Early administration of the second surfactant dose in preterm infants with severe respiratory distress syndrome

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The aim of this study was to determine whether early administration (2 hours after the first surfactant dose) of the second surfactant dose would be superior to late surfactant treatment (6 hours after the first surfactant dose) in preterm infants with severe respiratory distress syndrome.

Between June 2003 and March 2005, 40 newborns born with respiratory distress syndrome in Uludağ University Hospital were investigated in this prospective study. The inclusion criteria for the recruitment of the infants were: age ≤2 hours, birth weight between 600-2500 g, gestational age between 24-36 weeks, X-ray consistent with respiratory distress syndrome, and need for mechanical ventilation with inspiratory oxygen fraction ≥0.4 and mean airway pressure ≥7 cm H_2O to obtain arterial pressure of oxygen between 70-80 mmHg. Infants with lethal congenital anomalies or being treated with high-frequency oscillatory ventilation were excluded from the study. Birth weight, gestational age, gender, and Apgar scores were recorded and complications of the surfactant therapy were examined.

Twenty boys and 20 girls were enrolled in the study. The first surfactant dose was administered in the first hour of life in all infants. The second surfactant dose was given 2 hours after the first dose in 20 of them and 6 hours after the first dose in the other 20. Infants in both groups (early versus late) were similar with respect to gestational age, birth weight, gender, and the rate of prenatal corticosteroids. There were also no significant differences between the two groups in terms of the response to surfactant therapy and complications.

The results of this study show that administration of the second surfactant dose earlier is as effective as late administration, and it may be suggested that the second surfactant dose can be applied earlier in severe respiratory distress syndrome.

Key words: respiratory distress syndrome, exogenous surfactant, prematurity.

It was first shown by Avery and Mead in 1959 that surfactant deficiency resulted in respiratory distress syndrome (RDS) in preterm infants[1]. After Fujiwara et al.[2] reported the first promising results of surfactant replacement therapy in RDS, it has become a routine practice in neonatal intensive care units and has completely changed the natural history of RDS. Surfactant therapy leads to rapid improvement in oxygenation and decreased ventilatory support[3]. Systematic reviews showed that prophylactic surfactant therapy either with natural or synthetic surfactant resulted in reduction of up to 40% in mortality risk and 30-65% in pneumothorax risk[4-7]. After demonstrating the safety and efficacy of exogenous surfactant treatment in neonatal RDS, several further trials were conducted addressing the question of initial dosing, single or multiple administrations and timing of the surfactant treatment[8-10]. Early administration of surfactant in RDS treatment prevents alveolar damage and baro-volutrauma[11]. Preterm infants who do not receive prophylactic surfactant but have RDS should be treated as early as possible. This was supported with a review including four

randomized controlled trials. In that review, it was shown that early administration of the first dose of surfactant, such as within the first 30 minutes or the first 2 hours of life, decreased the risk of pneumothorax, pulmonary interstitial emphysema (PIE), chronic lung disease (CLD), and mortality[12].

The surfactant may be metabolized rapidly and functional inactivation of surfactant can occur. Hence, multiple doses were shown to be useful to overcome this metabolization and inactivation. In two randomized controlled studies, 70% of infants were given multiple surfactant doses, and it was shown that the multiple-dose regimen decreased pneumothorax risk; a trend for decreased mortality was also reported[13]. Retreatment strategies may be associated with the surfactant preparation that is used. There are a few studies comparing the timing of surfactant retreatment.

We therefore aimed to determine whether early administration (2 hours after the first surfactant dose) of the second surfactant dose would be superior to late surfactant treatment (6 hours after the first surfactant dose) in preterm infants with severe RDS.

