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The Effects of Inhaled β-Adrenergic Agonists in Transient Tachypnea of the Newborn

Esengul Keleş, MD[1], Arzu Gebeşçe, MD[1], Mehmet Demirdöven, MD[1], Hamza Yazgan, MD[1], Bülent Baştürk, MD[1], and Alparslan Tonbul, MD[1]

Abstract

Aim. To investigate the efficacy of an inhaled β-adrenergic agonists in transient tachypnea of the newborn (TTN). *Method*. We retrospectively analyzed a cohort of 51 term infants (Group 1) and 37 term infants (Group 2) monitored in the newborn intensive care unit diagnosed with TTN. Infants in Group 1 received humidified oxygen alone, and infants in Group 2 were administered the inhaled β-2 agonist plus humidified oxygen. *Results*. TTN clinical respiratory assessment, respiratory rate, oxygen saturation values, need for supplemental oxygen therapy, blood gas PH, PO_2, and duration of hospitalization were significantly improved in infants in Group 2 as compared with infants in Group 1 ($P < .05$). No statistically significant difference was observed with regard to blood glucose, potassium, heart rate, and PCO_2 ($P > .05$). *Conclusion*. Inhaled β-adrenergic agonist added to humidified oxygen was found to improve clinical and laboratory parameters. We believe that further studies should be conducted with larger groups to demonstrate the efficacy of β-2 agonists in TTN patients.

Keywords

neonatology, pulmonology, allergy/immunology, general pediatrics, critical care

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Introduction

Transient tachypnea of the newborn (TTN) is a common condition in the full-term or late preterm infant with an estimated incidence of between 0.5% and 2.8% of all deliveries.[1] TTN is a self-limiting condition. Treatment for TTN comprises supportive care, including supplemental oxygen, withholding of enteral feeds, and administration of intravenous fluids.[2,3]

TTN is thus a nontrivial cause of neonatal respiratory distress despite its transient nature; it may lead to the substantial consumption of health care resources. Infants rarely require mechanical ventilation and continuous positive airway pressure. Occasionally, some newborns develop severe hypoxemia that requires high concentrations of oxygen. Potential therapies for TTN must be based on an understanding of the physiology of normal fetal lung fluid clearance at birth. In the few minutes after birth, endogenous catecholamines and activation of the β-adrenergic system assist the lung epithelium to transition, from a secretory to an absorptive mode by inducing active sodium transport across the pulmonary epithelium.[4-6] Stimulation of β-adrenergic receptors with β-2 adrenergic agonists (β2AA) upregulates alveolar epithelial Na^+ transport by increasing the activity of ENaC (epithelial Na^+ channels) and Na^+-K^+-ATPase (sodium-potassium adenosine triphosphatase) and protein abundance at the plasma membrane.[7,8]

A wide range of drugs are commonly used to treat TTN, but evidence of their effectiveness is limited. In our study, inhaled salbutamol added to humidified oxygen was found to improve clinical and laboratory parameters. It also decreased the need for supplemental oxygen therapy and shortened the duration of hospitalization in the limited number of TTN patients that we studied. We believe that further studies should be conducted with larger groups to demonstrate the efficacy and reliability of β-2 agonists in TTN patients.

[1]Department of Pediatrics, Fatih University, Istanbul Esengül Keleş, MD, Department of Pediatrics, Fatih University, Istanbul

Corresponding Author:
Esengül Keleş, Department of Pediatrics, Fatih University, Sahilyolu Sk., No. 16 Dragos-Maltepe, Istanbul 34844, Turkey
Email: ekeles@fatih.edu.tr

Materials and Methods

Subjects

The present study was retrospectively conducted to evaluate the efficacy of an inhaled salbutamol, β2AA, in transient tachypnea of the newborn infants. Recordings from the term infants monitored and treated with the diagnosis of TNN in the Fatih University Newborn Intensive Care Unit between January 2009 and March 2013 were retrospectively studied. We analyzed the files of the 58 patients (Group1) who received supportive care and oxygen therapy between 2009 and 2011, and who also followed the protocol used in TTN cases at the Fatih University Newborn Intensive Care Unit. The treatment protocol for TTN was changed in our clinic after 2012, and we started to use of a single dose of inhaled salbutamol plus supportive therapy cases of TTN.

