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Comparison of Outcomes according to the Time of Initial Surfactant Treatment for Very Low Birth Weight Infants: A Multicenter Study

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Purpose : The prophylactic surfactant treatment has been found to improve patient outcomes, compared to the rescue treatment. We performed a multicenter study to determine the relationship between the timing of the initial surfactant treatment and patient outcomes.

Methods : One hundred and seventy one neonates, born at eight different centers, from January 1, 2004 to December 31, 2005, were enrolled. The included subjects were gestational age less than 34 weeks, birth weights less than 1500 g and had respiratory distress syndrome (RDS) that received surfactant. First, a group that received surfactant within two hours after birth was compared to a group that received surfactant after two hours. Next, a group that received surfactant within 30 minutes after birth was compared to a group that received surfactant after 30 minutes.

Results : The mean time after birth at which the initial surfactant was administered to neonates was 140.0 ± 114.3 minutes. The incidence of patent ductus arteriosus (PDA), duration of ventilatory support and hospital days were significantly reduced in the group that received surfactant within two hours after birth. The incidence of PDA and duration of ventilatory support were significantly reduced in the group that received surfactant within 30 minutes after birth.

Conclusion : Surfactant treatment should be provided to premature infants, as soon as possible.

Key Words : Pulmonary surfactant, Very low birth weight infants, Respiratory distress syndrome, Newborn

Respiratory distress syndrome (RDS) is the single most important cause of illnesses and deaths in preterm infants.[1] However, since surfactant replacement therapy has been available as a safe and an effective therapy of immaturity-related surfactant deficiency, since the early 1990s, it has been shown, by careful randomized trials, to reduce the morbidity and mortality of very premature newborns.[2]

Although it has been established that treating RDS with surfactant improves clinical outcomes, many newborns still require mechanical ventilation, which can cause lung injury in preterm infants with RDS, and contribute to the development of chronic lung disease and bronchopulmonary dysplasia (BPD).[1] An important question remains concerning the optimal timing of the treatment. There are two basic approaches to the treatment: prophylactic treatment and rescue treatment.[3] Prophylactic treatment is defined as the

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administration of surfactant through an endotracheal tube, at the time of the initial resuscitation after delivery. Rescue treatment is defined as the administration of surfactant to an intubated baby, several hours after birth and after RDS has been diagnosed.[4]

Many studies have been performed with regards to the optimal timing of the surfactant treatment and have found that the prophylactic treatment is better than that of the rescue treatment. Yet controversy remains over how to select infants for the prophylactic treatment, and how soon after birth to initiate the therapy. We conducted a multicenter study, at eight centers, to determine the relationship between the timing of the initial surfactant treatment and its associated prognosis.

Materials and Methods

1. Study centers

This trial was conducted in the neonatal intensive care units of Gangneung Asan Hospital, Kangbuk Samsung Hospital, Konkuk University Medical Center, Konyang University Hospital, Keimyung University Dongsan Medical Center, Dong-A University Medical Center, Sung-Ae Hospital, and Chosun University Hospital in the Republic of Korea. These Hospitals have level 2 and level 3 NICUs that have been established on the national basis, in South Korea. The trial was approved by the institutional review boards of all eight centers.

2. Subjects

One hundred and seventy one neonates who were born in the above eight centers, from January 1, 2004 to December 31, 2005, with birth weights of less than 1,500 g, diagnosed with RDS by clinical and radiographic criteria, and received surfactant treatment were included. RDS was defined as clinical respiratory distress in the presence of chest radiographic evidence of lung field granularity, small lung volumes and air bronchograms as well as fractional inspired concentration of oxygen (FiO_2) of 0.4 or more, and a ventilator mean airway pressure of 7.0 cm or more of water, or both. Twenty five neonates, with Apgar scores of 0-3 and who were initially treated with surfactant more than 9 hours after birth, were excluded. One hundred and forty six out of 171 neonates were eligible for the study. All patients received surfactant after diagnosis as RDS. Early rescue therapy is defined as receiving surfactant within 2 hours after birth, and late rescue therapy is defined as receiving surfactant 2 hours later after birth.

