Surfactant Treatment in Late Preterm and Term Newborns; Indications and Outcomes

Geç Preterm ve Term Yenidoğanlarda Sürfaktan Tedavisi; Endikasyonlar ve Sonuçlar

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ABSTRACT

Objective: Surfactant therapy (ST) has significantly reduced mortality and respiratory morbidities among preterm infants with respiratory distress syndrome (RDS). However, majority of late preterm and term infants with respiratory distress also suffer from non-RDS lung diseases. In some of these diseases, secondary surfactant deficiency may develop and ST can be beneficial. In this study we evaluated the indications and early outcomes of ST in late preterm and term infants.

Material and Methods: We retrospectively evaluated the medical records of 135 late preterm and term infants who underwent ST between January 2009 and December 2012. The clinical characteristics of the patients, their diagnoses, number of surfactant application and time of administration, FiO_2 requirements before and after ST (1st and 6th hours),duration of mechanical ventilation, and mortality rate were evaluated.

Results: Among135 late preterm and term patients treated with ST, 78 (57.8%) were given ST due to lung disease other than RDS and had longer mechanical ventilator duration. In addition, ≥ 2 doses of surfactant requirement, pulmonary hypertension and mortality rate were found to be higher in these infants. Among patients with RDS, as expected, FiO_2 requirement was found to decrease in the 1st and 6th hours after ST (0.60 to 0.50 & 0.37 and p <0.001). Sixteen percent of newborns with congenital pneumonia required repeated surfactant doses. The FiO_2 requirement after ST was decreased in 42 patients with congenital pneumonia (0.67 to 0.65 & 0.48 and p <0.001). Sixteen patients with severe meconium aspiration syndrome (median FiO_2; 0.98) and 25 patients supporting with high frequency oscillatory ventilation (HFOV) support did not benefit from ST (p = 0.71 and p = 0.964).

Conclusion: We observed that ST reduced oxygen requirement in the late preterm and term infants with RDS and congenital pneumonia. However, we found that ST was not beneficial in the infants who applied HFOV due to severe respiratory insufficiency. We think that prospective studies involving a larger number of patients are needed to determine treatment options in these patient groups.

Key Words: Meconium aspiration syndrome, Newborn, Pneumonia

ÖZ

Amaç: Sürfaktan tedavisi (ST) respiratuvar distres sendromlu (RDS) pretermlerde mortalite ve solunumsal morbiditeleri önemli oranda azaltmıştır. Bununla birlikte solunum sıkıntısı olan geç preterm ve term bebeklerin çoğunda RDS dışında akciğer hastalıkları da mevcuttur. Bu hastalıkların bir kısmında sekonder sürfaktan eksikliği gelişmekte ve ST'nin yararı olabilmektedir. Biz geç preterm ve term bebeklerde ST'nin endikasyonlarını ve erken dönem sonuçlarını değerlendirdik.

Gereç ve Yöntemler: Ocak 2009 - Aralık 2012 tarihleri arasında ST uygulanan 135 geç preterm ve term bebeğin medikal kayıtları retrospektif değerlendirildi. Hastaların demografik özellikleri, tanıları, sürfaktan uygulama sayısı ve uygulanma zamanı, ST öncesi ve sonrası (1. ve 6. saat) FiO_2 gereksinimleri, mekanik ventilasyon süresi ve mortalite oranları incelendi.

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Bulgular: Sürfaktan tedavisi uygulanan 135 geç preterm ve term bebeğin 78'ine (%57.8) RDS dışı akciğer hastalıkları nedeniyle ST verilmiş olup, bu hastaların mekanik ventilasyon süreleri daha uzun, ≥ 2 doz ST gereksinimi, pulmoner hipertansiyon ve mortalite oranları daha yüksekti. RDS'li hastaların ST sonrası 1. ve 6. saatlerdeki FiO_2 ihtiyacı beklendiği şekilde azaldı (0.60'dan 0.50 & 0.3, p< 0.001). Konjenital pnömonili yenidoğanların %16'sının tekrarlayan sürfaktan dozlarına ihtiyaç duyduğu görüldü. Konjenital pnömonisi olan 42 hastanın da ST sonrası FiO_2 gereksinimi azaldı (sırasıyla 0.77'den 0.65 & 0.48 ve p<0.001). Mekonyum aspirasyon sendromlu (ortanca FiO_2 0.98) 16 hasta ve yüksek frekanslı osilatuar ventilasyon (YFOV) desteğine ihtiyaç duyan 25 hasta ise (hastaların 13'ü MAS) ST'den yarar görmedi (p=0.71 ve p=0.964).

