samsung Seoul Hospital; Samsung Cheil Hospital; Kangnam Cha Hospital; and Soonchunhyang University Bucheon Hospital and diagnosed as RDS, and judged to require pulmonary surfactant instillation therapy between May 2002 and July 2004 were enrolled. The diagnosis of RDS and the judgment of the requirement for surfactant instillation therapy were made by the staff neonatologists at each participating hospital. Newborn infants who had a major congenital anomaly were excluded.

Institutional review board (Samsung Seoul Hospital, Seoul, Korea) approved the study protocol and informed consent was obtained from a parent before study participation.

Study protocol

Newfactan® or Surfacten® was randomly allocated and instilled to the newborn infants who were newly enrolled to the study during the study period. The order of allocation was individualized by each participating hospital. The two surfactants were alternatively allocated in two stratified blocks by birth weight, which are <1,500 g and ≥1,500 g block. However, in the hospitals where the infants with a birth weight of less than 1,500 g were in the minority, the allocation was done without stratification.

The method of surfactant instillation was the same among the four participating hospitals. Surfactant instillation was used as a rescue therapy. Newfactan® or Surfacten® was dissolved in 4 mL of 0.9% saline and 4 mL/kg of the dissolved solution was instilled into the trachea via endotracheal tube by using orogastric tube. To distribute the surfactant to the whole lung evenly, four-position method was used. Surfactant was instilled to a maximum of 3 doses according to the infant's condition. Second or third dose was given after 6 hr when the infant became worse clinically and radiologically at the staff neonatologist's discretion.

Outcome measures

The comparisons of outcome were also done by stratifying the subject infants into two subgroups by birth weight, which are <1,500 g group and ≥1,500 g group. Short-term responses to surfactant and acute complications include the total doses of surfactant instilled, response type, extubation rate, changes in respiratory parameters, air leak, patent ductus arteriosus, pulmonary hemorrhage, intraventricular hemorrhage, and short-term mortality during the 96 hr after surfactant instillation. Long-term outcome and complications include the total duration of intubation, bronchopulmonary dysplasia (BPD) and periventricular leukomalacia, and ultimate mortality.

We chose arterial-alveolar oxygen ratio ($a/APO_2=PaO_2/[713 \times FiO_2-PaCO_2/0.8]$) and ventilatory index (VI=mean airway pressure $\times FiO_2/PaO_2$) (10) as respiratory parameters. The response type to surfactant was defined into three types: 'Favorable' when VI dropped below 0.047 within 6 hr after surfactant instillation; 'Relapse' when VI rebounded above 0.047 between 6 and 96 hr after surfactant instillation among 'favorable' cases; and 'Poor' when VI did not drop below 0.047 within 6 hr after surfactant instillation (11). When the infant was already extubated, the response type was assigned to "Favorable", FiO_2 to 21%, and mean airway pressure (MAP) to 0 cmH_2O. Extubation was defined as a successful extubation that does not require re-intubation within 7 days after the extubation. Air leak includes pneumothrax, pneumomediastinum, and pulmonary interstitial emphysema. Patent ductus arteriosus was diagnosed by echocardiography and only symptomatic cases were identified. Intraventricular hemorrhage and periventricular leukomalacia were diagnosed by brain ultrasonography, and only high-grade (≥grade III) intraventricular hemorrhage was identified. Periventricular leukomalacia was identified only in infants who survived more than 28 days after birth. Pulmonary hemorrhage was diagnosed when the fresh blood gushed out of the endotracheal tube in the presence of typical chest radiography finding. The diagnosis of BPD was made in the infants who needed supplemental oxygen at 36 wk postmenstrual age (gestational age <32 wk) or for more than 28 days after birth (gestational age ≥32 wk) with consistent radiographic change (persistent hazy opacification or cystlike pattern of density and lucency) (11). BPD was also identified only in the infants who survived more than 28 days after birth.

Statistical methods

Statistical analyses were done by using SPSS version 11.5 (SPSS Inc. Chicago, IL, U.S.A.). All categorical variables were expressed as percent (%) and continuous variables were expressed as mean±standard deviation. Categorical variables between Newfactan® group and Surfacten® group were compared by chi-square test or Fisher's exact test. Continuous variables were compared by Student t-test or Mann-Whitney *U* test. Repeatedly measured variables like respiratory parameters were compared by using repeated measures ANOVA. *P* value of less than 0.05 was considered significant. The statistical analyses were supervised by a biomedical statistician at Samsung Seoul Hospital.