Patients diagnosed with RDS received surfactant endotracheally, at a dose of 120 mg/kg. Five aliquots were instilled in each of the following five positions: to the right upper up, the right lower up, the left upper up, the left lower up and the supine. We used Surfacten®(Surfactant, JW pharmaceutical, Mitsubishi Pharma Corporation, Japan)

3. Methods

A retrospective analysis was made of all patients. The information included the time at which the infants received surfactant of the first dose. First, we divided the early and delayed rescue treatment groups on the basis of 2 hours (time that received surfactant after birth), and thereby, compared the variables and outcomes of these groups.[2] Next, we divided the early rescue treatment group on the basis of 30 minutes (time that received surfactant after birth), and compared the variables and outcomes of these groups. We compared the survival rate, frequency of pneumothorax, BPD, intraventricular hemorrhage and patent

ductus arteriosus (PDA), and the duration of treatment with mechanical ventilation and hospital days between the two groups.

The diagnosis of BPD was made in the infants who needed supplemental oxygen at 36-week postmenstrual age (gestational age <32 weeks) or for more than 28 days after birth (gestational age ≥32 weeks) with consistent radiographic changes (persistent hazy opacification or cystlike pattern of density and lucency). BPD was also identified only in the infants who survived more than 28 days after birth. PDA was diagnosed by echocardiography, and only symptomatic case was identified. Intraventricular hemorrhage was diagnosed by brain ultrasonography, and only high-grade (≥grade III) intraventricular hemorrhage was identified.

4. Statistics

Data are expressed as the mean±SD. We analyzed the data with the paired t-test, chi-square test and Kaplan-Meier survival curves. A *P* value of less than 0.05 was considered significant. Statistical analyses were performed using Stata 8.0 statistical software.

Results

A total of 146 neonates with RDS that were born in the eight participating hospitals, from January 2004 to December 2005, were included in the study. There were 77 males and 69 females. Twin and triplet births accounted for 34 neonates (23.3 %). One hundred and two neonates (69.9%) were delivered by cesarean section. Ninety of the neonates (61.6%) were born to mothers that were treated with antenatal steroids (Table 1).

The mean value of time after birth when the initial surfactant was administered to the neonates was 140.0 ±114.3 minutes. Sixty seven neonates (46.5%) were treated with indomethacin for a PDA, and fifty two neonates (41.6%) were diagnosed with BPD. The number of patients that had pneumothorax and intraventricular hemorrhage was 17 and 13, respectively. The mean duration of mechanical ventilatory support was 15.1±18.7 days and for the hospital days was 67.9 ±40.1 days. One hundred and ten neonates (75.3%) survived (Table 1).

The group that received surfactant within 2 hours after birth included 84 neonates (58.0%); the group that received surfactant after 2 hours included 62 neonates (42.8%). There were no differences between the groups with regard to gestational age, birth weight, gender, multiple births, cesarean section delivery, and Apgar scores. Antenatal steroids were administered more to the infants in the early rescue treatment group than in the delayed rescue treatment group. However,

Table 1. Patient Characteristics at Birth and Their Outcomes

Variables	Characteristics
Gestational age (weeks)	28.1±2.0
Birth weight (g)	1084±258
Gender (male/female)	77/69
Twin & Triplet, n (%)	34 (23.3)
Cesarean section, n (%)	102 (69.9)
Prenatal steroid, n (%)	90 (61.6)
Apgar score	
1 minute	3.7±1.6
5 minute	6.4±1.1
Initial surfactant time (minutes)	140.0±114.3
PDA (with indomethacin)	67 (46.5%)
BPD (> PCA 36 wks)	52 (41.6%)
Pneumothorax	17 (11.6%)
IVH (> Grade III)	13 (9.4%)
Duration of mechanical ventilation (day)	15.1±18.7
Hospital day	67.9±40.1
Survival rate	110 (75.3%)

Abbreviations: PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage

the outcomes of these groups showed no significant differences in the survival rate and the frequency of pneumothorax, BPD and intraventricular hemorrhage. The frequency of PDA was significantly reduced in the group that received surfactant within 2 hours, and the duration of ventilator support and hospital days were also significantly shorter in such group (Table 2). The Kaplan–Meier survival curves, for the survival analysis, duration of ventilatory support and hospital days were used to compare the two groups using the log rank test. The results showed that the duration of ventilator support was significantly shorter in the group that received surfactant within 2 hours after birth. In addition, the Kaplan–Meier survival curves showed that the number of hospital days was shorter in the group that received the first dose of surfactant < 2 hours after birth. However, this difference was not statistically significant (Fig. 1, 2).