We retrospectively studied the records of the 40 term infants (Group 2) who were hospitalized with the diagnosis of TNN and administered salbutamol therapy. The demographic characteristics of the newborns are listed in Table 1.

Inclusion and Exclusion Criteria

Patients were eligible for enrollment if they had completed >36 weeks of gestational age, were <6 hours old at the time of enrollment, and had TTN. The diagnosis of TTN was established according to the criteria of Rawlings and Smith on the basis of radiologic and laboratory findings.[9]

Ten (7 in Group 1, 3 in Group 2) patients having hypoglycemia, hypocalcemia, polycythemia, meconium aspiration, congenital heart disease, or sepsis were excluded from the study. A total of 88 TNN patients who met these criteria were included in the study.

Chest X-rays, acute phase reactants, complete blood counts, blood glucose, and calcium levels were determined in all cases.

At enrollment (by the 6th hour), respiratory rate (breaths/min), heart rate (beats/min), blood oxygen saturation (O_2 Sat), fraction of inspired oxygen (FiO_2), complete blood count, blood glucose and potassium (K^+), arterial blood gases (PH, partial pressure of arterial oxygen [PaO_2], partial pressure of arterial carbon dioxide [$PaCO_2$]), and TTN clinical scores were extracted from the recordings. The scoring system of the Respiratory Distress Assessment Instrument was used for our hospital assessment of the TTN clinical score (see Table 2).[10]

Study Design

Fifty-one patients of Group 1 were administered oxygen and supportive therapies alone; 37 patients of Group 2 received a single dose of salbutamol solution at the standard dose (0.15 mg/kg) with an oxygen flow of 5 to 6 L/min that used a jet nebulizer.[11] Respiratory rate, heart rate, TTN clinic score, FiO_2, PaO_2, PCO_2, PH, blood glucose, and blood K^+ values of 0.5 and 4 hours were separately assessed for each patient in both groups and recorded. The level of respiratory support was categorized as shown in Table 3. All the patients in 2 groups were in level of 3 for respiratory support.

Intravenous fluids (60 mL/kg/day) were given for the first postnatal day; in no case was antibiotic therapy administered and no infants required mechanical ventilation and continuous positive airway pressure.

Table 1. Clinical Scoring of Transient Tachypnea of the Newborn.

	Score			
	0 Point	1 Point	2 Points	3 Points
Expiratory grunting	None	Intermittent	Continuous	—
Supraclavicular retraction	None	Mild	Moderate	Severe
Subcostal retraction	None	Mild	Moderate	Severe
Cyanosis	None	At extremities	Central	—
Nasal flaring	None	Mild	Moderate	Severe

Table 2. Level of Respiratory Support.

Level	Respiratory Support	Oxygen Concentration (%)
1	No oxygen	—
2	Intra-incubator oxygen	30
3	Hood	40
4	Nasal cannula	50 (5 L/min)
5	NCPAP (PEEP: 5 cm H_2O)	50-60

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 15 (SPSS Inc, Chicago, IL). For categorical variables, the χ^2 test was used. For group comparisons, the Student *t* test was used with a normal distribution, and the Mann-Whitney *U* and Kolmogorov-Smirnov tests with abnormal distributions. Variance analyses and Friedman variance analyses were used for repeated measurements. For descriptive statistics, percentage, minimum-maximum, median, mean, and standard deviation were used in accordance with the type and distribution of the variable. A result was considered statistically significant for values of $P < .05$.

Table 3. The Demographic Characteristics of the Infants and Maternal Factors.

