Inhaled Beta-2 Agonist Salbutamol for the Treatment of Transient Tachypnea of the Newborn

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Objective To evaluate the efficacy of inhaled salbutamol, a beta-2 adrenergic agonist, for the treatment of transient tachypnea of the newborn (TTN) and to determine whether inhaled salbutamol is safe in newborn infants.

Study design Inhaled salbutamol or normal saline solution was administered to 54 infants with gestational ages ranging from 34 to 39 weeks and TTN. The response to salbutamol therapy was evaluated by determining respiratory rate, clinical score of TTN, level of respiratory support, and fraction of inspired oxygen before and at 30 minutes and 1 and 4 hours after salbutamol nebulization.

Results Among the 54 infants with TTN, 32 received salbutamol and 22 received normal saline solution. After one dose, the salbutamol group showed significant improvements in respiratory rate, clinical score of TTN, fraction of inspired oxygen, and level of respiratory support ($P < .05$). After treatment, the mean pH, partial pressure of arterial oxygen, and partial pressure of arterial carbon dioxide values were better in the salbutamol group when compared with the placebo group ($P < .05$). Duration of hospitalization in the neonatal intensive care unit was also shorter for the salbutamol group ($P < .05$).

Conclusion Inhaled salbutamol treatment was effective with respect to both clinical and laboratory findings of TTN and without adverse events. *(J Pediatr 2011;159:398-403)*.

In the neonatal period, transient tachypnea of the newborn (TTN) is the most frequent cause of early respiratory distress because of delayed resorption of the fetal lung fluid, which fills the fetal airways.[1,2] Lung liquid clearance at birth is associated with the surge in fetal catecholamines acting via β-adrenergic receptors located in alveolar type II cells and driven by active sodium (Na^+) absorption by increased epithelial Na^+-channels (ENaC) and sodium-potassium adenosine triphosphatase (Na^+-K^+-ATPase) activity.[3] The inability of the fetal lung to switch from fluid secretion to fluid absorption and an immaturity in the expression of the ENaC may play an important role in the development of TTN.[4]

Stimulation of β-adrenergic receptors with beta-2 adrenergic agonists (β2AA) up-regulates alveolar epithelial Na^+ transport by increasing the activity of ENaC and Na^+-K^+-ATPase and protein abundance at the plasma membrane.[5,6] The potential therapeutic role of β2AA in hastening the resolution of alveolar pulmonary edema was suggested from animal and ex vivo human lung studies.[7,8] We conducted a randomized, double-blinded clinical trial of inhaled salbutamol for the treatment of TTN. We hypothesized that inhaled salbutamol would increase the rate of absorption of fetal lung fluid in newborns with TTN, thereby improving clinical outcomes. Our objective was to evaluate the efficacy of inhaled salbutamol, a β2AA, for this new indication, and to determine whether inhaled salbutamol is safe in newborn infants.

Methods

The study was performed at the Neonatal Intensive Care Unit (NICU) of Hacettepe University Children's Hospital, Ankara, Turkey, between January 2007 and January 2009. A total of 54 infants with TTN were randomly allocated in a double-blind placebo-controlled study to receive either inhaled salbutamol (n = 32) or an equal volume of normal saline solution placebo (n = 22) at the time of diagnosis. Informed consent was obtained from parents, and the study was approved by the local ethical committee.

Patients were eligible for enrollment if they were diagnosed with TTN and were <6 hours old. The diagnosis of TTN was according to the criteria of Rawlings and Smith[9] on the basis of radiologic and laboratory findings of (1) onset of tachypnea (respiratory rate exceeding 60 breaths/min) within 6 hours after birth; (2) persistence of tachypnea for at least 12 hours; (3) chest radiograph indicating at least one of the following: prominent central vascular

β2AA	Beta-2 adrenergic agonists
ENaC	Epithelial Na^+-channels
Fio_2	Fraction of inspired oxygen
K^+	Potassium
Na^+	Sodium
Na^+-K^+-ATPase	Sodium-potassium adenosine triphosphatase
NICU	Neonatal intensive care unit
O_2 Sat	Blood oxygen saturation
$Paco_2$	Partial pressure of arterial carbon dioxide
Pao_2	Partial pressure of arterial oxygen
TTN	Transient tachypnea of the newborn

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The authors declare no conflicts of interest.