The group that received surfactant within 30 minutes after birth included 24 neonates (16.4%), and the group that received surfactant after 30 minutes included 122 neonates (83.6%). There were no significant differences in the gestational age, birth weight, gender, multiple births, cesarean section deliveries, antenatal steroid therapy, and Apgar scores between the two groups. In addition, there were no differences in the survival rate, frequency of pneumothorax, BPD, intraventricular hemorrhage and duration of hospital days. The incidence of PDA, however, was significantly reduced in the group that received surfactant within 30 minutes, and the duration of ventilator support was also significantly shorter (Table 3). The Kaplan–Meier survival curves for the duration of ventilator support

Table 2. Comparison of the variables and outcomes according to treatment group

Variables	Before 2 hours	After 2 hours	*P*-value
Number	84 (58.0%)	62 (42.0 %)	
Gestational age (weeks)	28.2 ± 2.0	28.2 ± 2.0	0.28
Birth weight (g)	1075 ± 257	1097 ± 261	0.69
Sex (male/female)	41/43	36/26	0.27
Twin & Triplet, n (%)	15 (17.9)	19 (30.6)	0.19
Cesarean section, n (%)	60 (71.4)	42 (67.7)	0.63
Prenatal steroid, n (%)	61 (72.6)	29 (46.8)	<0.05
Apgar score			
1 minute	3.8 ± 1.5	3.6 ± 1.8	0.26
5 minute	6.4 ± 1.1	6.4 ± 1.2	0.57
PDA, n (%)	30 (30.6)	37 (59.7)	<0.05
BPD, n (%)	29 (41.4)	23 (41.8)	0.97
Pneumothorax , n (%)	10 (11.9)	7 (11.3)	0.91
IVH (> Grade III)	4 (5.2)	9 (14.6)	0.06
Duration of mechanical ventilation (day)	9.0 ± 12.8	21.0 ± 20.7	< 0.05
Hospital day	81.4 ± 28.6	87.0 ± 33.1	< 0.05
Survival rate (%)	67 (80.0)	43 (69.4)	0.15

Abbreviations: PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage

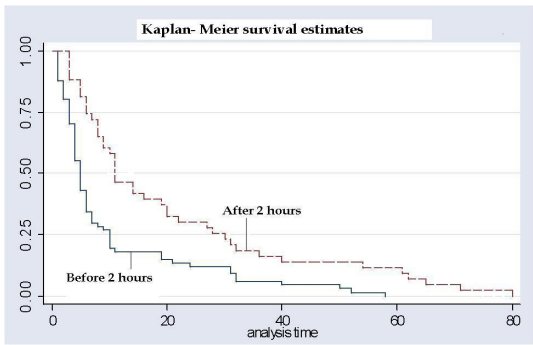

Fig. 1. Comparison of the duration of ventilator support by initial time of surfactant treatment.

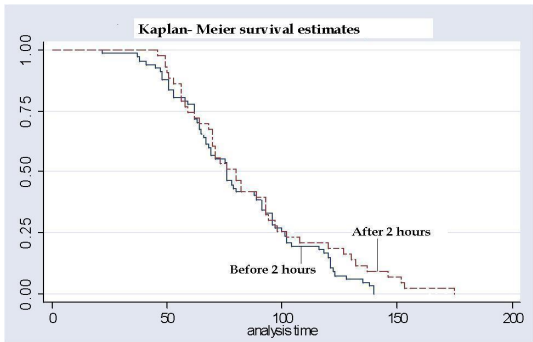

Fig. 2. Comparison of hospital days by initial treatment time of surfactant.