Material and Methods

This prospective and randomized study was performed between June 2003 and March 2005. The infants who were admitted to the Neonatal Intensive Care Unit of Uludağ University Faculty of Medicine with RDS diagnosis were included in this study. The inclusion criteria for the infants were: age ≤2 hours, birth weight between 600-2500 g, gestational age between 24-36 weeks, X-ray consistent with RDS, and need for mechanical ventilation with inspiratory oxygen fraction (FiO_2) ≥0.4 and mean airway pressure (MAP) ≥7 cm H_2O to obtain arterial pressure of oxygen (PaO_2) between 70-80 mmHg. Infants with lethal congenital anomalies (e.g., lung malformations, congenital diaphragmatic hernia) or those being treated with high-frequency oscillatory ventilation were excluded from the study. The study was approved by the Ethics Committee, and informed parental consent was obtained for all infants.

The infants who fulfilled the inclusion criteria were given the first surfactant dose in the first hour of life. Infants who still needed a FiO_2 ≥0.4 and a MAP ≥7 cm H_2O were accepted as insufficient responders and were randomly divided into two groups for the second surfactant dose. The second surfactant dose was given either 2 or 6 hours after the first dose (20 infants in each group). Blood gas analysis was performed before the first and second surfactant doses, and at 12, 24 and 48 hours after the first surfactant dose. The results of the blood gas analyses were recorded.

The infants were intubated, and their conventional ventilation included synchronized intermittent mechanical ventilation (SIMV) with an inspiratory time of 0.35-0.40 s, positive inspiratory pressure over 20 mmHg, positive end-expiratory pressure between 4-6 cm H_2O, and respiratory rate of 20/minute. X-ray was performed and the position of the endotracheal tube was corrected by radiography, and careful auscultation of bilateral chest sounds during positive pressure ventilation with anesthesia bag was done. Before surfactant administration, PaO_2 was monitored by continuous pulse oximeter and was stabilized. The surfactant used in this study was beractant (Survanta; Abbott Laboratories, North Chicago, IL, USA), a modified bovine lung extract. Beractant at a dosage of 100 mg/kg body weight was administered in 4 aliquots via a small feeding tube introduced to the tip of the endotracheal tube. Positive pressure ventilation was administered for 2 minutes between each aliquot and infants remained in supine position during surfactant administration. The endotracheal tube was not suctioned for the first 6 hours after surfactant administration unless it was clinically necessary. After the first dose, decrease of the ventilatory settings was attempted. The infants were evaluated 2 hours after the first surfactant dose and if FiO_2 ≥0.4 and a MAP ≥7 cm H_2O persisted or there was still radiographic evidence of RDS, the second surfactant dose was administered either immediately (2 hours after first dose) or 6 hours after the first surfactant dose as described above. None of the infants received a third dose of surfactant.

In the study, analyzed variables were either related to the mother (prenatal corticosteroids and cesarean delivery) or the infant (gestational age, birth weight, Apgar score at 1 and 5 minutes and gender). Complications such as pneumothorax, pulmonary hemorrhage (bright red blood in endotracheal tube associated with

acute respiratory deterioration), patent ductus arteriosus (PDA) (characteristic murmur or echocardiographic confirmation), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), death after three days of life, and bronchopulmonary dysplasia (BPD) were also followed. Resuscitation after birth, inotropic agent and dexamethasone use, duration of ventilatory therapy, and length of hospital stay were also investigated. The percentage of improvement in the arteriolar/alveolar ratio (a/ADO_2) associated with every surfactant dose was the dependent variable and was calculated using the formula: $PaO_2/(FiO_2$ X 713 - $PaCO_2/0.8)$. It was calculated before the first and second surfactant doses, and at 12, 24 and 48 hours after the first surfactant dose. The effects of the first and second surfactant doses were evaluated according to the improvement percentages in a/ADO_2 between the first and second surfactant dose and between the second dose and 12 hours later. If FiO2 was ≤0.3, peak inspiratory pressure (PIP) was between 14-18 cmH2O and ventilatory rate was <20/minute, the weaning procedure was started. When the ventilatory rate was 6/minute, if the infants were stable with $PaCO_2$ <60 mmHg for an 8-hour period, they were extubated to nasal continuous positive airway pressure (CPAP).