RESULTS

Demographic variables

Of a total of 492 newborn infants, 224 infants were given Newfactan® (Newfactan® group) and 268 infants were given Surfacten® (Surfacten® group), and 253 infants had the birth weight of less than 1,500 g (<1,500 g group) and 239 infants had the birth weight of more than 1,500 g (≥1,500 g group). The followings are the distribution of enrolled infants according to the participating hospital: 180 infants in Samsung Seoul Hospital; 156 infants in Samsung Cheil Hospital; 124 infants in Kangnam Cha Hospital; 32 infants in Soonchunhyang University Bucheon Hospital (Fig. 1). A total of 112 extremely low birth weight infants were included in <1,500 g group, which consisted of 13 infants with a birth weight of <600 g, 41 infants with a birth weight of 600-799 g, and 58 infants with a birth weight of 800-1,000 g (Fig. 1).

There were no significant differences in birth weight (1,074±255 g for Newfactan® group versus 1,031±276 g for Surfacten® group) and gestational age (28.1±2.3 vs. 28.4±2.6 wk) between Newfactan® group and Surfacten® group in <1,500 g group as well as in ≥1,500 g (birth weight 2,496±714 vs. 2,346±596 g, gestational age 35.2±3.0 vs. 34.6±3.0 wk). There were no significant differences in sex ratio between Newfactan® group and Surfacten® group in both birth weight groups (Table 1).

Perinatal variables

There were no significant differences in perinatal variables between Newfactan® group and Surfacten® group in both <1,500 g group and ≥1,500 g group (Table 1).

The respiratory parameters just before the surfactant instillation indicating the severity of RDS, such as FiO_2, MAP, VI, and a/APO_2 were not significantly different between Newfactan® group and Surfacten® group in both birth weight groups (pretreatment values in Fig. 2, 3).

Short-term responses to surfactant and acute complications

In <1,500 g group, the total doses of surfactant instilled were not significantly different between Newfactan® group

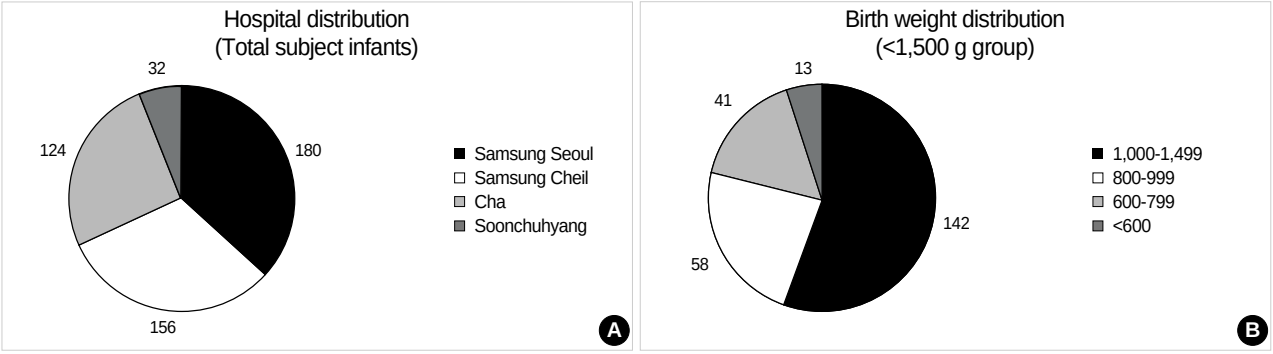

Fig. 1. The distribution of total subject infants according to the participating hospitals (A) and the distribution of the infants in <1,500 g group according to birth weight (B). The figures designate the number of infants.

Table 1. Comparisons of demographic and perinatal variables between Newfactan® group and Surfacten® group

