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ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 990–997

www.jcma-online.com

Original Article

The effect of inhaled salbutamol on the outcomes of transient tachypnea of the newborn

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Received October 25, 2017; accepted January 31, 2018

Abstract

Background: Transient tachypnea of the newborn (TTN) is a self-limiting disease that results from a reduction in the rate of lung fluid clearance in neonates. A delay in lung fluid absorption in neonates disrupts the transition from intrauterine to extrauterine life. Use of beta-adrenergic antagonists, such as salbutamol, accelerates lung fluid clearance. The current study aimed to evaluate the effect of inhaled salbutamol on the clinical progression of TTN treatment.

Methods: In the current triple-blind clinical trial, a total of 148 inpatients diagnosed with TTN were randomly divided into 2 groups. The treatment group (n = 74) received inhaled salbutamol and the placebo group (n = 74) received inhaled normal saline. The drug administration was started 6 h after birth and continued in the case of continued respiratory distress and the need for oxygen as adjuvant therapy for up to 72 h maximum after the initiation of treatment. To evaluate the response to treatment with inhaled salbutamol, we assessed the respiratory rate (RR), heart rate (HR), fraction of inspired oxygen (FIO2) level, and O_2 saturation at intervals of 30 min as well as 1 h and 4 h after drug administration. The results were compared between the groups.

Results: The results of the current study indicated a significant difference between the treatment and placebo groups in the treatment duration, hospitalization duration, need for continuous positive airway pressure therapy (CPAP), and time of oral feeding initiation. In addition, no complication was observed during the treatment. It is noteworthy that, following the improvement of disease symptoms and reduction of hospitalization. This reduction may decrease the treatment costs and anxiety of parents, which was associated with proper mental and economic outcomes.

Conclusion: Although, in the current study, drug administration was continued for 72 h maximum, the prescription of at most 4 doses of salbutamol may have had maximum efficiency in the remediation process. To evaluate the therapeutic role of inhaled salbutamol, further studies are recommended.

Keywords: Inhaled; Newborn; Salbutamol; Transient tachypnea

1. Introduction

Respiratory diseases are very common among newborns and transient tachypnea of the newborn (TTN) is one of the most common. TTN results in admission to a neonatal intensive care unit (NICU) for treatment of the reduction in the rate of lung fluid clearance after birth. A delay in lung fluid absorption in neonates disrupts the transition from intrauterine to extrauterine life.[1–4]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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https://doi.org/10.1016/j.jcma.2018.01.015

In some newborns, TTN exacerbates to prolonged tachypnea, which may result in respiratory failure (hypoxia, respiratory fatigue, and acidosis) and the requirement for intubation and mechanical ventilation. Additionally, a very low number of such infants may develop air leakage from the lung (as pneumothorax and pneumomediastinum). The risk of such complications is increased in patients undergoing continuous positive airway pressure therapy (CPAP) therapy. However, some of these patients develop pulmonary hypertension, also called malignant TTN.[5–7]

TTN is controlled via supportive treatment, hyperbaric oxygenation therapy, antibiotic therapy, and liquid therapy. In addition to the preservative treatments, the effect of Lasix®, epinephrine,[8] inhaled salbutamol,[9] and limitation in fluid intake[9] was assessed during TTN.

Foetal catecholamines (adrenaline and glucocorticoids) are released through the stimulation of beta-adrenergic receptors in alveolar type 2 cells in response to labour stress. Such conditions result in an increase in epithelial sodium channels and sodium-potassium triphosphates (Na-K-ATPase) pumps on the surface of the membrane and, consequently, the respiratory active mode transits from the secretion of chloride and liquids to the reabsorption of sodium.[10] Infants' lungs are unable to transition the respiratory-mode from secretion to reabsorption of liquids; in addition, lung immaturity in the expression of sodium channels on the surface of epithelial cells can play a remarkable role in the incidence of TTN.[11] Stimulation of beta-adrenergic receptors by beta-adrenergic agonists, such as salbutamol, is effective in increasing the activity of epithelial sodium channels and Na-K-ATPase pumps.[12] Different studies have investigated patients with TTN focusing on the effects of both oral and injection furosemide, inhaled epinephrine, and an inhaled β2 antagonist (salbutamol). They reported inefficiency of epinephrine and furosemide on the duration of TTN.[13] In addition, use of salbutamol as a standard treatment needs more investigation.[9] Hence, since TTN is a self-limiting disease and one of the most common respiratory complications in newborns, more targeted investigations are required to reduce the duration of the disease. The current study aimed at evaluating the effects of inhaled salbutamol on the clinical process of TTN.