Sonuç: Respiratuvar distres sendromlu ve konjenital pnömonili term ve geç preterm bebeklerde ST'nin oksijen gereksinimini azalttığı sonucuna varıldı. Bununla birlikte, ciddi solunum yetmezliği nedeniyle YFOV gereksinimi olan bebeklerde ST'nin yararlı olmadığı saptandı. Bu hasta gruplarında tedavi seçeneklerinin belirlenmesi için daha fazla hasta sayısını içeren prospektif çalışmalara ihtiyaç olduğu düşünüldü.

Anahtar Sözcükler: Mekonyum aspirasyon sendromu, Yenidoğan, Pnömoni

INTRODUCTION

Severe respiratory distress in the neonatal period is characterized by nasal flaring, groaning and retraction with decreased lung compliance secondary to pulmonary parenchymal disease. Whereas respiratory distress syndrome (RDS) is the most common cause of respiratory distress in preterm infants, lung diseases other than RDS are more common in late preterm and term infants (1). Transient tachypnea of the newborn and meconium aspiration syndrome (MAS) are the most common causes of respiratory distress in term newborns (2).

If there is no contraindication such as congenital diaphragmatic hernia in newborn period, primarily noninvasive ventilatory support is preferred for treatment of respiratory distress. However, some patients develop progressive respiratory failure, and noninvasive ventilatory support may not be adequate. These patients may need additional therapies such as surfactant administration and inhale nitric oxide therapy with intubation and mechanical ventilation. The need for intubation and mechanical ventilation in 34, 36 and 39-week infants has been reported as 6%, 3% and 0.3%, respectively (3).

Nasal continuous positive airway pressure (CPAP) support with surfactant therapy (ST) is the main component of RDS treatment in preterm infants. Surfactant therapy restores oxygenation, shortens the duration of mechanical ventilation and decreases the incidence of air leak and mortality among these infants (4). Secondary surfactant deficiency may develop with inactivation or rapid depletion of endogenous surfactant in lung diseases except RDS such as meconium aspiration syndrome, congenital pneumonia-sepsis, and pulmonary hemorrhage (5). The number of randomized studies investigating the effectiveness of surfactant in lung diseases in except RDS late preterm and term infants is limited (6).

In this study, we retrospectively evaluated the indications and short-term pulmonary outcomes of the late preterm and term infants after ST, which was added to invasive mechanical support due to severe respiratory distress.

MATERIAL AND METHODS

This study was conducted in our hospital between January 2009 and December 2012. Approximately 20.000 neonates are born each year and level III neonatal intensive care is given with more than 120 beds in this center. This study was approved by the ethic committee of our hospital.

The study included infants older than $34^{0/7}$ gestational week who were admitted to the neonatal intensive care unit due to respiratory distress and who needed mechanical ventilation support and ST at follow-up. The list of all infants for whom surfactant (beractant or poractant alfa) was administered between the specified dates was obtained from the hospital pharmacy. We found that, surfactant was taken from the hospital pharmacy for 207 late preterm and term newborns. The files and intensive care medical records of all these infants were evaluated. A total of 135 infants with complete intensive care follow-up data were retrospectively evaluated.

Patients' clinical and demographic characteristics, diagnosis, type of the ventilation support, indications of surfactant therapy (based on clinical, chest radiograph and blood gas analysis), time of surfactant administration, the need of oxygen and ventilation support immediately before, and 1 and 6 hours after ST, duration of mechanical ventilation, length of hospital stay, and mortality status were recorded. Only responses to the first dose of ST were compared in patients who received two or more doses of surfactant.

Fraction of the inspired oxygen (FiO_2), peak inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP) values of the patients receiving mechanical ventilatory support in our unit are recorded hourly and when the setup is changed. Hourly FiO_2, mean airway pressure (MAP), rate and amplitude (ΔP) values are recorded in the patients receiving high frequency oscillatory ventilation (HFOV). At least once chest radiograph and blood gas analysis are performed at 1st and 6th hours after the treatment in patients receiving surfactant in our unit. Blood gas samples are collected with capillary tubes unless there is no pulmonary hypertension or severe hypoxemia. Frequent PCO_2 monitoring is carried out with transcutaneous carbon dioxide monitorization in the patients requiring HFOV.