	Group 1 (n = 51)	Group 2 (n = 37)	*P*
Gender (females/males)	17/34	10/27	.797
Elective cesarean delivery	44 (86%)	33 (89%)	1.000
Maternal asthma/diabetes	0 (0%)	2 (5%)	.493
Birth weight, g (mean ± SD)	3424 ± 404	3380 ± 276	.585
Gestational age, weeks (mean ± SD)	38.4 ± 1.1	38.2 ± 1.0	.584
White blood cell count (mean ± SD)	15.8 ± 4.7	15.8 ± 4.2	.913
Hemoglobin, g/dL (mean ± SD)	16.8 ± 1.9	16.6 ± 1.9	.982
Apgar score, 5th minute (median [interquartile range])	10 (8-10)	9 (7-10)	.125
O_2 saturation, % (mean ± SD)	99 ± 1	99 ± 1	.590

Results

The gestational ages (mean ± SD) ranged from 37 to 40 weeks (Table 3). The demographic characteristics of the 2 groups were not different ($P > .05$). The median duration of hospitalization was 1 day shorter in the salbutamol group than in the control group ($P < .05$).

Numerical values of the TTN score, respiratory rate, heart rate, FiO_2, PaO_2, PCO_2, PH, blood glucose, and blood K^+ are given in Table 4. After salbutamol administration, there were significant improvements in TTN score, respiratory rate, FiO_2, PH, and PO_2 ($P < .05$). No statistically significant differences were found in PCO_2 among the blood gas measurements, in blood glucose and blood potassium among the biochemical measurements, or in the heart rate ($P > .05$).

Discussion

TTN is a clinical syndrome associated with respiratory distress usually seen shortly after delivery in infants. Delayed resorption of pulmonary fluid has been accepted as the central problem in TTN.[12] Fluid fills the air spaces and moves into the interstitium; it pools in perivascular tissues and interlobar fissures and is eventually cleared by the lymphatics or absorbed into small blood vessels. The excess lung water in TTN leads to decreased pulmonary compliance. Tachypnea develops to compensate for the increased work of breathing associated with reduced compliance.

Based on this physiopathology, previous studies have sought to determine if use of oral or intravenous furosemide could provide excretion of the extra fluid in the lung interstitium. It has been determined, however, that furosemide had no effect on the course of TTN.[13,14]

Fluid restriction may nevertheless be beneficial in the management of severe TTN only. In a trial of 73 preterm and term infants with TTN, a post hoc analysis demonstrated that fluid restriction, compared with standard therapy, reduced the duration of respiratory support for the subset of patients (n = 26) who had severe TTN (defined as requiring respiratory support for >48 hours) without adverse effects.[15]

The currently accepted mechanism of transepithelial movement of lung fluid at the time of birth is by passive movement of Na^+ through ENaC, which is believed to be closed during fetal life but activated by adrenergic stimulation near birth.[16]

Table 4. Values Before and 4 Hours After the Administration of Salbutamol and Humidified Oxygen.

	Group 1 (n = 51)	Group 2 (n = 37)	*P*
TTN clinical score (n)[a]			
Before treatment	7 (6-8)	7 (6-8)	>.05
After treatment	7 (5-8)	2 (1-4)	<.05
P	>.05	<.05	
Respiratory rate (breaths/min)[b]			
Before treatment	73 ± 5	72 ± 6	>.05
After treatment	72 ± 6	60 ± 6	<.05
P	>.05	<.05	
Heart rate (beats/min)[b]			
Before treatment	137 ± 7	136 ± 6	>.05
After treatment	136 ± 10	134 ± 7	>.05
P	>.05	>.05	
FiO_2 (%)[a]			
Before treatment	60 (40-70)	60 (30-60)	>.05
After treatment	60 (45-70)	30 (21-45)	<.05
P	>.05	<.05	
PaO_2 (mm Hg)[b]			
Before treatment	57 ± 20	56 ± 21	>.05
After treatment	53 ± 17	72 ± 17	<.05
P	>.05	<.05	
$PaCO_2$ (mm Hg)[b]			
Before treatment	48 ± 5	46 ± 85	>.05
After treatment	50 ± 4	45 ± 6	>.05
P	>.05	>.05	
pH[b]			
Before treatment	7.31 ± 0.04	7.27 ± 0.05	>.05
After treatment	7.32 ± 0.03	7.39 ± 0.05	<.05
P	>.05	<.05	
Serum K^+ (mEq/L)[b]			
Before treatment	5.0 ± 7	5.5 ± 5	>.05
After treatment	5.0 ± 5	5.3 ± 5	>.05
P	>.05	>.05	
Serum glucose (mg/dL)[b]			
Before treatment	104 ± 7	106 ± 5	>.05
After treatment	109 ± 11	109 ± 6	>.05
P	>.05	>.05	
Duration of hospitalization (days)[a]	3 (2-10)	2 (2-6)	<.05