2. Methods

The current triple-blind, randomized, clinical trial (registration NO. IRCT2016081329336N1) was conducted during a year in the NICU of Imam Khomeini Hospital affiliated with Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The following symptoms were assessed in all patients with TTN based on the clinical and paraclinical criteria of TTN: the incidence of tachypnea (RR > 60) within the first 6 h of birth and the CXR index, including at least one of the following symptoms: congestion of central lung vessels, thickening of the interlobar fissures due to high altitude pulmonary oedema, symmetrical hilar congestion, hyperaeration, mean flattening of the diaphragm or an increased posteroanterior chest diameter or both. The exclusion criteria were the need for mechanical ventilation during the study, congenital malformation, perinatal asphyxia, hypocalcemia, confirmed systemic infection (positive blood culture), meconium aspiration, respiratory distress syndrome (based on the radiographs), intrauterine growth retardation, history of foetal distress, pneumonitis, congenital heart disease, disseminated intravascular coagulation (DIC), multi-organ failure, hypoxaemia, hypoglycaemia, and polycythaemia.

A total of 151 newborns with TTN were enrolled in the study and, after dropouts, a total of 148 infants (74 cases in each group) were followed up (Fig. 1). The objectives of the study were completely explained to the parents, and those in agreement provided written informed consent. The study protocol was designed based on the Ethical Principles for Medical Research, Declaration of Helsinki, and the study was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (ajums.REC.1393.390). The eligible cases were randomly assigned into one of the study groups using a table of random numbers. No significant difference was observed between the groups regarding heart rate, O_2 saturation, FIO_2, and respiratory rate.

Salbutamol or normal saline (placebo) was administered to the treatment or control group, respectively. Patients inhaled the salbutamol/normal saline through the jet ultrasonic nebulizer with the oxygen flow at 5–6 L/min within 20 min each time. In the case of continuation of respiratory distress and the need for oxygen therapy, the drug was administered every 6 h for a maximum 72 h after the initiation of treatment. The salbutamol dose was 0.15 mg/kg of body weight. Serum therapy and empirical antibiotic treatment were similarly administered to both groups. Respiratory rate (RR), heart rate (HR), level of fraction of inspired oxygen (FIO2) and O_2 saturation were assessed at the intervals of 30 min as well as 1 h and 4 h after receiving each dose. The TTN scoring system (Table 1) was used to assess the infant respiratory status after the administration of each dose.[8]

The level of oxygen therapy in the patients was determined based on Table 2. In the cases with mild respiratory distress (score <5) lasting < 4 h monitoring, as well as adjuvant oxygen therapy, was continued. CPAP therapy was performed in patients with moderate (score 5 to 8) or mild respiratory distress for more than 4 h. The mechanical ventilation was employed in patients with severe respiratory distress (score >8), apnoea, or gasping.[14]

At the beginning of the study, the cell blood count (CBC), arterial blood gas (ABG), calcium, glucose, potassium, and C-reactive protein (CRP) levels were assessed. Blood cultures were analysed 12 h after the onset of treatment, and potassium and ABG were controlled. During the study, the duration of hospitalization, time of oral feeding initiation, duration of oxygen therapy, and need for nasal CPAP therapy and mechanical ventilation were recorded. Patients were cared for by the assistants and NICU nurses who were blind to the study objectives and nature of the groups. All patients, physicians, and statistics experts were blind to the drug and placebo

