Experimental
&
Clinical Article

Usage of Surfactant and Evaluation of Lung Problems in Late Preterm Infants

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ABSTRACT

OBJECTIVE: We aimed to evaluate surfactant frequency and surfactant indications, as well as lung problems in late preterm infants.

STUDY DESIGN: This retrospective and cross-sectional study was carried out by HSU Izmir Dr. Behcet Uz Pediatric Diseases and Surgery Research and Training Hospital. Infants who were born late preterm between January 2016 and January 2022 were hospitalized in the NICU due to respiratory distress in the first 24 hours. Lung problems and surfactant administration of these infants were evaluated. The frequency of surfactant dosages, their indications, and their effects were examined. As the control group, patients who were admitted to the NICU in the same period due to respiratory distress with similar indications but did not receive surfactant were considered.

RESULTS: It was observed that surfactant was not administered to 105 infants and surfactant was administered to 106 infants. The median gestational week of the infants included in the study was 35 (34/36) weeks and the birth weight was 2185 (1780/2590) grams. A significant difference was observed in birth weight between the groups (p<0.001). Invasive ventilation was required in 52.1% of all cases and noninvasive ventilation was required in 33.6%. In the delivery room, the need for resuscitation and intubation was higher in the group requiring surfactant (p=0.001). The most common lung pathology in the surfactant group was RDS.

CONCLUSION: It must not be forgotten that infants who are born late preterm infants are preterm infants and the evaluation of antenatal steroid administration must not be ignored.

Keywords: Late preterm, Prematurity, Respiratory distress syndrome, Surfactant

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Introduction

Late preterm infants, which constitute 75% of all preterm births, are infants born at $34^{0/7}$-$36^{6/7}$ weeks. Compared to term infants, the incidence of anemia, apnea, asphyxia, hypoglycemia, hyperglycemia, hypercalcemia, hypocalcemia, hypomagnesemia, hypothermia, indirect hyperbilirubinemia, infection, and respiratory morbidity is higher in late preterm infants. The most important cause of morbidity and mortality in late preterms is lung problems (1). Late preterm infants were classified as "near-term" in the past because they have similar weights to term infants and appear healthy. However, this is not true. Because late preterm infants have immature lungs and have suboptimal surfactant production. Premature infants must be followed up by a team experienced and knowledgeable about the problems of prematurity to recognize and treat complications that may emerge because of prematurity (1,2). The better the problems that cause mortality and morbidity in these infants are known, the better these problems can be addressed.

Material and Method

Among all these problems, respiratory distress syndrome (RDS) can result in serious morbidity and mortality for pre-

mature infants. The present study had a retrospective and cross-sectional design and was conducted with infants who were born late preterm in HSU Izmir Dr. Behcet Uz Pediatrics and Surgery Training and Research Hospital Level IV Neonatal Intensive Care Unit (NICU) between January 1, 2016, and January 1, 2022, and were admitted to our hospital NICU because of respiratory distress in the first 24 hours. The purpose was to evaluate lung problems and surfactant use in these cases. In the evaluation of the lung problems in late preterm infants included in the study, the purpose was to determine the use of repeated-dose surfactant, the effects of surfactant on short-term prognosis, and the indications for surfactant administration by comparing the findings of the cases with and without surfactant.

The cases who were born late preterm who developed respiratory distress in the first 24 hours between January 1, 2016, and January 1, 2022, and who were hospitalized in the NICU of our hospital were included in the study. Major congenital anomalies, all cardiopathies, genetic syndromes, congenital diaphragmatic hernia, other preterm cases without late preterm, and cases whose data could not be accessed were not included in the study.

