Does inhaled salbutamol before surfactant therapy have any beneficial effect?

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Beta $(\beta)_2$ adrenergic receptors are present in alveolar type II cells. Previously, the beneficial effects of inhaled salbutamol treatment on respiratory outcomes were shown in premature infants with transient tachypnea of the newborn. We hypothesized that inhaled salbutamol would increase the effects of surfactant on oxygenation in premature infants with respiratory distress syndrome (RDS). Inhaled salbutamol (0.15 mg/kg) or normal saline solution (0.30 ml/kg) was administered as a single dose by micropump nebulizer 10 minutes before the first dose of surfactant (Poractant alfa) treatment in 40 infants with gestational ages ranging from 26 to 36 weeks. The effects of salbutamol therapy were evaluated by determining the duration of respiratory support, number of doses of surfactant, respiratory rate, heart rate, fraction of inspired oxygen, and partial pressure of arterial oxygen before and after salbutamol nebulization. No statistically significant difference was detected between the two groups in duration of respiratory support, number of doses of surfactant, respiratory rate, fraction of inspired oxygen, or partial pressure of arterial oxygen. In this study, no significant effect of inhaled salbutamol treatment on the surfactant therapy in premature infants with RDS was detected.

Key words: newborn, neonate, premature, infant, respiratory distress syndrome, RDS, salbutamol, inhaled salbutamol.

Respiratory distress syndrome (RDS) accounts for approximately half of the causes of respiratory distress in newborns of all gestational ages. Especially in premature infants, its incidence increases in conjunction with decreasing gestational age. The development of the exogenous surfactant for treatment of RDS is one of the most important advances in the history of newborn medicine. Although RDS-related morbidity and mortality have decreased with the usage of surfactant, it remains an issue of importance, since survival rates of very preterm infants have increased. As a result, investigations concerning developments in the efficacy of surfactant therapy continue.[1,2]

It has been demonstrated that inhaled salbutamol treatment improved pulmonary mechanics in ventilated premature infants with respiratory failure, respiratory distress and chronic lung disease.[3-6] The beneficial effects of inhaled salbutamol treatment on respiratory outcomes in transient tachypnea of the newborn (TTN) have also been shown.[7] Beta $(\beta)_2$ adrenergic receptors are widely distributed in the respiratory tract, and are found not only in airway smooth muscle cells, but also in other cells in the lung, such as epithelial and endothelial cells, alveolar type II cells, and mast cells. Salbutamol is a selective β_2 adrenergic agonist. It promotes the production of intracellular cyclic adenosine monophosphate (cAMP), which enhances the binding of intracellular calcium to the cell membrane. This action decreases the calcium concentration within cells and results in the relaxation of

smooth muscle and bronchodilation.[8,9]

We hypothesized that inhaled salbutamol would increase the effects of surfactant in premature infants with RDS. Our objective was to investigate whether a single dose of inhaled salbutamol would increase the effects of the surfactant on oxygenation and whether it is safe for use in premature infants with RDS.

Material and Methods

The study was performed at the Neonatal Intensive Care Unit (NICU) of Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey, between October 2010 and January 2012. The infants included in this study were less than 37 weeks' gestational age (range, 26-36 weeks) at birth, and had clinical and radiographic evidence of RDS. Synchronized intermittent mechanical ventilation or noninvasive nasal continuous positive airway pressure was applied in all patients throughout the study period. A total of 40 premature neonates with RDS were randomly allocated in a double-blind placebo-controlled study to receive either inhaled salbutamol (n=20) or an equal volume of normal saline solution placebo (n=20) at the time of diagnosis on the first day of life (Fig. 1). Inhaled salbutamol (0.15 mg/kg) or normal saline solution (0.30 ml/kg) was administered as a single dose by micropump nebulizer 10 minutes before the first dose of surfactant (Poractant alfa, 200 mg/kg) treatment. Surfactant was given through the intubation cannula in all patients according to the INSURE protocol. Patients with other respiratory disorders (TTN, meconium aspiration, pneumonitis, iatrogenic lung injury, congenital diaphragmatic hernia, air leakages, congenital heart diseases), arrhythmia, chromosomal anomalies, congenital malformations or anomalies, severe hypoxia, suspected or proven sepsis, congenital infections, multiple organ failure syndrome, disseminated intravascular coagulation, inherited metabolic disorders, immune/non-immune hydrops fetalis, twin-to-twin transfusion syndrome, congenital tumors, or non-respiratory disorders (hypocalcemia, persistent hypoglycemia, polycythemia) likely to cause respiratory symptoms; newborns with a history of premature rupture of membranes, maternal diabetes, maternal asthma, or maternal
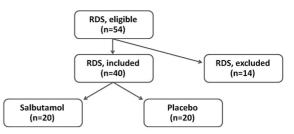