Abbreviations: TTN, transient tachypnea of the newborn; IQR, interquartile range; SD, standard deviation.
[a]Median (IQR).
[b]Mean ± SD.

It is thought that there is a relationship between the level of endogenous catecholamines released during birth and lung fluid clearance. From this point of view, Aslan et al[6] investigated the association between TTN and β-adrenergic receptor (ADRB 1-2) polymorphisms that are found in type II alveolar cells and that activate Na^+K^+-ATPase by increasing ENaC expression, thus providing absorption of transepithelial sodium. As a result of that study the B1GIy49GIy polymorphism was found to be significantly higher in patients diagnosed with TTN as compared to the control group. The presence of homozygote ADRB1, Ser49Gly, was found to be a risk factor in these patients.

Ex vivo stimulation of lung tissue with an exogenous β-adrenergic agonist has been shown to stimulate lung fluid absorption in both human and animal models.[17-20] In addition, recent in vivo and in vitro models for pulmonary edema suggest that intravenous injection of albuterol (salbutamol), a β-adrenergic agonist, stimulates lung fluid absorption.[21,22]

In another study, Greennough and Lagercrantz et al[23] investigated catecholamine abnormalities in newborns diagnosed with TTN. It was thought that TTN was associated with relatively low levels of epinephrine, which is known to mediate fetal lung fluid absorption.

Kao et al[24] investigated if providing exogenous epinephrine could be a valuable diagnostic and therapeutic intervention for this common condition. They did not find a difference between the 2 groups regarding the rate of tachypnea resolution. On the other hand, for newborns with a diagnosis of TNN, an increase in the persistence of a wheezy chest, childhood asthma, and a familial atopic predisposition later in life were found.[25] Impairment of the β-adrenergic system, if persistent, would predispose such children to have subsequent difficulty with asthma.[26,27] This is consistent with the recent prospective study that suggested that decreased lung function is a predisposing factor for the development of wheezing.[28]

Based on these data and the study of Armangil et al,[29] the treatment protocol used in the newborn intensive care unit of our hospital was changed.[30] A single-dose administration of inhaled salbutamol was initiated in newborns admitted to the neonatal intensive care unit with the diagnosis of TTN after 2012. In this study, TTN newborns who received humidified oxygen therapy alone between 2009 and 2011 were retrospectively compared with those administered single-dose salbutamol therapy between 2012 and 2013. The decreases in respiratory rate, FiO_2, TTN clinical score, and duration of hospitalization were significant in the salbutamol group. These findings suggest that β2AA is an effective treatment option for the clinical course of TTN and reduces the severity of tachypnea over time. A Respiratory Distress Assessment Instrument scoring system was used in our clinic to define the TTN clinical score; this scoring system was preferred because it is noninvasive, easily determined, and shows low interobserver variability.[10]

In our retrospective clinical trial, the decrease in the respiratory support score demonstrates the effectiveness of salbutamol therapy. No recorded adverse effect was observed after a single-dose treatment with salbutamol. Nevertheless, larger prospective studies are necessary to verify the efficacy of inhaled salbutamol as a therapeutic intervention for this common respiratory condition.

Author Contribution

Esengül Keleş contributed in data collection Arzu Gebeşçe, AlparslanTonbul & Bülent Bastürk helped in data collection, Mehmet Demirdöven translated the manuscript in English, Hamza Yazgan contributed to manuscript writing.

Declaration of Conflicting Interests

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