The average number of babies applying to our hospital is 1200 per year. Since a 5-year file review was considered for n=6000 patients, n=6000 patients were calculated. The incidence of RDS in the late preterm period is "Prevalence and morbidity of late preterm infants: current status in a medical center of Northern Taiwan" and "Neonatal Outcome of the Late Preterm Infant the Singapore Story" and "Ankara, Türkiye: General Directorate for Health Research Türkiye: SAGEM;2017" studies were taken as reference and it was found to be 1.2% (p=0.012), sampling error When (3%) and Power (80%) are taken; 106 patients for the study group and 106 patients for the control group 105 patients will be included in the study, and a total of 211 patients were included in the study.

The data of the patients who were born late preterm between January 1, 2016, and January 1, 2022, and were hospitalized in the NICU of our hospital because of respiratory distress in the first 24 hours regarding gestation week, gender, surfactant administration indications, mechanical ventilator need, mortality, and length of hospital stay were recorded and analyzed with the hospital information system. Our study was carried out by Izmir Dr. Behcet Uz Pediatric Disease and Pediatric Surgery Training and Research Hospital and was evaluated by the Clinical Research Ethics Committee with protocol number 755 and received approval with the decision numbered 2022/13-10 dated 13.10.2022. In addition, our study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, and local laws and regulations were adhered to during the study.

Statistical Analysis

The data were evaluated by using the IBM-SPSS (Version 24.0) statistical package program in the computer medium. Numbers, percentages, Mean ± Standard Deviation (SD), minimum (min), and maximum (max) values were used for descriptive statistics. The Chi-Square Test was used to compare the categorical data, the Shapiro-Wilk Test was used for the comparison of continuous data, and the Mann-Whitney U Test was used for the comparison of groups if they were not normally distributed as a result of the normality test. For statistical significance, $p \leq 0.05$ was accepted. Odds Ratio (95% CI) was calculated for risk factors and independent variables with $p<0.05$ were included in the univariate analysis. These variables were inserted into the Stepwise Forward Logistic Regression Model and Adjusted Odds Ratios were determined for risk factors.

Results

A total of 211 cases who were born late preterm and developed respiratory distress in the first 24 hours were included in the study. It was determined that surfactant was administered to 106 cases, and surfactant was not administered to 105 cases. The median gestational week was found to be 35 (34/36) weeks and 60.1% of the cases that had a median birth weight of 2185 (1780/2590) grams were male. The birth rate with C/S was 89.6%. The mortality rate of the cases was 1.9%. The antenatal steroid was administered to 27 (12.8%) of 211 cases included in the study. Although the number of patients who underwent positive pressure ventilation (PBV) in the delivery room was 71 (33.6%), the number of patients who were intubated in the delivery room was 112 (53.1%). When the diagnoses of the patients who were included in the study were examined, it was found that 74 (35.1%) were diagnosed with Transient Tachypnea of the Newborn (TTN), 120 (56.9%) were diagnosed with RDS, and 17 (8.1%) were followed in the NICU with the diagnosis of pneumonia. Invasive mechanical ventilation was needed in 110 (52.1%) cases and noninvasive mechanical ventilation was required in 71 (33.6%) cases. Of the total 211 cases included in the study, 120 cases were followed up with a diagnosis of RDS. However, surfactant was applied to only 84 cases with a diagnosis of RDS. The reason for this is that the remaining 36 cases were observed as stage 1 RDS and did not require surfactant. The general characteristics of the cases included in the study are given in table I.

When 106 cases that needed surfactant were examined, the median gestational week was found to be 34.5 (34/35) weeks. The median birth weight was 1872 (1640/2320) grams. When 105 cases who were not administered surfactant were examined, the median gestational week of the cases was found to be 35 (34/36). The median birth weight was 2400 (2100/2715) grams. When the cases who received and did not receive surfactant were compared, the C/S ratio was high (90.6%) in both groups and more than half of the cases were male. Although