The modified Ballard examination was used for estimating the postnatal gestational age[14]. IVH was evaluated by cranial ultrasound examinations, which were performed by the same pediatric radiologist and diagnosed using the Papile classification system[15]. BPD was defined as oxygen dependency at 36 weeks' postconceptional age for <32 gestational age or at 28 days of age for >32 gestational age. Grading was done according to Northway classification[16,17]. NEC diagnosis was defined and diagnosed using Bell criteria[18]. PVL was diagnosed according to Hill et al.[19]. PDA was diagnosed by demonstrating the patency of the ductus by echocardiography. Pneumothorax was defined on chest radiographs. Bacteria cultured from blood or tracheal aspirate accompanied by clinical deterioration and increased C-reactive protein (CRP) concentrations were diagnosed as sepsis.

For statistical analysis, Mann-Whitney U test was used for comparison of the groups. For the comparison of categorical data, chi-square and Fisher's exact chi-square tests were used. Values of $p<0.05$ were considered to be significant.

Results

A total of 40 infants were enrolled in this study. The first surfactant dose was administered in the first hour of life in all of them. Twenty (50%) of the infants received the second surfactant dose 2 hours after the first dose (2-h group, Group 1) and the remaining 20 (50%) received a second dose 6 hours after the first dose (6-h group, Group 2). No significant differences in gestational age, birth weight, mode of delivery (cesarean section), Apgar scores at 1 and 5 minutes, gender, rate of antenatal glucocorticoid administration, resuscitation at birth, and dopamine, dexamethasone, inhaled steroid, inhaled salbutamol and furosemide treatments were observed between the two groups. Table I shows the characteristics of the two groups.

Table I. Characteristics of the Two Groups

Variables related with mother and infant	2-hour group (n=20) (Group 1)	6-h group (n=20) (Group 2)	P value
Antenatal corticosteroids	6 (30%)	6 (30%)	>0.05
Cesarean section	14 (70%)	18 (90%)	>0.05
Birth weight	1279±399	1304±415	>0.05
Gestational week	29.5±2.37	30.1±2.63	>0.05
APGAR at 1 minute	4.50±1.79	4.95±1.39	>0.05
APGAR at 5 minutes	7.55±1.39	7.55±1.14	>0.05
Male gender	11 (55%)	9 (45%)	>0.05
Resuscitation at birth	17 (85%)	17 (85%)	>0.05
Dopamine administration	18 (90%)	19 (95%)	>0.05
Dexamethasone	6 (30%)	7 (35%)	>0.05
Inhaled steroids	6 (30%)	7 (35%)	>0.05
Inhaled salbutamol	6 (30%)	7 (35%)	>0.05
Furosemide administration	6 (30%)	7 (35%)	>0.05

The arteriolar/alveolar oxygenation ratio was used to determine the severity of RDS, and there were no significant differences between the two groups (Table II). Improvement rates in a/ADO_2 were also similar between the two groups (Table III). The rates of complications such as PIE, pneumothorax, pulmonary hemorrhage, PDA, IVH, PVL, NEC, death after the third day of life, BPD, day of weaning from ventilator, days on CPAP, duration of oxygen dependency, and total number of hospitalization days were similar in both groups (Table IV). Eleven (27.5%) of the babies were smaller than 1000 g (subgroups 1 [2-h] and 2 [6-h]). Six (55%) were in the 2-h group (Subgroup 1) and 4 (66.7%) of these were male; the remaining 5 (45%) were in the 6-h group (Subgroup 2) and 2 (40%) of them were male. However, these differences were not statistically significant ($p>0.05$). There were no significant differences between the two subgroups in gestational age, birth weight, mode of delivery (caesarean section), Apgar scores at 1 and 5 minutes, gender, rate of antenatal glucocorticoid administration, resuscitation at birth, and dopamine and dexamethasone treatments (Table V). Improvement rates in a/ADO2 were also similar for both of the subgroups (Table VI). When evaluated regarding complications after surfactant administration, there were no significant differences between the two subgroups (Table VII).