Fig. 1. The flowchart of patients included in the study

bronchodilator drug use; and newborns who died on the first day of life were excluded. Informed consent was obtained from all parents, and the study was approved by the local ethical committee (HEK 07/149-15).

The effects of salbutamol therapy were evaluated by determining the duration of respiratory support, number of doses of surfactant, respiratory rate, heart rate, fraction of inspired oxygen (FiO_2), PaO_2/FiO_2 ratio, MAP (Mean Airway Pressure), OI (Oxygenation Index), oxygen saturation, and partial pressure of arterial oxygen and carbon dioxide before and four hours after salbutamol nebulization.

Preparation and administration of nebulized solutions were performed by a NICU nurse. Parents and investigators remained blinded to the administered medications throughout the study period.

Statistical analyses were performed with PASW Statistics 18 for Windows (Chicago, IL, USA). Normally distributed variables were analyzed with parametric tests (independent or dependent samples t-test). Non-normally distributed variables were analyzed with Mann-Whitney U test. Fisher's exact test and χ^2 tests were used for categorical and qualitative variables. For descriptive statistics, percent, minimum-maximum-median, mean, and standard deviation were used in accordance with the type and distribution of the variable. Values of $p<0.05$ were considered to be significant.

Results

There were no differences between the two groups in demographic, maternal and neonatal characteristics (Table I). No statistically significant difference was detected between the two groups in duration of respiratory support, number of doses of surfactant, respiratory rate, heart rate, FiO_2, PaO_2/FiO_2 ratio, MAP,

Table I. The Demographic Characteristics of the Infants and Maternal Features.

	Salbutamol Group (n=20)	Control Group (n=20)	P value
Gender (F/M)	13/7	9/11	0.204
Spontaneous/IVF	14/6	15/5	0.723
Gestational age (weeks ± SD)	30.4±2.5	30.5±1.7	0.883
Birth weight (g ± SD)	1378±499	1356±379	0.876
AGA/SGA/LGA	13/7/0	15/5/0	0.490
Maternal age (y)	31.3±3.3	29.9±4.1	0.260
Antenatal steroid, n (%)	15 (75.0%)	18 (90.0%)	0.358
Apgar score (5th min)*	7.5 (5-10)	7.0 (6-9)	0.192
Hemoglobin (g/dl)	16.0±2.3	16.9±2.1	0.198
Hematocrit (%)	47.3±6.4	50.2±6.3	0.157
White blood cell count (/mm^3)	13110±7444	8890±4862	0.049
Duration of hospitalization (d)*	23(7-23)	25(9-49)	0.779
Exitus, n (%)	1 (5%)	2 (10%)	1.00
Maternal diseases			
Preeclampsia, n (%)	7 (35.0%)	3 (15.0%)	
Thrombophilia, n (%)	0 (0%)	2 (10.0%)	
Hypertension, n (%)	3 (15.0%)	1 (2.5%)	0.144
Goiter (hypothyroisidism), n (%)	2 (10.0%)	2 (10.0%)	
Maternal drug use			
Heparin, n (%)	2 (5.0%)	2 (10.0%)	
α-methyl dopa, n (%)	3 (15.0%)	1 (5.0%)	
Ca channel blocker, n (%)	3 (15.0%)	3 (15.0%)	
Aspirin, n (%)	2 (10.0%)	0 (0%)	
MgSO$_4$, n (%)	2 (10.0%)	0 (0%)	

IVF: in vitro fertilization; AGA/SGA/LGA, appropriate-, small-, large- for gestational age;
* median (minimum-maximum value)

OI, oxygen saturation, and partial pressure of arterial oxygen and carbon dioxide before and after salbutamol nebulization. Changes in the heart rate, respiratory rate, and FiO_2 over time in the salbutamol and placebo groups were shown on Figure 2. There were also no differences between the salbutamol and control groups with respect to serum K^+ or glucose levels (Table II).