the rate of antenatal steroid administration was low, it was similar in both groups. When APGAR 1st min and 5th min scores were compared in the groups, it was found that surfactant was applied to the group with a lower APGAR score (p=0.001). It was observed that the patients who needed surfactant had a higher need for positive pressure ventilation (PPV) and intubation in the delivery room (p=0.001). As we know, surfactant treatment is not only given in RDS but also in TTN and congenital pneumonia. When the indications of the cases in need of surfactant were examined, it was observed that 84 of 106 cases (79.2%) were administered surfactant with the diagnosis of RDS. When we look at the indications of the cases where surfactant was applied, most of them were diagnosed with RDS. It was determined that half of the remaining 22 cases were given surfactant with the diagnosis of TTN, and the other half with the diagnosis of congenital pneumonia. When the diagnoses of 105 patients who were not administered surfactant were examined, it was seen that 36 (34.3%) patients were followed up with the diagnosis of RDS (p=0.001). The reason why there is no need for surfactants even though they are followed with the diagnosis of RDS is that these cases are followed as stage 1 RDS. The characteristics of the patients who need and do not need surfactant are given in table II.

Hemodynamically significant PDA (hsPDA) was detected in 29 (27.4%) of 106 patients who needed surfactant. Although it was found that 95 (89.6%) of the cases treated with surfactant needed invasive mechanical ventilation, 15 (14.3%) of the cases that did not receive surfactant needed invasive mechanical ventilation and 8 (7.5%) of the cases treated with surfactant needed noninvasive mechanical ventilation, 63 (60%) of the cases who did not receive surfactant needed noninvasive mechanical ventilation (p=0.001). The length of hospitalization stay was 28 days in patients who received surfactant. On the other hand, the length of hospitalization stay was 13 days for those who did not take surfactant. The short-term clinical follow-up of the cases included in the study is given in table III.

It was found in the present study that infants with a birth weight of 1690 grams and below may need to be administered surfactant in the follow-up. It was found that the usage of surfactants increased as the birth weight decreased. A significant need was detected for surfactant in intubated infants and the usage of surfactant in the delivery room was significantly higher in intubated infants (p<0.001). The treatment of surfactant was higher in infants with a low APGAR 1st min score. In the multi-logistic regression analysis, AUC= 0.735 was calculated if the birth weight was ≤ 1690 grams. The results of the multi-logistic regression analysis are given in table IV.

When evaluated in terms of multiple-dose surfactant use, it was found that the group that most frequently needed multiple doses of surfactant was those who were followed up with the diagnosis of RDS (94.3%). It shows us that these infants may need repeated doses of surfactant. In the present study, when the cases in which a single dose of Surfactant was applied were examined, surfactant was administered to 96.6% of the cases who needed mechanical ventilation. It is considered that the need for Surfactant may be high in patients receiving MV support.

Table I: *General characteristics of the cases included in the study*

	Median (Q1/Q3) or n (%)
Gestational age (weeks)*	35 (34/36)
Birth weight (grams)*	2185 (1780/2590)
Male gender**	127 (60.1)
Birth with C&S**	189 (89.6)
Primiparous pregnancy**	42 (19.9)
Multiple pregnancy**	35 (16.6)
Mortality**	4 (1.9)
Length of hospital stay (days)*	18 (10/30)
Number of intubated days (days)*	1 (0/4)
Time oxygen is taken (days)*	6 (3/10)
APGAR 1st min*	7 (6/7)
APGAR 5th min*	8 (7/8)
Antenatal steroid**	27 (12.8)
Positive Pressure Ventilation in the delivery room**	71 (33.6)
Intubation frequency in the delivery room**	112 (53.1)
Transient Tachypnea of the Newborn**	74 (35.1)
Respiratory Distress Syndrome**	120 (56.9)
Pneumonia**	17 (8.1)
Need for invasive ventilation**	110 (52.1)
Need for noninvasive ventilation**	71 (33.6)

**Median (Q1/Q3). ** n (%).*

Table II: *Evaluation of cases included in the study according to surfactant administration*