Table II. Comparison of Arteriolar/Alveolar Oxygenation Ratios (a/ADO_2) Between the Two Groups

Severity of RDS (a/ADO_2)	2-hour group (n=20) (Group 1)	6-h group (n=20) (Group 2)	P value
0 hours	0.166±0.172	0.240±0.229	>0.05
2 hours	0.308±0.266	0.353±0.223	>0.05
12 hours	0.403±0.251	0.486±0.341	>0.05
24 hours	0.555±0.343	0.695±0.250	>0.05
48 hours	0.627±0.378	0.793±0.401	>0.05

RDS: Respiratory distress syndrome.

Table III. Comparison of a/ADO_2 Improvement Ratios Between the Two Groups

a/ADO_2 improvement ratio as a response to surfactant therapy	2-hour group (n=20) (Group 1)	6-h group (n=20) (Group 2)	P value
Improvement ratio from the first dose to second dose	98%	94%	>0.05
Improvement ratio from the second dose to 12 hours	70%	77%	>0.05
Improvement ratio from 12 hours to 24 hours	52%	43%	>0.05
Improvement ratio from 24 hours to 48 hours	34%	27%	>0.05

a/ADO_2: Arteriolar/alveolar oxygenation ratios.

Table IV. Complications Seen After Surfactant Administration

Complications	2-hour group (n=20) (Group 1)	6-h group (n=20) (Group 2)	P value
Pulmonary interstitial emphysema	0	1 (5%)	>0.05
Pneumothorax	1 (5%)	2 (10%)	>0.05
Pulmonary hemorrhage	1 (5%)	0	>0.05
Patent ductus arteriosus	2 (10%)	2 (10%)	>0.05
Intraventricular hemorrhage	8 (40%)	6 (30%)	>0.05
Periventricular leukomalacia	2 (10%)	2 (10%)	>0.05
Necrotizing enterocolitis	1 (5%)	1 (5%)	>0.05
Death after third day of life	1 (5%)	1 (5%)	>0.05
Bronchopulmonary dysplasia	6 (30%)	7 (35%)	>0.05
Oxygen dependency (days)	43.00±29.18 d	39.65±39.58 d	>0.05
Duration of hospitalization (days)	56.70±31.97 d	50.90±39.67 d	>0.05

Table V. Characteristics of the Infants Weighing <1000 Grams in Both Groups

Variables related with mother and infant	2-h group (n=6) (Subgroup 1)	6-h group (n=5) (Subgroup 2)	P value
Antenatal corticosteroids	2 (33.3%)	3 (60%)	>0.05
Cesarean section	4 (66.7%)	3 (60%)	>0.05
Birth weight	867±74.05	826±100.3	>0.05
Gestational week	28.5±1.83	27.1±1.00	>0.05
APGAR at 1 minute	4.66±1.86	4.60±0.54	>0.05
APGAR at 5 minutes	7.66±1.5	7.20±0.83	>0.05
Male gender	4 (66.3%)	2 (40%)	>0.05
Resuscitation at birth	6 (100%)	5 (100%)	>0.05
Dopamine administration	5 (83.3%)	5 (100%)	>0.05
Dexamethasone	4 (66.7%)	4 (80%)	>0.05
Inhaled steroids	4 (66.7%)	4 (80%)	>0.05
Inhaled salbutamol	4 (66.7%)	4 (80%)	>0.05
Furosemide administration	4 (66.7%)	4 (80%)	>0.05

Table VI. Comparison of the Two Groups Regarding a/ADO_2 Improvement Ratios in Infants Weighing <1000 Grams

a/ADO_2 improvement ratio as a response to surfactant therapy	2-hour group (n=6) (Subgroup 1)	6-h group (n=5) (Subgroup 2)	P value
Improvement ratio from the first dose to second dose	58%	63%	>0.05
Improvement ratio from the second dose to 12 hours	35%	45%	>0.05
Improvement ratio from 12 hours to 24 hours	42%	52%	>0.05
Improvement ratio from 24 hours to 48 hours	30%	35%	>0.05

a/ADO_2: Arteriolar/alveolar oxygenation ratios.