	<1,500 g (n=253)			≥1,500 g (n=239)		
	Newfactan (n=99)	Surfacten® (n=154)	*p*	Newfactan (n=125)	Surfacten® (n=114)	*p*
Birth weight (g)	1,074±255	1,031±276	0.21	2,496±714	2,346±596	0.08
Gestational age (wk)	28.4±2.6	28.1±2.3	0.19	35.2±3.0	34.6±3.0	0.10
Male sex (%)	45 (46)	85 (58)	0.08	65 (57)	70 (65)	0.21
1 min Apgar score	3.4±1.7	3.1±1.6	0.27	6.6±1.8	6.1±2.1	0.08
5 min Apgar score	6.0±1.6	5.5±2.2	0.34	8.0±1.4	7.7±1.7	0.22
Twin (%)	30 (30)	56 (36)	0.32	23 (18)	28 (25)	0.25
PPROM (%)	30 (33)	47 (33)	1.00	26 (23)	34 (31)	0.18
SGA (%)	17 (17)	22 (14)	0.54	2 (2)	4 (4)	0.35
C/S (%)	70 (72)	121 (80)	0.15	96 (79)	87 (80)	0.93
PIH (%)	19 (19)	40 (26)	0.23	6 (5)	10 (9)	0.22
Chorioamnionitis (%)	18 (27)	15 (16)	0.07	1 (1)	2 (3)	0.51
Antenatal steroid (%)	48 (52)	70 (48)	0.55	24 (20)	23 (21)	0.86

PPROM, Preterm premature rupture of membrane; SGA, Small for gestational age; C/S, Caesarean section delivery; PIH, Pregnancy induced hypertension.

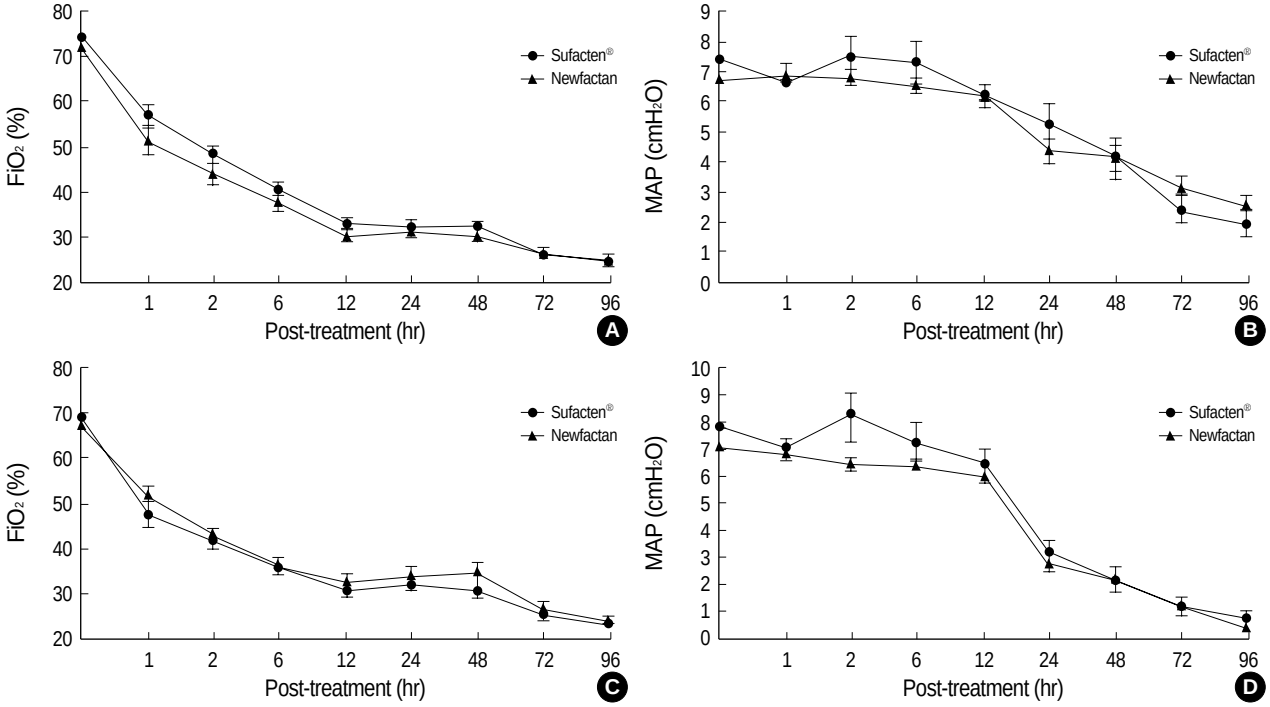

Fig. 2. The time courses of FiO_2 and mean airway pressure (MAP) over the 96 hr after surfactant instillation between Newfactan® group and Surfacten® group in <1,500 g group and ≥1,500 g group. (A) FiO_2 in <1,500 g group; (B) Mean airway pressure in <1,500 g group; (C) FiO_2 in ≥1,500 g group; (D) mean airway pressure in ≥1,500 g group. There were no significant differences in the time courses of FiO_2 and mean airway pressure in both <1,500 g group and ≥1,500 g group.