	Cases with surfactant administration (n=106)	Cases without surfactant administration (n=105)	*p*
Gestational age (weeks)*	34.5 (34/35)	35 (34/36)	0.451[u]
Birth weight (grams)*	1872 (1640/2320)	2400 (2100/2715)	**<0.001[u]**
Male gender **	60	66	0.40
Birth with C&S **	96 (90.6)	93 (88.6)	0.66
Primiparous pregnancy **	21 (19.8)	21 (20.0)	0.99
Multiple pregnancy**	19 (17.9)	16 (15.2)	0.71
Mortality **	4 (3.8)	0 (0)	0.12
APGAR 1 min *	6.5 (6/7)	7 (7/8)	**0.001[u]**
APGAR 5th min *	7.5 (7/8)	8 (8/9)	**0.001[u]**
Antenatal Steroid **	14 (13.2)	13 (12.4)	0.99
PBV in the delivery room **	50 (47.2)	21 (20)	**0.001[c]**
Intubation in the delivery room **	97 (91.5)	15 (14.3)	**0.001[c]**
Transient Tachypnea of the Newborn **	11 (10.4)	63 (60)	**0.001[c]**
Respiratory Distress Syndrome **	84 (79.2)	36 (34.3)	**0.001[c]**
Pneumonia **	11 (10.4)	6 (5.7)	**0.001[c]**

u: Mann Whitney U test (Monte Carlo), c: Pearson Chi-Square Test (Monte Carlo), f: Fisher Exact Test (Monte Carlo), ff: Fisher Freeman Halton Test (Monte Carlo)

Table III. *Short-Term Clinical Follow-up Data of the Cases Included in the Study*

	Cases with surfactant treatment (n=106)	Cases without surfactant treatment (n=105)	*p*
hs PDA **	29 (27.4)	3 (2.9)	<0.001c
Use of inotropes **	24 (22.6)	2 (1.9)	<0.001c
Bronchopulmonary dysplasia **	9 (8.5)	0 (0)	0.009c
Invasive ventilation requirement **	95 (89.6)	15 (14.3)	0.001ff
Noninvasive ventilation requirement **	8 (7.5)	63 (60)	0.001ff
Stage 1-2 Intraventricular bleeding **	24 (22.6)	10 (9.5)	0.001ff
Stage 3-4 Intraventricular bleeding **	5 (4.7)	0 (0)	0.001ff
Total intubation time (days) *	3 (2/5)	0 (0)	0.001u
Length of stay in hospital (days)*	28 (17/42)	13 (10/18)	0.001u
Total oxygen delivery time (days)*	8 (5/10)	5 (3/7)	0.001u

u: Mann Whitney U test (Monte Carlo), c: Pearson Chi-Square Test (Monte Carlo), f:Fisher Exact Test (Monte Carlo),ff:Fisher Freeman Halton Test (Monte Carlo)

Table IV: *Risk Factors in Multilogistic Regression Analysis*

	B	SE	p	Odds Ratio	95% Confidence Interval for Odds Ratio	
					Lower Bound	Upper Bound
Birth Weight (≤1690 grams)	-2.996	1.032	0.004	20.0	2.647	151.217
Problem in pregnancy (None)	1.953	0.699	0.005	7.1	1.791	27.763
Intubation (Yes)	-5.181	1.052	<0.001	177.9	22.619	1398.932
Steroid (Yes)	-1.930	0.930	0.038	6.9	1.114	42.633
Number of intubated days (↑)	0.186	0.097	0.056	1.2	0.995	1.458
Apgar 1st min (↓)	-1.016	0.444	0.022	2.8	1.158	6.593
Constant	12.901	3.358	<0.001			
Dependent Variable: Surfactant	Predicted Surfactant None = 91.9		Predicted Surfactant =96.2		Predicted: 94.1 P Model<0.001	

Multiple Logistic Regression (Method = Backward Stepwise (Wald)), B: Regression Coefficients, SE: Standard Error