Table 3. Comparison of the Variables and Outcomes according to Treatment Group

Variables	Before 30 min	After 30 min	*P*-value
Number	24 (16.4%)	122 (83.6 %)	
Gestational age (weeks)	27.8±1.9	28.2±2.0	0.38
Birth weight (g)	1003±257	1101±256	0.09
Sex (male/female)	10/14	67/55	0.24
Twin & Triplet, n (%)	1 (4.1)	33 (27.0)	0.05
Cesarean section, n (%)	18 (75.0)	84 (69.9)	0.55
Prenatal steroid, n (%)	17 (70.8)	73 (59.8)	0.31
Apgar score			
1minute	3.4±1.6	3.8±1.6	0.27
5minute	6.3±1.0	6.4±1.2	0.81
PDA, n (%)	4 (17.3)	63 (52.1)	<0.05
BPD, n (%)	2 (8.3)	15 (12.3)	0.58
Pneumothorax, n (%)	8 (40.0)	44 (42.0)	0.87
IVH (> Grade III)	1 (4.2)	9 (10.2)	0.43
Duration of mechanical ventilation (day)	7.2±11.3	16.7±19.4	<0.05
Hospital day	69.1±42.3	67.6±39.8	0.87
Survival rate (%)	19 (79.2)	91 (74.6)	0.63

Abbreviations: PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage

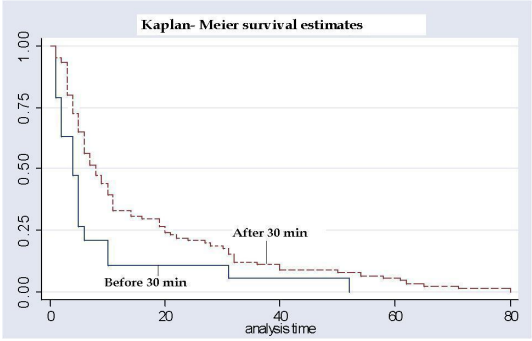

Fig. 3. Comparison of the duration of ventilatory support by initial time of surfactant treatment.

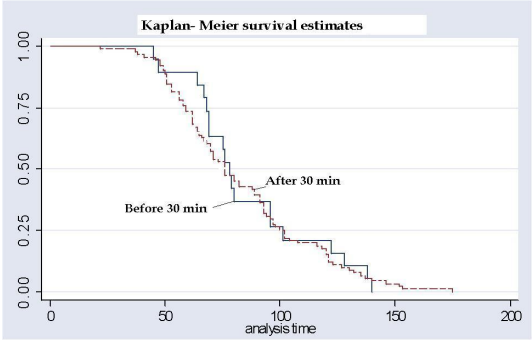

Fig. 4. Comparison of hospital days by initial time of surfactant treatment.

and hospital days were used to compare these two groups, using the log rank test; the result showed that the duration of ventilatory support was significantly shorter in the group that received surfactant within 30 minutes after birth. However, the number of hospital days showed no significant difference (Fig. 3, 4).

Discussion

Artificial surfactant that can be administered through the trachea was introduced by Fujiwara et al[5] in the 1980's, and has been widely used since then. As a result, the treatment with surfactant has significantly improved the neonatal morbidity and mortality.[2, 6–9] Many investigators, however, have raised the question concerning the timing of the initial surfactant treatment. Various studies have investigated whether the surfactant should be given as the prophylactic treatment or as the rescue treatment.[2–4, 9–13] Kendig et al. performed a multicenter randomized trial and concluded that the survival was improved in the group that was treated with prophylactic surfactant, particularly in the subgroup of patients delivered at 26 weeks of gestation or earlier.[10] Egberts et al. also reported that prophylaxis should be considered as the best therapeutic approach for those newborns with an increased risk for developing RDS and BPD.[11] Infants that receive prophylactic treatment had a decreased risk of pneumothorax, pulmonary interstitial emphysema, BPD, mortality, and death.[2, 4, 10–14]