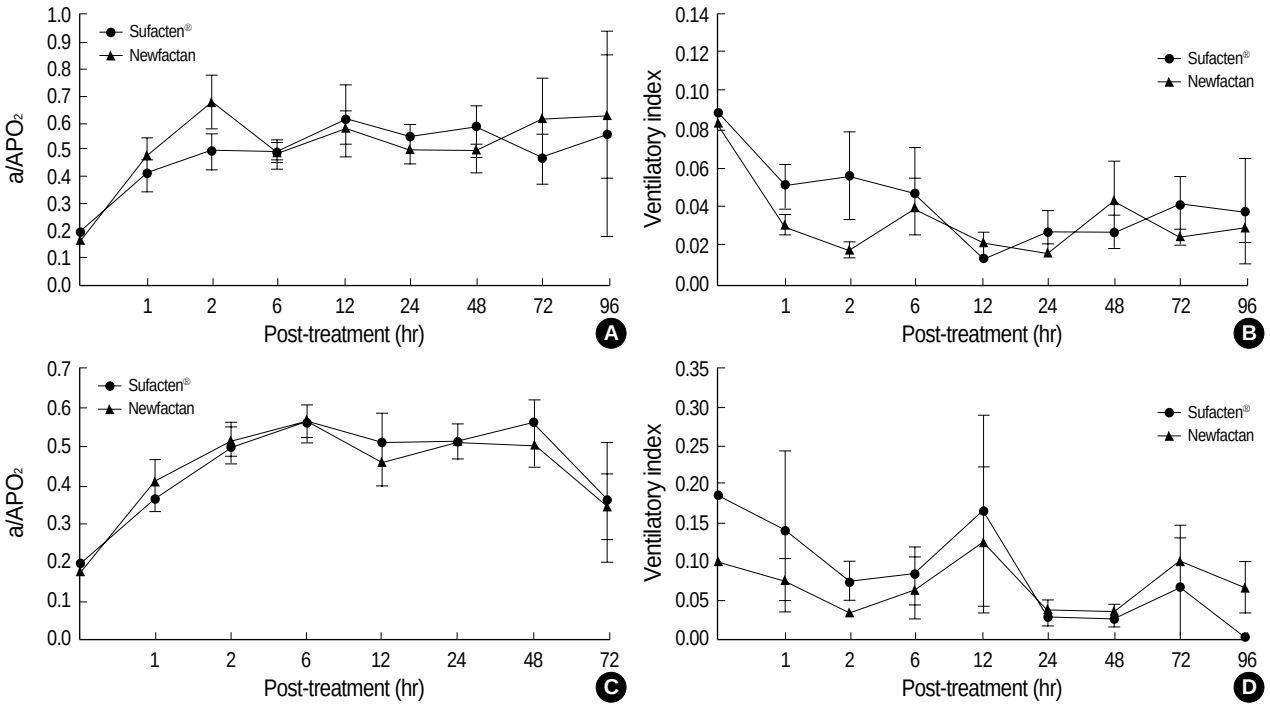

Fig. 3. The time courses of arterial-alveolar oxygen ratio (a/APO_2) and ventilatory index (VI) over the 96 hr after surfactant instillation between Newfactan® group and Surfacten® group in <1,500 g group and ≥1,500 g group. (A) a/APO_2 in <1,500 g group; (B) VI in <1,500 g group; (C) a/APO_2 in ≥1,500 g group; (D) VI in ≥1,500 g group. There were no significant differences in the time courses of a/APO_2 and VI in both <1,500 g group and ≥1,500 g group.

Table 2. Comparisons of the total doses of surfactant instillation, the response type to surfactant, and extubation rate by the 96 hr after surfactant instillation between Newfactan® group and Surfacten® group

	<1,500 g (n=253)			≥1,500 g (n=239)		
	Newfactan® n=99	Surfacten® n=154	*p*	Newfactan® n=125	Surfacten® n=144	*p*
1 Dose (%)	74 (75)	118 (77)	0.21	109 (87)	102 (90)	0.37
2 Doses (%)	23 (23)	35 (23)	0.21	16 (13)	12 (10)	0.37
3 Doses (%)	2 (2)	0	0.21	0	0	0.37
'Favorable' type (%)	83 (84)	134 (87)	0.38	104 (83)	96 (84)	0.91
'Poor' type (%)	9 (9)	15 (10)	0.38	14 (11)	13 (11)	0.91
'Relapse' type (%)	7 (7)	5 (3)	0.38	7 (6)	5 (5)	0.91
Extubation (%)	46 (55)	68 (52)	0.73	100 (83)	93 (89)	0.15