Discussion

Late preterm infants were followed and treated as accepted as term infants in the period when the definition of late preterm was not known and awareness was not formed. However, late preterms are physiologically and metabolically immature when compared to the term. Awareness of late preterms has been raised since the definition of late preterm has been known all over the world since 2006 (3). Recent studies emphasize that the risk of mortality and morbidity in late preterms is higher, contrary to popular belief, and that these infants must be approached more carefully (4). Late preterm birth rates are between 9.4% and 20.1% Among all births in Türkiye. There has been a 25% increase in late preterm births since 1990 (4). It is considered that the reasons for this increase are the improvements in antenatal care, the increase in elective C/S births, the increase in multiple pregnancies secondary to the widespread use of assisted reproductive techniques, and the advanced shift in maternal age (5). Studies also show that 30% of all late preterm infants have a history of hospitalization, and approximately 50-80% of these infants are followed up because of lung problems (6). For this reason, it is critical to know the management of late preterms in terms of the respiratory system.

When the delivery methods of the late preterm cases included in the study were evaluated, it was found that 89.6% were born with C/S, which was high in both groups. In other studies conducted on late preterm infants, the increase in C/S birth rates with the increase in accompanying maternal problems in late preterm infants is remarkable. Several studies reported different rates between 48.9% and 76.1% (7, 8-10). The high rate in The present study may be because of the high rate of cesarean sections in our country and antenatal infant and maternal medical problems. The American College of Obstetrics and Gynecology (ACOG) does not recommend induced vaginal or planned cesarean delivery before 39 weeks of pregnancy unless a clear medical indication is found (11). This supports the preference for cesarean section only in the presence of necessary medical indications and shows that late preterms will be healthier in the postnatal period.

The median birth weight of the infants was 2185 (1780/2590) grams in the present study. Although the median birth weight of the infants who needed surfactant was 1872 grams, the median birth weight of the infants who were not administered surfactant was 2400 grams. In the definition of late preterm, a distinction is made according to gestational weeks. However, it was shown in the present study that respiratory morbidity occurs more frequently and severely in the follow-up of late preterms with lower birth weight. It was determined that these infants need more surfactant. In studies investigating the indications for hospitalization in the NICU of late preterms and investigating the causes of mortality and morbidity in late preterms in our country, the median birth weight was reported to be 2384±502 and 2068.1±299.4 grams (4,12). Late preterm birth weights were similar in both studies, which supports the present study. Our study is important in terms of showing the relationship between birth weight and surfactant treatment.

Antenatal steroid application (ANS) increases lung capacity by accelerating the development of type 1 and type 2 cells on the alveolar surface. Surfactant production increases with the stimulation of type 2 cells (13). Currently, antenatal steroid administration is recommended before 34 weeks. For this reason, late preterms cannot receive ANS treatment to prevent surfactant deficiency (14). Only 12.8% of 211 late preterm cases included in the present study had ANS application. Antenatal steroid administration was similar between the groups. In a study that evaluated the effectiveness of betamethasone application to pregnant women with a high risk of delivery in the late preterm stage, it was reported that the need for CPAP decreased, severe respiratory failure, the frequency of transient tachypnea of the newborn (TTN), and the need for surfactant were decreased (15). In a meta-analysis of antenatal steroids applied to pregnant women with a high risk of late preterm delivery, it was shown at a moderate level of evidence that the need for respiratory support and resuscitation in the delivery room of late preterms decreases significantly as a result of ANS applied, but causes an increase in the risk of hypoglycemia (16). It was stated in the 2019 update of the RDS Management in the European Consensus Guide that the application of ANS in late preterm deliveries may be beneficial for the prevention of lung problems (17,18). As a result of the present study, it was found that approximately 80% of late preterms needed surfactant with the diagnosis of RDS. For this reason, it would be beneficial to apply the ANS application, which prevents the development of RDS, also in late preterm births.