The mean time after birth when the initial surfactant was administered to the neonates was 140.0±114.3 min, in our study. In the case of infants with very low

birth weight, born from 1996 to 2003 at Gangneung Asan Hospital, the mean time for the initial surfactant was 285 min, and the rate of providing initial surfactant within 2 hours after birth was only 11%. On the other hand, in a large North American cohort, among 47,608 infants with less than 30 weeks gestation, born between 1998 and 2000, 27% received surfactant in the delivery room, and 44% received surfactant by 30 minutes of age.[3] The first dose of surfactant was administered at a median time after 50 minutes from birth. By comparison, the mean time of the initial surfactant treatment was late in Korea. The prophylactic surfactant treatment is covered by insurance in premature infants of gestational age 30 weeks or birth weight of 1,250 g in Korea. As such, the time of surfactant treatment is much faster.

Prophylactic administration of surfactant offers the theoretical advantage of replacing surfactant before the onset of respiratory disease, decreasing the need for ventilator support and avoiding secondary barotraumas, which may result in even shorter periods of assisted ventilation. Such concerns have been confirmed by numerous studies.[9, 12, 15–17] In our study, the duration of ventilatory support was significantly shorter in the group that received surfactant within 30 minutes, and within 2 hours after birth, than the group that received surfactant after 30 minutes and 2 hours after birth, respectively, even though we used the surfactant as the rescue treatment.

Studies that compared the surfactant treatment on the basis of 2 hours after delivery have concluded that the early treatment leads to a decreased risk for acute pulmonary injury (pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality, as well as BPD, compared to the delaying treatment of such infants until the established RDS has developed.[1, 18–21] In a Korean study, the early surfactant replacement group was shown to have a decreased duration of ventilatory support.[22] However, some studies did not show a difference in hospital days.[19, 20] However, the results of our study showed that the number of hospital days was significantly reduced when surfactant was received within 2 hours; however, not in the group that received surfactant within 30 minutes.

This study has important limitations. Despite the study design being a multicenter study, the limitation mostly stems from its small sample size and its retrospective design. Perhaps a larger group of infants would have resulted in different outcomes for the group that received surfactant within 30 minutes of birth.

In conclusion, early surfactant treatment was associated with a decrease in the duration of ventilatory support and hospital days. Future studies should focus on the obstacles of providing early surfactant treatment. Our findings suggest that surfactant should be provided prophylactically, as soon as possible after birth.

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= 국 문 초 록 =

다기관 연구를 통한 극소저체중출생아에서 초기 폐표면활성제 투여의 시간에 따른 결과 비교

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목적 : 미숙아에서 호흡곤란증후군으로 진단 후에 치료하는 것보다 예방적으로 일찍 폐표면활성제를 투여하였을 때 환자들의 예후가 좋다는 것이 많이 보고되고 있다. 저자들은 다기관 연구를 통해 초기 폐표면활성제 투여의 시간과 그에 따른 결과를 비교 분석하였다.

방법 : 2004년 1월부터 2005년 12월까지 8개의 병원에서 태어난 출생체중 1,500 g 미만, 재태연령 34주미만의 환아들 중 호흡곤란증후군으로 진단된 환아들 171명을 대상으로 하였다. 우선 폐표면활성제 투여시간을 출생 후 2시간을 기준으로 나누어 군간 비교 분석하였고, 그 다음으로 투여시간을 출생 후 30분을 기준으로 나누어 군간 결과를 비교 분석하였다.

결과 : 환아들의 초기 폐표면활성제 투여시간은 평균 140.0±114.3분이었다. 동맥관개존증 발생률, 인공호흡기기간, 입원기간은 출생 후2시간 이내에 폐표면활성제를 투여한 군이2시간이후에 투여한 군에 비해 통계적으로 의미있게 적었다. 30분이내에 폐표면활성제를 투여한 군도 30분이후에 투여한 군에 비해 동맥관개존증 발생률과 인공호흡기간이 의미있게 감소하였다.

결론 : 미숙아에서 폐표면활성제는 출생 후 가능한 빠른 시간내에 투여하는 것이 좋다.

중심 단어 : 폐표면활성제, 호흡곤란증후군, 저출생체중아, 신생