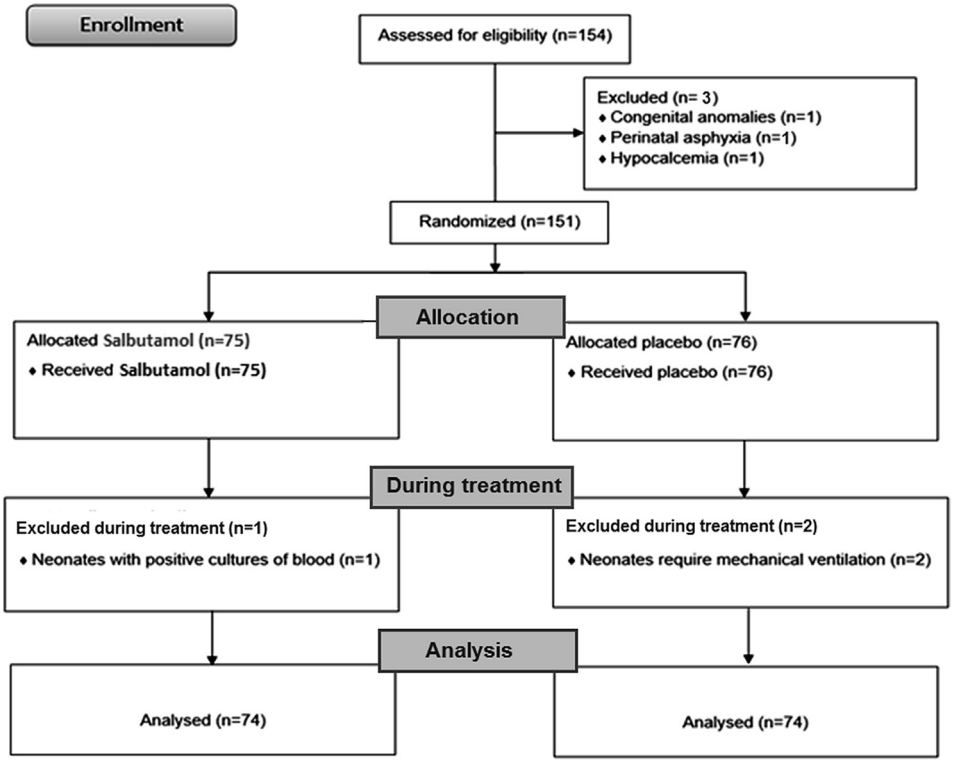

Fig. 1. The procedure of inclusion and analysis of the study subjects.

Table 1
Criteria for respiratory status assessment and TTN scoring in the study subjects after receiving each dose.

Score	0 Point	1 Point	2 Points	3 Points
Expiratory Grunting	None	Intermittent	Continuous	_
Supraclavicular Retraction	None	Mild	Moderate	Severe
Subcostal Retraction	None	At	Central	_
Cyanosis	None	Extremities	Moderate	Severe

Table 2
Criteria for oxygen therapy assessment in the study subjects.

Score	0	1	2
Respiratory rate	40–60	60–80	>80
Need for oxygen therapy	No	≤50%	>50%
Retraction	No	Mild-moderate	Severe
Moaning	No	By stimulation	Continuous
Breathing sound	Easy to hear	Reduced	Difficult to hear
Prematurity	>34 weeks	30–34 weeks	<30 weeks

preparations and administrations, as well as treatment procedures. The following variables were determined based on the study objectives: age, gender, weight, duration of hospitalization, time of oral feeding initiation, O_2 saturation value, type of employed ventilation, and maternal health status. Data were recorded with a researcher-made questionnaire.

The data were analysed with SPSS version 15. The quantitative and qualitative variables were compared between the groups using *t* and chi-squared tests, respectively. $p < 0.05$ was considered as the level of significance.

3. Results

The results of the current study indicated that, of 148 infants with TTN, 101 (68.24%) were male and 47 (31.75%) female. The number of males was significantly higher than the number of females ($p < 0.05$). The treatment group included 54 males and 20 females, and the control group consisted of 47 males and 27 females. No significant difference was observed between the groups regarding gender distributions ($p > 0.05$).

The mean age of the mothers was 26.53 ± 5.58 and 27.92 ± 5.75 years in the treatment and control groups, respectively. No significant difference was observed between the groups regarding the mean age of the mothers ($p > 0.05$). The results of the current study indicated that 131 (88.51%) mothers were completely healthy and only 17 (11.5%) had diabetes, of which 2 (1.4%) also had high blood pressure. No significant difference was observed between the groups regarding the distribution of healthy and non-healthy mothers ($p > 0.05$). The highest number of pregnancies was 7, which was observed in 2.38% of the mothers; most of them (34.5%) were primiparous. The mean gestational age was 37.6 ± 1.49 and 37.4 ± 1.89 weeks in the treatment and control groups, respectively. No significant difference was observed between the groups regarding the gestational age ($p = 0.4$).

In the current study, 126 (85%) infants with TTN were delivered by a caesarean procedure and 22 (15%) cases gave birth vaginally. The mean weight of the infants was 3.02 ± 1.15 kg; ranging from 2.5 to 4 kg. No significant difference was observed between the groups regarding infants' weights ($p = 0.9$).

No significant difference was observed between the treatment and control groups regarding the TTN score (8.41 ± 1.84; 8.82 ± 2.11, $p = 0.208$) and degree of respiratory distress (6.03 ± 0.70; 6.18 ± 0.99, $p = 0.297$).

The mean number of doses in the treatment and control groups was 4.36 ± 2.84 and 8.17 ± 3.37, respectively (Fig. 2). The mean time of need for oxygen was 30.36 ± 19.52 and 58.92 ± 33.87 h in the treatment and control groups, respectively. The results showed a significant difference between the groups for the duration of oxygen therapy ($p < 0.001$). According to the results of the current study, the mean time of oral feeding initiation was 36.92 ± 19.08 and 67.18 ± 41.12 h in the treatment and control groups, respectively. There was a significant difference between the groups regarding the time of oral feeding initiation ($p < 0.001$). The mean duration of hospitalization in the study population was 3.94 ± 1.32 and 5.66 ± 2.32 day in the treatment and control groups, respectively. The results showed a significant difference between the groups in the duration of hospitalization ($p < 0.001$) (Table 3).