No adverse effects were observed in our study after single-dose treatment with inhaled salbutamol or saline solution.

Discussion

Despite the significant advancements in neonatology, RDS is still common and causes significant morbidity and mortality in premature infants. Increasing the effectiveness of the surfactant therapy may decrease the need of mechanical ventilation, related complications and duration of hospitalization of premature infants with RDS. However, thus far, no medicine has been proven to increase the effect of the surfactant.

In this study, we aimed to investigate whether inhaled salbutamol, applied before surfactant therapy, could increase the effect of the surfactant, since its beneficial effects on pulmonary mechanics and respiratory outcomes in premature infants with respiratory failure, respiratory distress, TTN, and especially chronic lung disease have been demonstrated. This is the first study investigating the efficacy of a single dose of inhaled salbutamol treatment on surfactant therapy in premature infants with RDS on the first day of life. In this study, no significant effect of the inhaled salbutamol treatment on the surfactant therapy in premature infants with RDS was detected. Radioligand binding studies on lobectomy specimens have shown β_2-receptor density to

Table II. The Comparison of Respiratory, Clinical and Laboratory Findings of the Salbutamol and Placebo Groups.

	Salbutamol Group (n=20)	Control Group (n=20)	*P* value
Respiratory rate (breaths/min)			
Before	60.9±9.5	64.5±8.5	.242
After (4th hour)	58.9±6.5	59.6±3.2	.667
P value	.116	.003	.129
Heart rate			
Before	159.2±13.2	154.7±9.3	.056
After (4th hour)	149.5±11.3	146.6±8.1	.165
P value	.000	.000	.397
FiO_2 (%)*			
Before	52.5 (40-100)	55.0 (40-80)	.640
After (4th hour)	30.0 (21-40)	27.5 (21-30)	.134
P value	.000	.000	.751
O_2 saturation (%)			
Before	89.4±4.3	90.1±3.4	.570
After (4th hour)	94.2±2.8	92.9±2.3	.118
P value	.000	.000	.066
PaO_2 (mmHg)			
Before	52.7±13.6	52.8±21.6	.640
After (4th hour)	60.1±13.4	56.8±21.2	.242
P value	.071	.414	.577
Pa_{CO2} (mmHg)			
Before	48.4±9.5	46.7±8.4	.557
After (4th hour)	42.4±9.4	43.3±10.1	.780
P value	.021	.206	.475
PaO_2/FiO_2			
Before	0.95±0.36	1.00±0.43	.744
After (4th hour)	1.36±0.48	1.34±0.54	.925
P value			
MAP	7.05±0.85	6.23±0.58	.211
OI	8.27±3.07	3.16±0.98	.640
pH			
Before	7.26±0.07	7.28±0.06	.410
After (4th hour)	7.30±0.07	7.29±0.06	.341
P value	.048	.325	.330
Surfactant doses*	1 (1-5)	2 (1-5)	.127
Serum K^+ (mEq/L)			
Before	4.1±0.7	4.0±0.6	.691
After (4th hour)	3.9±0.8	4.1±0.6	.489
P value	.482	.612	.389
Serum glucose (mg/dL)			
Before	71.6±33.4	63.3±28.1	.512
After (4th hour)	114±43.7	111.8±29.7	.850
P value	.000	.000	.634
Duration of respiratory support			
MV (h)*	24 (0-600)	48 (0-480)	.383
CPAP (h)*	45.5 (6-840)	44.0 (0-262)	.355
Oxygen support (h)*	24 (19-744)	24 (0-596)	.165

MV, mechanical ventilation; CPAP, continuous positive airway pressure
* median (minimum-maximum value)

increase throughout the respiratory tract, with high levels in the central lung and alveolar region.[8] Although pulmonary mechanics such as airway pressure and resistance and lung compliance were not evaluated in this study, we suggest that a sufficient amount of the inhaled salbutamol may fail to reach the distal airways of the lungs due to the low pulmonary compliance and high airway pressure caused by RDS.