The target level of oxygen saturation in our clinic is usually over 93%, but under 100% in infants older than 34 weeks. Surfactant is administered to infants with radiological findings of RDS such as fine reticular infiltrations, air bronchograms and insufficient ventilation on chest radiograph and with a FiO_2

requirement higher than 0.40. In the late preterm and term RDS infants, ST is frequently applied in the presence of higher FiO_2 requirement. Surfactant therapy can be administered in patients followed-up with lung diseases except RDS according to diagnosis, clinical status, blood gas values, mechanical ventilatory pressure values and oxygen need of patients on recommendations by a pediatrician / neonatologist. There are no established clear criteria for the diagnosis of pneumonia in the newborn period. In our clinic, a patient is considered to have congenital pneumonia-sepsis in the case of elevated acute phase reactants (C-reactive protein or IL-6) or the presence of purulent tracheal secretions with infiltration on chest radiograph, and antibiotherapy is completed to at least 10 days even there is no growth in the blood culture.

Statistical Analysis

Normal distribution of the data was studied with Kolmogorov-Smirnov or Shapiro-Wilk according to the number of observations. Since the assumption of normal distribution was not provided, data were expressed as median and interquartile range (IQR). Mann Whitney U test was used for the independent group comparisons. Friedman test was used for the temporal change followed by Conover method for the paired comparisons. The significant level was set at 0.05 in all tests. All analyses were carried out utilizing SPSS for Windows (Statistical Package for Social Sciences) version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Among 135 late preterm and term infants, the median gestational age was found to be 35 weeks (range: 34 – 42), and median birth weight 2655 g (range: 1640 – 4460). Of the patients, 66.7% were boys, and the rate of cesarean sections was found 79% (Table I). The number of patients receiving ST for RDS, congenital pneumonia or sepsis, MAS, congenital diaphragmatic hernia and hydrops fetalis was 57 (42.2%), 42 (31.1%), 16 (11.9%), 7 (5.2%) and 6 (4.4%), respectively (Table II). Birth weight and gestational age were found to be lower among patients with RDS, while duration of mechanical ventilation, pulmonary hypertension and mortality rate were higher in patients who received surfactant due to non-RDS pulmonary diseases (Table II).

Surfactant therapy was administered for median 3.5 hours in 57 infants diagnosed with RDS. The requirement for oxygen and pressure gradually decreased in these infants after ST ($p<0.001$ and $p=0.006$, Table III, Figure 1). Thirty of RDS patients were weaned off mechanical ventilatin within 6 hours after ST. Only two patients required a second dose of surfactant. ST was applied for median 15.5 hours in 42 infants diagnosed with congenital pneumonia. The need for FiO_2 decreased at 1st and 6th hours after ST (from 0.77 to 0.65 & 0.48 and $p<0.001$, Table IV, Figure 1). Seven (16.6%) of the patients who received ST with the diagnosis of congenital pneumonia received 2 or 3 doses of ST. Among 16 patients who received ST with a diagnosis of MAS, no decrease was observed in FiO_2 requirement at 1st

Table I: Demographic and clinical characteristics of patients with RDS and non-RDS lung disease.

Characteristic	All patient n=135	RDS n=57	non-RDS lung disease, n=78	
Birth weight median (min-max)	2660 (1630-4460)	2400 (1860-3540)	2890 (1630-4460)	<0.001
Gestational age median (min-max)	35 (34-42)	35 (34-38)	36 (34-42)	<0.001
Male, *	90 (66.7)	36 (63.2)	54 (69.2)	0.579
Cesarean section, *	107 (79.3)	47 (82.5)	60 (76.9)	0.570
Apgar score at 5 th minute, median (min-max)	8 (1-9)	9 (3-9)	8 (1-9)	0.011
Antenatal steroid use, *	37 (27.4)	21 (36.8)	16 (20.5)	0.03
Maternal diabetes, *	15 (11.1)	7 (12.3)	6 (7.7)	0.51
Preeclampsia, *	5 (3.7)	2 (3.5)	3 (3.8)	1.0
PROM or PPROM, *	8 (5.9)	3 (5.8)	5 (6.4)	1.0
Timing of surfactant (hour) median (min-max)	21 (15.6)	3.5 (0.4-73)	7.2 (0.4-95)	0.13
Number of surfactant application, median (min-max)	1 (1-4)	1 (1-2)	1 (1-4)	0.027
Duration of mechanical ventilation (hour) median (min-max)	24 (1-860)	8 (1-355)	51 (4-860)	<0.001
Duration of hospitalization (day) median (min-max)	24 (3-860)	9 (3-78)	11 (1-50)	0.74
Pulmonary hypertension, *	10 (1-78)	5 (8.8)	23 (29.5)	<0.001
Mortality, *	28 (20.7)	3 (5.3)	26 (33.8)	<0.001