Table VII. Complications Seen After Surfactant Administration in Infants Weighing <1000 Grams

Complications	2-hour group (n=6) (Subgroup 1)	6-h group (n=5) (Subgroup 2)	P value
Pulmonary interstitial emphysema	0	1 (20%)	>0.05
Pneumothorax	1 (16.7%)	1 (20%)	>0.05
Pulmonary hemorrhage	1 (16.6%)	0	>0.05
Patent ductus arteriosus	0	1 (20%)	>0.05
Intraventricular hemorrhage	4 (66.7%)	3 (60%)	>0.05
Periventricular leukomalacia	2 (33.3%)	1 (20%)	>0.05
Necrotizing enterocolitis	1 (16.7%)	1 (20%)	>0.05
Death after third day of life	1 (16.7%)	1 (20%)	>0.05
Bronchopulmonary dysplasia	4 (66.7%)	4 (80%)	>0.05
Oxygen dependency (days)	61.16±35.45 d	89.80±49.37 d	>0.05
Duration of hospitalization (days)	70.66±33.50 d	97.00±53.07 d	>0.05

Discussion

Exogenous surfactant has been used effectively and safely in the management of RDS. The recommended initial surfactant dose is 100 mg/kg/dose, but additional doses are usually administered in severe cases. The response to surfactant therapy depends on the quality of surfactant, the administration time, route of administration, and the surfactant dose. Surfactant administration as early as possible prevents the collapse of the lungs and also decreases the need of mechanical ventilation[20,21]. In a study with immature neonatal lambs, manual ventilation performed with high pressure after surfactant administration worsened the effect of the surfactant[22]. Prophylactic surfactant administration is most effective when it is given with the first breath or in the first 10 minutes of life[23]. It was shown that the

incidence of pneumothorax, PIE and mortality decreased significantly with prophylactic surfactant treatment compared with rescue treatment strategies[9,10,24-26]. We compared the administration time of the second surfactant doses (2-h versus 6-h) in infants with severe RDS. There were no significant differences between the two groups with respect to delivery mode, antenatal corticosteroid administration rate, birth weight, gender, gestational age, resuscitation at birth, and the medications used in the postnatal period (dopamine, dexamethasone, furosemide).

When we evaluated the infants weighing <1000 g, there were also no significant differences between the two groups of infants with respect to delivery mode, antenatal corticosteroid administration rate, birth weight, resuscitation at birth, and the medications used in the postnatal period (dopamine, dexamethasone, furosemide). According to the gestational week of these severe immature infants, Subgroup 1 had smaller gestational age compared with Subgroup 2 (27.1±1.00 and 28.5±1.83, respectively). Subgroup 1 included 4 (66.3%) males while subgroup 2 included 2 (40%) males, but this difference was not significant.

We evaluated the severity of RDS by a/ADO2 ratio in our study. The rate was initially low but it increased after surfactant treatment and reached a maximum at 48 hours. There were no significant differences between the two groups with respect to a/ADO2 ratio. The improvement in the a/ADO2 ratio was more evident after the first surfactant dose in both groups. This increase decreased after the second surfactant dose. This may be especially true as surfactant treatment improves oxygenation and decreases mechanical ventilation. Functional residual capacity improves after surfactant treatment and this leads to increased oxygenation. This may explain the improvement in the a/ADO2 ratio. The large portion of functional residual capacity improves immediately with administration of the first surfactant dose. Therefore, it is an expected finding that the increase will be more evident after the first dose of surfactant. Although the improvement in oxygenation continues, there seems to be a decrease in improvement of oxygenation after the second surfactant dose because the major portion of the functional residual capacity of the infant has developed after the first surfactant dose. This may also be partially explained by inhibition of the surfactant. Figueras-Aloy et al.[27] reported similar a/ADO2 improvement rates between the two groups including 57 preterm infants who were given the second dose of surfactant at 2 or 6 hours after the first dose. In that study, 20 of 57 infants had a birth weight <1000 g. Our results were similar to theirs. In that study, the improvement in a/ADO2 ratio was more clear in infants weighing <1000 g in the 2-h surfactant group. Therefore, they recommended that the second surfactant dose be administered earlier than the routine administration in very preterm babies (<1000 g). However, we found no significant improvement in a/ADO2 ratio in very preterm babies weighing <1000 g, and this may be associated with the smaller number of the very preterm infants in our study compared with their study (11 versus 20, respectively).