Table 4. Comparisons of the total duration of intubation, the incidence of long-term complications, and the ultimate mortality between Newfactan group and Surfacten® group

	<1,500 g (n=253)			≥1,500 g (n=239)		
	Newfactan® n=99	Surfacten® n=154	*p*	Newfactan® n=125	Surfacten® n=144	*p*
Intubation duration (d)	14.3± 18.6	12.2± 18.8	0.38	3.7± 3.2	3.6± 2.6	0.66
BPD* (%)	10 (13)	10 (9)	0.12	1 (1)	1 (0)	0.27
PVL* (%)	1 (1)	9 (8)	0.12	5 (5)	2 (2)	0.12
Mortality (%)	18 (20)	32 (24)	0.50	4 (4)	4 (4)	0.87

BPD, Bronchopulmonary dysplasia; PVL, Periventricular leukomalacia.
*BPD and PVL was identified only in the infants who survived more than 28 days after birth.

and Surfacten® group. 75% of the infants in Newfactan® group and 77% of the infants in Surfacten® group received only one dose of surfactant, and 23% of the infants in both Newfactan® group and Surfacten® group received two doses. Only two infants in Newfactan® group received three doses of surfactant. There was no significant difference in the response type to surfactant between Newfactan® group and Surfacten® group. The 'Favorable' type was observed in 84% of the infants in Newfactan® group and in 87% of the infants in Surfacten® group. The 'Poor' type was observed in 9% of the infants in Newfactan® group and 10% of the infants in Surfacten® group. The 'Relapse' type was observed in 7% of the infants in Newfactan® group, and in 3% of the infants in Surfacten® group. The extubation rate by the 96 hr after surfactant instillation was not significantly different between Newfactan® group and Surfacten® group. 55% of the infants in Newfactan® group, and 52% of the infants in Surfacten® group were extubated by the 96 hr after surfactant instillation (Table 2).

In ≥1,500 g group, the total doses of surfactant instilled were not significantly different between Newfactan® group and Surfacten® group (one dose 87 vs. 90%, two doses 13 vs. 10%). No infants in either group received three doses of surfactant. There was no significant difference in the response type to surfactant between Newfactan® group and Surfacten® group ('Favorable' 83 vs. 84%, 'Poor' 11 vs. 11%, 'Relapse' 6 vs. 5%). The extubation rate by the 96 hr after surfactant instillation was not significantly different between Newfactan® group and Surfacten® group (83 vs. 89%) (Table 2).

Table 3. Comparisons of the incidences of acute complications and short-term mortality during the 96 hr after surfactant instillation between Newfactan group and Surfacten® group

	<1,500 g (n=253)			≥1,500 g (n=239)		
	Newfactan® n=99	Surfacten® n=154	*p*	Newfactan® n=125	Surfacten® n=144	*p*
Air leak (%)	10 (10)	13 (9)	0.73	10 (8)	8 (7)	0.75
PDA (%)	62 (63)	82 (55)	0.24	26 (21)	34 (30)	0.11
PH (%)	16 (16)	15 (10)	0.13	4 (3)	2 (2)	0.48
High-grade IVH (%)	5 (5)	9 (7)	0.70	0	2 (2)	0.15
Mortality (%)	11 (12)	15 (10)	0.67	5 (4)	5 (5)	0.87

PDA, Patent ductus arteriosus; PH, Pulmonary hemorrhage; IVH, Intraventricular hemorrhage.

The time courses of FiO_2, MAP, a/APO_2 and VI over the 96 hr after surfactant instillation were not significantly different between Newfactan® group and Surfacten® group in both birth weight groups (Fig. 2, 3).

The incidences of air leak, patent ductus arteriosus, pulmonary hemorrhage, and high-grade intraventricular hemorrhage, and short-term mortality during the 96 hr after surfactant instillation were not significantly different between Newfactan® group and Surfacten® group in both birth weight groups (Table 3).