*** n(%), **PROM:** Premature rupture of membranes, **PPROM:**Prolonged premature rupture of membranes, **RDS:** Respiratory distress syndrome.*

Table II: Surfactant treatment indications for late preterm and term infants.

Indication	n (%)
RDS*	57 (42.2)
Non-RDS lung disease	78 (57.8)
Congenital pneumonia sepsis	42 (31.1)
Meconium aspiration syndrome	16 (11.9)
Congenital diaphragmatic hernia	7 (5.2)
Pulmonary hypoplasia	3 (2.2)
Hydrops fetalis	6 (4.4)
Pulmonary hemorrhage	4 (2.9)
Total	**135 (%100)**

***RDS:** respiratory distress syndrome.*

Table III: Oxygen and pressure requirements before and after ST in patients with respiratory distress syndrome.

	Before ST Median (IQR)	After ST 1. hour Median (IQR)	After ST 6. hour Median (IQR)	p
$Fi0_2$ (n=57)	0.60 (31.5)	0.50 (22)	0.37 (17)	<0.001
PEEP (n=57)	5 (1)	5 (3)	5 (1)	0.006
PIP (n=27)	18 (3)	18 (3)	17 (2)	0.004

***FiO_2:** Fraction of inspired oxygen, **IQR**: interquartile range, **PEEP:** positive end expiratory pressure, **PIP:** positive inspiration* pressure,

***ST:** Surfactant therapy.*

Table IV. Oxygen requirements before and after ST in patients with congenital pneumonia and meconium aspiration syndrome.

Diagnosis	$FİO_2$ Requirement			p
	Before ST Median (IQR)	After ST 1, hour Median (IQR)	After ST 6, hour Median (IQR)	
Congenital pneumonia, (n=42)	0.77 (44)	0.65 (51)	0.48 (43)	<0.001
Meconium aspiration syndrome, (n=16)	0.98 (13.5)	0.98 (11)	0.97 (20)	0.717

FiO_2: *fraction of inspired oxygen,* **IQR:** *interquartile range,* ***ST:** Surfactant therapy*

Table V: Oxygen and pressure requirements before and after ST in patients receiving HFOV support.

	Before ST Median (IQR)	After ST 1. hour Median (IQR)	After ST 6. hour Median (IQR)	p
$Fi0_2$ (n=22)	1.0 (2.25)	1.0 (2)	1.0 (2)	0.964
MAP (n=21)	13 (3)	13 (3)	15 (5)	0.127

***HFOV:** High frequency oscillatory ventilation, **IQR:** Interquartile range, **MAP:** Mean airway pressure*

and 6th hours after ST (from 0.98 to 0.98 & 0.97 and p=0.717, Table IV, Figure 1). The number of patients was not sufficient to evaluate short-term outcomes of ST in patients with pulmonary diseases other than congenital pneumonia, RDS and MAS.

Of the 135 patients, 25 were monitored at HFOV at the time of decision for surfactant administration, since the conventional ventilation support was insufficient. Of these infants, 2 were diagnosed with RDS, 1 with congenital pneumonia, 13 with MAS, 6 with congenital diaphragmatic hernia (CDH), 1 with pulmonary hypoplasia, and 2 with hydrops fetalis. In this group of patient, while FiO_2 requirement did not decrease at 1st and 6th hours after surfactant therapy, an increase in pressure (MAP) requirement was observed, which was statistically insignificant (p=0.964 and p=0.127, respectively; Table V, Figure 1).