Surfactant treatment has some complications, one of which is PIE. A reverse correlation exists between birth weight and PIE. Yu et al.[28] reported the PIE rates as 32% and 22% in infants weighing <1000 g and >1000 g, respectively. This ratio decreased with the increase in new ventilatory strategies and use of surfactant. Gortner et al.[25] reported PIE in 3.9% of infants. In our study, PIE was determined in no infant in Group 1 and in 5% in Group 2, but the difference was not statistically significant. Figueras-Aloy et al.[27] reported the frequencies of interstitial emphysema as 10.3% and 10.7% in their 2-h and 6-h groups, respectively. In our study, PIE was not found in infants weighing <1000 g in subgroup 1 (2-h) and was determined at a rate of 20% in subgroup 2 (6-h) (n: 1); however, this difference was not statistically significant and it was thought to be associated with the small number of patients. Figueras-Aloy et al.[27] reported the frequency of interstitial emphysema as 0% and 22.7% in the very preterm infants in the 2-h and 6-h groups, respectively. Thus, our results were concordant with the findings in the literature.

Pneumothorax is another complication, and Berg et al.[29] reported its frequency in RDS as between 20.7% and 39.7%. Sly et al.[30] reported the pneumothorax frequency as 14%. The incidence of pneumothorax decreased markedly after the use of surfactant therapy

and new ventilatory strategies[31]. Gortner et al.[25] reported the pneumothorax rate as 3.9% after surfactant administration. Figueras-Aloy et al.[27] found pneumothorax in 10.3% and 14.3% of infants after the second surfactant dose in the 2-h and 6-h groups, respectively. In our study, pneumothorax developed after the second surfactant dose administration in 5% and 10% of infants in Groups 1 and 2, respectively, but the difference was not statistically significant. When the babies <1000 g were evaluated, Figueras-Aloy et al.[27] reported pneumothorax frequency as 22.2% and 18.2% in the early and late groups, respectively. We found pneumothorax in 16.7% and 20% of the infants in subgroups 1 and 2, respectively, and these rates were similar to those in the literature.

The American Academy of Pediatrics reported a BPD frequency of 23% for infants weighing <1500 g in 1995-1996[32]. The frequency of BPD reversely correlates with gestational age and birth weight. Gortner et al.[25] reported BPD frequency as 23%. Figueras-Aloy et al.[27] found BPD in 86.2% of the infants who received the second surfactant dose earlier and in 67.9% of the infants who received it later. They also reported BPD development in 66.7% and 81.8% of the infants <1000 g who were given the second surfactant dose early or late, respectively. In our study, we found BPD in 30% and 35% of the infants in Groups 1 and 2, respectively. BPD frequency increased as the gestational age and birth weight decreased; thus, our results are consistent with the literature.