0022-3476/$ - see front matter. 10.1016/j.jpeds.2011.02.028

markings, widened interlobar fissures of pleural fluid, symmetrical perihilar congestion, hyperaeration as evidenced by flattening and depression of the diaphragmatic domes or increased anteroposterior diameter, or both; and (4) exclusion of other known respiratory disorders (meconium aspiration, respiratory distress syndrome, pneumonitis, congenital heart diseases), and nonrespiratory disorders (hypocalcemia, persistent hypoglycemia, polycythemia) likely to cause tachypnea. Excluding criteria for acute respiratory distress syndrome were as follow: no predisposing factor such as diffuse pulmonary opacities on radiography, severe hypoxia, sepsis, the syndrome of multiple organ failure, disseminated intravascular coagulation, and iatrogenic lung injury (higher respiratory support techniques such as high tidal volumes and pressure support). Respiratory distress syndrome was excluded if there was no reticulogranuler pattern on the x-ray film and no surfactant therapy. Meconium aspiration syndrome was excluded if there were no x-ray findings (irregular pattern of increased density throughout the lung) and no meconium staining of the skin. Infants who received diuretics and antibiotics were excluded from the study.

At enrollment (by the 6th hour), 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 [$Paco_2$]), respiratory rate (breaths/min), heart rate (beats/min), blood oxygen saturation (O_2 Sat), fraction of inspired oxygen (Fio_2), and TTN clinical score were determined for all patients. A clinical evaluation of respiratory distress was performed with a new TTN clinical score that we developed by use of the Respiratory Distress Assessment Instrument scoring system,[10] which was used for babies with wheezing. Expiratory grunting, supraclavicular retraction, subcostal retraction, cyanosis, and nasal flaring were evaluated separately and scored from 0 to 3 as in Table I. The TTN clinical score was determined before treatment and after treatment at 30 minutes and 1 and 4 hours (0.5, 1, and 4 hours) (range 0-13 points).

The TTN scores were determined by one physician. The bedside nurse was blinded to group assignment and thus to the administered drug. A respiratory rate of more than 60 breaths/min was defined as tachypnea.[11]

Salbutamol or Placebo Treatment

Patients were randomized in a blinded manner to receive one nebulized dose of either 0.9% normal saline solution 4 mL (placebo), or a solution of salbutamol 4 mL (Ventolin Nebules 2.5 mg) in 0.9% saline solution. The standard dose of salbutamol was 0.15 mg/kg.[12] Solutions were given with a jet type nebulizer with continuous flow of oxygen at 5 to 6 L/min. One dose was administered over the course of 20 minutes, and vital signs were monitored for 4 hours. 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.

Table I. Clinical scorring of TTN

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 II. 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 cmH_2O)	50–60

nCPAP, Nasal continuous positive airway pressure; *PEEP*, positive end-expiratory pressure.

At 0.5, 1, and 4 hours after drug administration, respiratory rate, heart rate, O_2 Sat, Fio_2, and the clinical TTN score were recorded. The goal was to keep the O_2 Sat between 85% to 93%. The level of respiratory support was assigned as in Table II. The duration of total respiratory support was calculated in hours as a total oxygen support via the incubator, nasal cannule, oxygen hood, or nasal continuous positive airway pressure.

At 4 hours after treatment, arterial blood gases, serum K^+, and glucose levels were measured again. The duration of total respiratory support was recorded along with the duration of hospitalization. The intravenous fluids were given as 60 mL/kg/d for term babies and 80 mL/kg/d for preterm infants for the first postnatal day. Demographic characteristics of newborns are listed in Table III.

Statistical Evaluation

Statistical analyses were performed with the Statistical Package for Social Sciences-SPSS version 15 software (SPSS Inc, Chicago, Illinois). For categorical variables, the χ^2 test was used. For group comparisons, the Student t test was used in normal distribution and the Mann-Whitney U test was used in case of abnormal distribution. For repeating measurements, variance analyses and Friedman variance analyses were used. For descriptive statistics, percent, minimum-maximum-median, mean, and standard derivation were used in accordance with the type and distribution of the variable. A P value $<.05$ was considered statistically significant.

Results

The gestational ages (mean ± SD) ranged between 34 and 39 weeks (Table III). There were no differences between the two groups in demographic characteristics ($P > .05$). The median duration of hospitalization was 2 days shorter for the salbutamol group than the control group.