It has been shown in animal studies that density and affinity of β receptors may increase with gestational age.[10] Therefore, it is possible that early premature infants might have poorer responses to salbutamol than
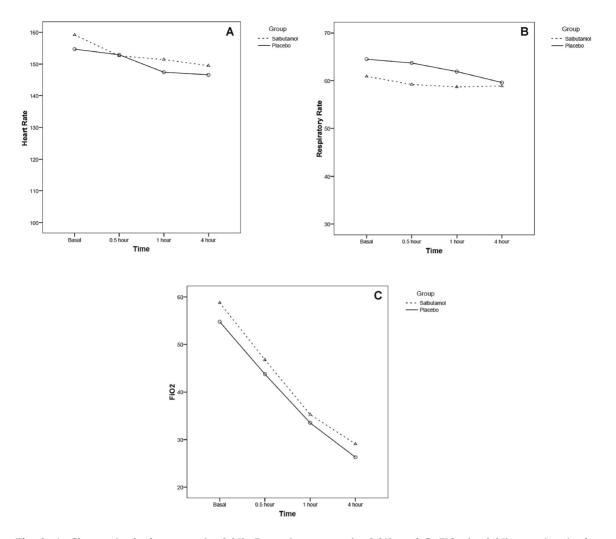
Fig. 2. **A**, Changes in the heart rate (p>0.05), **B**, respiratory rate (p>0.05), and **C**, FiO$_2$ (p>0.05) over time in the salbutamol and placebo groups.

term or late preterm infants. Although to our knowledge there are no studies investigating the relationship between gestational age and density and affinity of β$_2$ receptors within the airways, it may be presumed that premature infants have less β$_2$ receptors than term infants. We believe that we were unable to obtain an adequate response to salbutamol because our study was performed in premature infants. Another reason may be the administration of surfactant just after the salbutamol treatment because short-acting β$_2$-agonists, such as salbutamol, are hydrophilic, and access the active site of the β$_2$-adrenoceptor directly from the extracellular aqueous compartment.[8] The environment that becomes hydrophobic with the application of the surfactant may have decreased the effect of salbutamol, which remains unabsorbed by bronchial mucosal cells.

In a previous placebo-controlled study, the efficacy of inhaled salbutamol was studied for treatment of TTN in infants with gestational ages of 34-39 weeks. Significant decreases detected in respiratory rate, FiO$_2$, TTN clinical score, and duration of hospitalization were significant in the salbutamol group.[7] Although the gestational age range of our study population differs from this study, we did not find a significant difference in the duration of respiratory support, number of doses of surfactant, respiratory rate, heart rate, FiO$_2$, oxygen saturation, or partial pressure of arterial oxygen and carbon dioxide between the salbutamol and control groups.

Lee et al.[4] performed a randomized placebo-controlled study that investigated the bronchodilator aerosol administered by metered dose inhaler and spacer (MDIS) in premature infants with RDS at a postnatal age of 1 week. The infants included in that study (n=10) were less than 34 weeks of gestational age at birth, had RDS and required mechanical ventilation.[4] They had concluded that single doses of both salbutamol and ipratropium bromide given by MDIS had useful short-term effects in ventilator-dependent neonates with RDS without any clinically significant side effects.[4] The gestational age range of that study population was similar to that of our study, but doses of salbutamol and route of administration were different. In contrast to that study, we did not find any significant difference in beneficial short-term effects on gas exchange and ventilatory efficiency between the salbutamol and control groups.

We also evaluated the salbutamol group for adverse effects. While serious bronchospasm, arrhythmias, hypokalemia, and hyperglycemia caused by glycogenolysis have been reported in the literature rarely,[9] no adverse effects were observed in our study after single-dose treatment with inhaled salbutamol or saline solution.

Larger studies are needed to determine whether inhaled salbutamol increases the effects of surfactant in premature infants with RDS.

Acknowledgement

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