In many studies conducted so far, it was reported that the need for respiratory support and surfactant because of respiratory distress and related early-period morbidities in late preterm infants is much higher than in term infants (19). In their study, Wang et al. stated that the risk of developing respiratory distress is nine times higher in late preterms than in term (20). Respiratory problems occur more frequently and more severely as the gestational week decreases (21). As a common result of many clinical studies, when late preterms were evaluated according to their gestational weeks, the frequency of RDS at the 34th gestational week was 7.4-13.7%, 4.5-6.4% at 35th gestational week, and 2.3-3.6% at 36th gestational week (22). Kitsommart et al. conducted a study in Canada and reported that TTN had a frequency of 47% and RDS with a frequency of 37.3% among respiratory problems in late preterms (23). In the present study investigating the indications for surfactant administration in term infants administered surfactant because of respiratory failure, it was found that from 56 term infants who were administered surfactant,

30 term infants were administered surfactant with the diagnosis of congenital pneumonia and 22 term infants were administered surfactant with the diagnosis of TTN (24). Our recent study showed that surfactant treatment administered in the early period significantly reduces mortality in term infants with severe respiratory failure because of secondary surfactant deficiency caused by TTN and pneumonia (24). In the present study, when the diagnoses of the infants included in the study were examined, it was found that 74 (35.1%) cases were diagnosed with TTN, 120 cases (56.9%) with the diagnosis of RDS, and 17 cases (8.1%) with the diagnosis of pneumonia in the NICU. Compared with the literature data, the incidence of RDS in late preterms who were administered surfactant because of respiratory distress was found to be nearly 80% higher in the present study than in the literature. This may be associated with the very low rates of antenatal steroids in our country, but the high rates of elective C/S delivery. RDS, which causes serious mortality and morbidity, is seen at a rate that cannot be ignored in late preterms. For this reason, it is very important to evaluate these infants in terms of antenatal steroids and to stabilize them with a T-piece revitalizer, especially in the delivery room.

Ozdogan et al. (14) found that the MV requirement of late preterm infants was 15%, and Binarbaşı et al. (4) reported it to be 9.5%. In the present study, 110 (52.1%) of the cases needed invasive and 71 (33.6%) noninvasive MVs. The reason for the higher rate of MV needs in the present study when compared to the literature might be that the present study is the first study with a large case series on late preterms followed up because of respiratory distress. In the present study, it was found that 47.2% of the cases administered surfactant were administered PBV in the delivery room, 91.5% of the infants were intubated, 20% of the infants who were not administered surfactant were administered PBV and only 14.3% were intubated. It was also found that the need for surfactant was higher in the patients who underwent PPV and intubation in the delivery room. Surfactant administration to late preterm infants intubated in the delivery room as soon as possible is very effective in reducing morbidity and mortality. For this reason, it would be beneficial to apply Surfactant to infants intubated in the delivery room as soon as possible after stabilization.

The present study is the first to be brought to the literature with a large case series investigating the short and long-term effects and indications of surfactants in late preterm cases hospitalized because of respiratory distress. RDS was found to be the most common surfactant administration indication in late preterm infants. This result that was obtained as the result of the present study is very important for the treatment and follow-up of late preterm infants hospitalized in the NICUs because of respiratory distress. The longer these infants are kept in the womb, the more they are prevented from surfactant deficiency and possible respiratory morbidities. Also, routine administration of ANS in late preterm births will prevent surfactant deficiency in the postnatal period. In conclusion, it must not be forgotten that late preterm infants are still premature infants, more sensitive and knowledgeable about follow-up and treatment approaches must be done. The data of the present study create a limitation in the evaluation of the discussion because there is no other study with a large case series similar to the present study in the literature. For this reason, it shows the necessity of conducting more studies on this subject.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of SUAM Clinical Research (Ethics approval reference number: 755 date 13.10.2022). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. / The datasets and code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: OY., and SAO. designed the study; OY., SAO., SC. and TGY. collected and analyzed data; OY. and SAO. wrote the manuscript; SC., and TGY. gave technical support and conceptual advice. All authors read and approved the final manuscript.

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