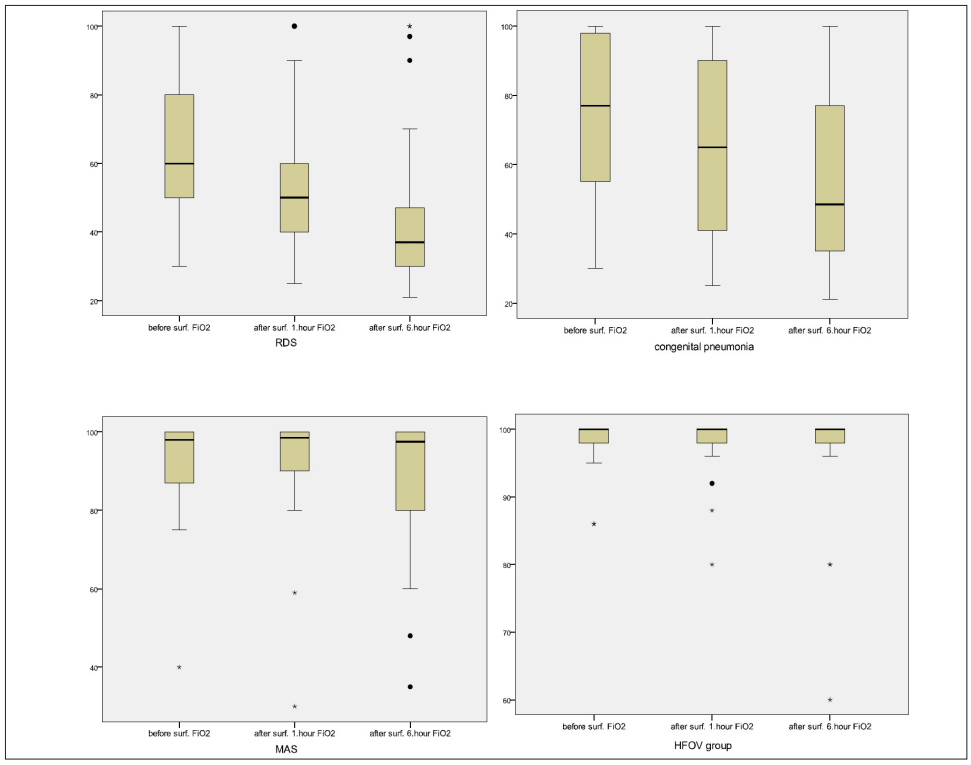

Figure I: Oxygen requirements before and after, **ST**(Supfactat Therapy) in patients with, **RDS** (Respiatory Distress Syndrome), congenital pneumonia, meconium aspiration syndrome and receiving HFOV support.

DISCUSSION

Among the late preterm and term infants who received mechanical ventilation and ST, the leading non-RDS disease was congenital pneumonia (Table II). Surfactant therapy with nasal CPAP is the standard application in RDS management of preterm infants. Surfactant therapy increases survival in these patients without changing neurologic or developmental outcomes (4,7). Current recommendation for preterm infant with RDS is to administer ST if FiO_2 requirement is above 0.40 despite CPAP support (8). In the late preterm and term infants with respiratory distress, an accepted limit of FiO_2 value for surfactant administration has not been clearly reported. However, higher SPO_2 levels are accepted by the majority of clinicians in late preterm and term infants because of sufficient endogenous surfactant (9). In our study, median FiO_2 requirement was 0.60 immediately before ST in patients diagnosed with RDS. The requirement for oxygen and ventilation gradually decreased at 1st and 6th hours after ST in these patients (Table III). In addition, 30 (53%) patients weaned off mechanical ventilator within 6 hours following ST. Among patients who received surfactant due to RDS, we found decreased requirement for PIP and PEEP. However, it would not be appropriate to comment on this issue, because mean airway pressures were not recorded.