Pulmonary hemorrhage, another complication of surfactant therapy, was reported to be higher with natural surfactant preparations (5-6%) compared with synthetic ones (1-3%) (33). Braun et al. (34) found pulmonary hemorrhage in 1.8% and 3% of the infants weighing <1500 g and who were <32 gestational weeks, before and after surfactant administration, respectively. Gortner et al.[25] found no pulmonary hemorrhage after the early surfactant administration but they determined pulmonary hemorrhage in 1.2% of the infants who received late surfactant. Figueras-Aloy et al.[27] reported pulmonary hemorrhage at frequencies of 13.8% and 3.6% after early and late second surfactant dose administration, respectively. In our study, pulmonary hemorrhage after early and late second surfactant dose was reported at rates of 5% and 0%, respectively. These results were also concordant with the literature. IVH is usually seen in premature infants. The incidence of IVH was reported to be 20% in the 1990's (35). Herting et al.[36] reported IVH frequency as 43%, and 21% of them were grades 3 and 4. Köksal et al.[37] reported its incidence as 15% in our neonatal intensive care unit (NICU) in an early study, and grades 1, 2, 3 and 4 were reported at rates of 50%, 17%, 11%, and 22%, respectively. Figueras-Aloy et al.[27] reported IVH incidences of 27.6% and 25.9% in the 2-h and 6-h groups, respectively. In our present study, we found IVH in 8 of the infants (40%) in Group 1. None of the mothers of these infants received antenatal steroids before delivery. Although all of the infants had resuscitation during birth, no advanced resuscitation or intubation was performed to the infants with IVH compared with the infants without IVH. IVH was determined in 6 infants (30%) in Group 2, and three mothers had received antenatal steroid and all of these infants were <1000 g. The high IVH incidence in Group 1 in our study may be associated with no administration of antenatal steroids, low birth weight and trauma related with resuscitation. PDA, NEC and PVL are the other complications seen after surfactant administration. Our results with respect to these complications are shown in Tables IV and VII, and we found all of our results to be comparable with the literature.

The overall durations of mechanical ventilation, CPAP therapy and oxygen dependency in infants in Group 1 were found as 11.7±8.17 days, 15.05±10.62 days and 43.00±29.18 days, respectively. The duration of these therapies in the infants in Group 2 were 12.25±9.57 days, 13.95±11.13 days and 39.65±39.58 days, respectively, and there were no significant differences between the two groups ($p>0.05$). We found the duration of mechanical ventilation, CPAP and oxygen dependency in subgroups 1 and 2 as 22.3±15.3 days, 20.3±15.1 days, 61.16±35.45 days and 31.2±20.23 days, 22.8±18.15 days, 89.80±49.37 days, respectively. There were no significant differences between two subgroups. This may be associated with the small number of patients. Although these differences were not statistically significant, these results showed that the durations of mechanical ventilation

and oxygen dependency were longer in infants <1000 g compared with the others (>1000 g), and this was concordant with the literature. The length of hospital stay increased as the gestational age and birth weight decreased. Egberts et al.[38] reported length of hospital stay as 65-71 days in infants with RDS. Also, Gortner et al.[25] found the length of hospital stay to range between 61 and 63 days in infants with RDS. The lengths of hospital stay in the infants in Groups 1 and 2 were 56.70±31.97 days and 50.90±39.67 days, respectively, in our study. As expected, hospital stay was longer in the very preterm babies (<1000 g), as 70.66±33.50 days and 97.00±53.07 days in subgroups 1 and 2, respectively. Although the duration in subgroup 1 was shorter than in subgroup 2, the difference was not statistically significant ($p>0.05$). This may be associated with the limited number of our study population.

The mortality rate in RDS increases as the gestational age and birth weight decrease. Mortality in RDS occurs mainly due to IVH, BPD and infections. Death due to RDS was reported to be 32% in 1970 but decreased to 11% in 1994 with the development of ventilatory strategies and use of surfactant[39]. Gortner et al.[25] reported the mortality rate as 3.2%. Figueras-Aloy et al.[27] found mortality rates as 3.4% and 10.7% in infants in the early and late second surfactant dose groups, respectively. Although, it was three times higher in the late group, the difference was not found to be significant. In our study, the rate of death after the third day of life was found to be 5% in both groups, and this was similar to the literature.

In conclusion, exogenous surfactant therapy has become standard for the treatment of premature infants with RDS. The studies are ongoing for predicting the appropriate use of surfactant. Although the general approach is to give the second surfactant dose 6 hours after the first dose, some studies have suggested that early surfactant administration improved oxygenation and decreased the complications. In our study, our results showed that there were no significant differences between the groups who were given the second surfactant dose 2 hours or 6 hours after the first dose. The improvement in oxygenation in infants weighing <1000 g reported by Figueras-Aloy et al.[27] was not seen in our study. This may be associated with the small number of patients in this study. Although we conclude that the second surfactant dose can be administered 2 hours after the first dose in severe RDS, further prospective studies investigating the administration time of surfactant with more patients must be conducted.

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