Long-term outcome and complications

Total duration of intubation was not significantly different between Newfactan® group and Surfacten® group (14.3±18.6 days versus 12.2±18.8 days) in <1,500 g group, as well as in ≥1,500 g group (3.7±3.2 vs. 3.6±2.6 days). The incidences of BPD and periventricular leukomalacia and the ultimate mortality were not different between two surfactant groups in both birth weight groups (Table 4).

DISCUSSION

Our data showed that there were no significant differences in the efficacy in the treatment of RDS and in the incidence of acute complications occurring around the surfactant instillation therapy between Newfactan® and Surfacten®. In the ultimate mortality and long-term complications including BPD and periventricular leukomalacia, there were also no differences between the two surfactants.

There has been an urgent need for the clinical data that could support the clinical comparability of Newfactan®, a less

expensive domestically-developed surfactant, to Surfacten® for Newfactan® to be used nation-wide as a primary pulmonary surfactant agent in the treatment of RDS in Korea. The results of the first clinical comparative study were already published in 2000 (8). However, because it had a relatively small sample size and lacks the population of extremely low birth infants whose birth weight was less than 800 g, further large-scale clinical study has been required. Our study has a clinical significance in that it is a multi-center study enrolled as many as 492 newborn infants, especially 112 extremely low birth weight infants whose birth weight was less than 1,000 g. Although the data were not shown, like in <1,500 g group and ≥1,500 g group, there were also no statistically significant difference in the short-term responses and acute complications and long-term outcome and complications between Newfactan® group and Surfacten® group in the subgroup of infants whose birth weight was less than 1,000 g.

The two surfactants were alternatively allocated with stratified block randomization, which is <1,500 g and ≥1,500 g block. However, at a part of participating hospitals where the infants with a birth weight of less than 1,500 g were in the minority, the allocation was done without stratification. This seems to be the origin of the size discrepancy between the two surfactant groups in <1,500 g group. Due to the vague reliance on Surfacten® over Newfactan®, the attending physicians seem to have prescribed Surfacten® instead of Newfactan® in Newfactan's turn of the original allocation order at those hospitals when the birth weight of newly enrolled infant was less than 1,500 g, resulting in the disruption of the original allocation order. This problem of disordered randomization may be a major drawback of our study. Nevertheless, the results of our study are not thought to be nullified. We also compared the outcome by stratifying the subject infants by birth weight. After the stratification, there were no statistically significant differences in demographic and perinatal variables between the two surfactant groups in both <1,500 g group and ≥ 1,500 g group. This implicates that the two surfactant groups in each stratum are similar in baseline conditions and therefore comparable to each other. Therefore, the results of our study are considered to remain to be valid.

The reason why we stratified the subject infants by birth weight is that the etiology and clinical course of RDS in each subgroup were considered to be different. The etiology of RDS in <1,500 g group may be primarily attributable to absolute deficiency of pulmonary surfactant pool and its course may be complicated due to a number of problems arising from the prematurity itself. On the other hand, the etiology of RDS in ≥1,500 g group may be more complex. Besides the absolute deficiency of surfactant pool, conditions that lead to secondary surfactant inactivation such as asphyxia, infection and aspiration of meconium or blood might be responsible (1, 13). However, the clinical course of RDS in ≥1,500 g group may be, if not all, uncomplicated. Once the RDS has resolved, the majority of infants in this group seem to go uneventful until the discharge. This rationale for the stratification seems to be partially validated by our data. The extubation rate, the incidence of patent ductus arteriosus, pulmonary hemorrhage, and high-grade intraventricular hemorrhage, and short-term mortality during the 96 hr after surfactant instillation, total duration of intubation, and the ultimate mortality were significantly different between <1,500 g group and ≥1,500 g group. However, contrary to our expectation, the total doses of surfactant instillation and the response to surfactant instillation therapy were not different between the two birth weight groups. This stratification in the outcome analyses are considered to have made our results more clinically relevant.

In the time courses of a/APO_2 and VI in ≥1,500 g group, there is a tendency that respiratory status is aggravated again later in the course after surfactant instillation. However, this finding might have originated from the fact that a/APO_2 and VI were obtained only from the infants who took the blood gas analysis. Because the infants who took blood gas analysis until later in the course after surfactant instillation might have had relatively severe and complicated course of RDS, these later aggravations observed in the time courses of a/APO_2 and VI might be the reflections of these infants.

In the present multi-center post-marketing comparative study, Newfactan® showed no differences in the efficacy in the treatment of RDS and in the incidences of acute and long-term complications, compared to Surfacten® in both <1,500 g group and ≥1,500 g group.

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