Results of the studies about the effectiveness of ST in late preterm and term infants with non-RDS pulmonary diseases varied depending on the underlying disease, patient population, and inclusion criteria (6). Therefore, there are no clear recommendations on whether ST should be applied in most of non-RDS diseases. Secondary surfactant deficiency may develop with inactivation or rapid depletion of endogenous surfactant in non-RDS lung diseases such as MAS, congenital pneumonia-sepsis, and pulmonary hemorrhage (5). There are studies reporting improved oxygenation and decreased FiO_2 requirement with ST in preterm and term infants diagnosed with pneumonia (9-11). However, there is no randomized controlled trial evaluating the effectiveness of ST in early onset neonatal pneumonia (12). Therefore, there is no clear advice to administer ST in congenital pneumonia (12). We found that median FiO_2 requirement was decreased from 0.77 before ST to 0.65 and 0.48 at 1st and 6th hours after ST, respectively ($p<0.001$, Table IV). Herting et al.(11) reported that median FiO_2 requirement decreased from 0.84 before ST to 0.5 at 1st hour after ST in patients who received surfactant therapy with the diagnosis of group B streptococcal pneumonia. In our study, ST was applied at median 15th hour in patients with congenital pneumonia. Similarly, Deshpande et al. reported that they administered ST at median 19th hour in late preterm and term infants with congenital pneumonia (9). Later ST application in patients with congenital pneumonia may be related to increasingly deteriorating respiratory distress within the first 24 hours of life and expectation to reach relatively higher FiO_2 values in this group of patients. Among the patients who received ST due to congenital pneumonia-sepsis, seven of them (16.7%) required second or third doses of ST. It has been reported that preterm infants with congenital pneumonia may be in need of repeat doses of ST (13). However, this may not be appropriate for term infants with similar conditions (9). This is more clear for ST in respiratory distress related to MAS. In a meta-analysis of 4 randomized studies, ST has been demonstrated to decrease progressive respiratory failure requiring support with ECMO

in infants with MAS (14). However, ST did not change the incidence of mortality and air leaks in this group of patients. In our study, among the patients who received surfactant for MAS, we did not find a decrease in FiO_2 requirement after ST (p=0.71, Table IV). This might be explained by the fact that we preferred ST as rescue treatment in most patients with MAS. FiO_2 requirement was high (median 0.98) just before ST in these patients with severe respiratory failure, and no decrease was observed in FiO_2 requirement at 1st and 6th hours after ST (respectively median FiO_2 0.98 and 0.97, Table IV, Figure 1).

In a large study which randomized more than 500 infants with congenital diaphragmatic hernia, ST did not provide any benefit. Moreover, higher ECMO requirement and mortality rates have been reported in ST group. Based on this result, ST is not routinely recommended in these patients (15). On the other hand, it has been found that desaturated phosphatidylcholine turnover is more rapid in infants with CDH, but it is not clear whether this leads to secondary surfactant insufficiency (16). In a survey among numerous centers in Europe, 45% of infants with CDH were reported to receive ST (17). Surfactant therapy is not routinely applied to the patients with CDH in our center. However, 7 of the infants who received ST had CDH. FiO_2 requirement was 1.0 before ST in all these patients with CHD and 6 infants (4.4%) were on HFOV support at the time of ST administration. Surfactant therapy was administered as the last option in these patients in our center where ECMO could not be performed. FiO_2 requirement did not decrease in any of our patients with CDH, and 2 of them (1.5%) died before the 6th hour. This suggests that hypoxemic patients despite HFOV support should be transferred to a center where ECMO is available.

Twenty-five (18.5%) of the 135 patients received HFOV support at the time of ST administration. HFOV is not an initial mode of ventilation in our unit. In all of these patients, conventional ventilation options (e.g. SIMV, PSV, volume targeted ventilation) were insufficient in providing oxygenation or ventilation. We found that FiO_2 requirement and MAP (with a statistically insignificant increase) did not decrease in patients who needed HFOV for severe respiratory failure (p=0.964 and p=0.127, respectively; Table V). We could not find any literature data about this issue. These results may guide further well designed prospective studies to evaluate the effectiveness of surfactant in groups of patients with severe respiratory failure who are in need of HFOV support.

The limitations of this study include being retrospective, single center study and lack of calculation of oxygenation index before and after ST. FiO_2 changes of the patients were made as to keep this value between the target saturation range (93-99%). However, the target might be tried to be kept at the upper half of the target range for the patients with persistent pulmonary hypertension, and at the lower half of the target range for the patients with a gestational week of 34 to 35. However, evaluation of FiO_2 requirement before ST and at 1st and 6th hours after ST might somewhat normalize this problem. Another limitation of this study is not evaluating the patients applied inhaled nitric oxide thereapy.

CONCLUSION

In this study including late preterm and term infants who received ST and required invasive MV, we found that oxygen requirement decreased after ST in patients with RDS and congenital pneumonia. Additional ST applications may be needed in patients with congenital pneumonia. The number of patients was not sufficient to make a comment about patient groups other than RDS and congenital pneumonia. However, we believe that ST is not beneficial especially in patients requiring HFOV due to severe respiratory failure, and advanced treatment options such as ECMO can be preferred in these patients.

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