The results of the current study showed that CPAP therapy was employed for all subjects, except 13 infants; 2 subjects required mechanical ventilation and both were delivered via caesarean section from healthy mothers. CPAP was employed for all subjects in the treatment group, except for 20 infants. In addition, the mean CPAP run time was 11.41 ± 12.20 and 21.68 ± 22.82 h in the treatment and control groups, respectively. There was a significant difference between the groups in CPAP run times ($p = 0.001$) (Table 3).

On average, the levels of PCO_2, HCO_3, PO_2, and pH increased after the treatment compared with those of pre-treatment and the results showed significant differences in this regard ($p > 0.05$).

The mean level of potassium before and after the treatment was 4.44 ± 3.32 and 4.11 ± 0.25 mEq/L, respectively. The mean level of serum glucose in the study population before and after the treatment was 69.4 ± 5.2 and 72.3 ± 6.8 mg/dL, respectively. No significant difference was observed between the groups regarding the levels of potassium and glucose before and after the treatment ($p > 0.05$).

Changing trends of HR, RR, FIO_2, and SO_2 between the first and last doses are shown in Fig. 3 and Fig. 4. A comparison of the variables between the groups is shown in Table 4.

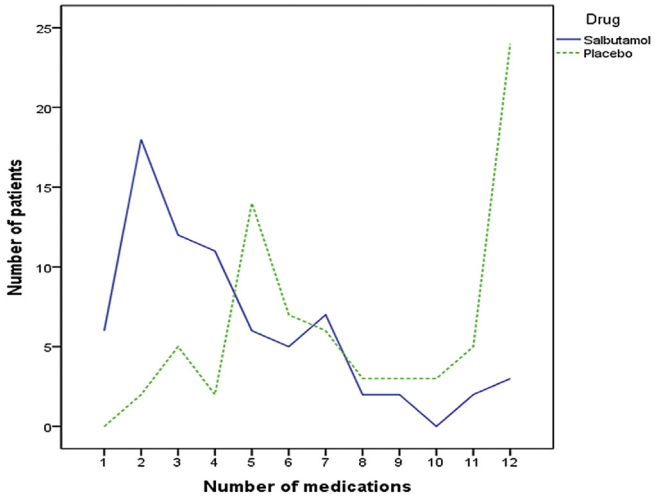

Fig. 2. Number of patients based on dose numbers in the study groups.

4. Discussion

TTN causes a delay in lung fluid absorption and cannot be easily distinguished from other neonatal respiratory complications. Hence, due to the time-consuming diagnostic process, newborns who develop TTN symptoms should be treated to prevent complications.[15,16]

The routine treatments included liquid therapy, antibiotic therapy, oxygen therapy, and supportive treatments. Other potential treatments relied on the physiology of normal clearance of lung fluid and other therapeutic challenges were conducted to accelerate the absorption of lung fluid. Antibiotic therapy and fluid therapy doses were increased if the treatment procedure and duration of hospitalization was prolonged.[4]

In the current study, most of the 148 infants with TTN were male, and a significant difference was observed in the gender distribution. Additionally, the incidence rate of disease was higher among the infants delivered by caesarean section, compared to the infants delivered vaginally. A significant difference was observed between the number of caesarean and vaginally delivered infants, which may be attributed to the lack of labour pain resulting from a lack of stress hormone

Table 3
Comparison of infants based on the administered medicine.

Variable	Treatment Group	Control Group	*p*
Female	20	27	0.2
Male	54	47	
Gestational age, week	37.6 ± 1.49	37.4 ± 1.89	0.4
Birth weight, kg	2.81 ± 0.44	2.81 ± 0.5	0.9
Mother's age, year	26.92 ± 4.88	26.82 ± 5.25	0.8
Duration of Hospital Stay, day	3.94 ± 1.32	5.66 ± 2.32	<0.001
Time of oral feeding initiation, hour	36.92 ± 19.08	67.18 ± 41.12	<0.001
TTN Score, before treatment	8.41 ± 1.84	8.82 ± 2.11	0.208
Degree of respiratory distress, before treatment[a]	6.03 ± 0.70	6.18 ± 0.99	0.297
Duration of need for oxygen therapy, hour	30.36 ± 19.52	58.92 ± 33.87	<0.001
Duration of need for CPAP therapy, hour	11.41 ± 12.20	21.68 ± 22.82	0.001

[a] According to Acute Care of At-Risk Newborns (ACoRN) respiratory distress.

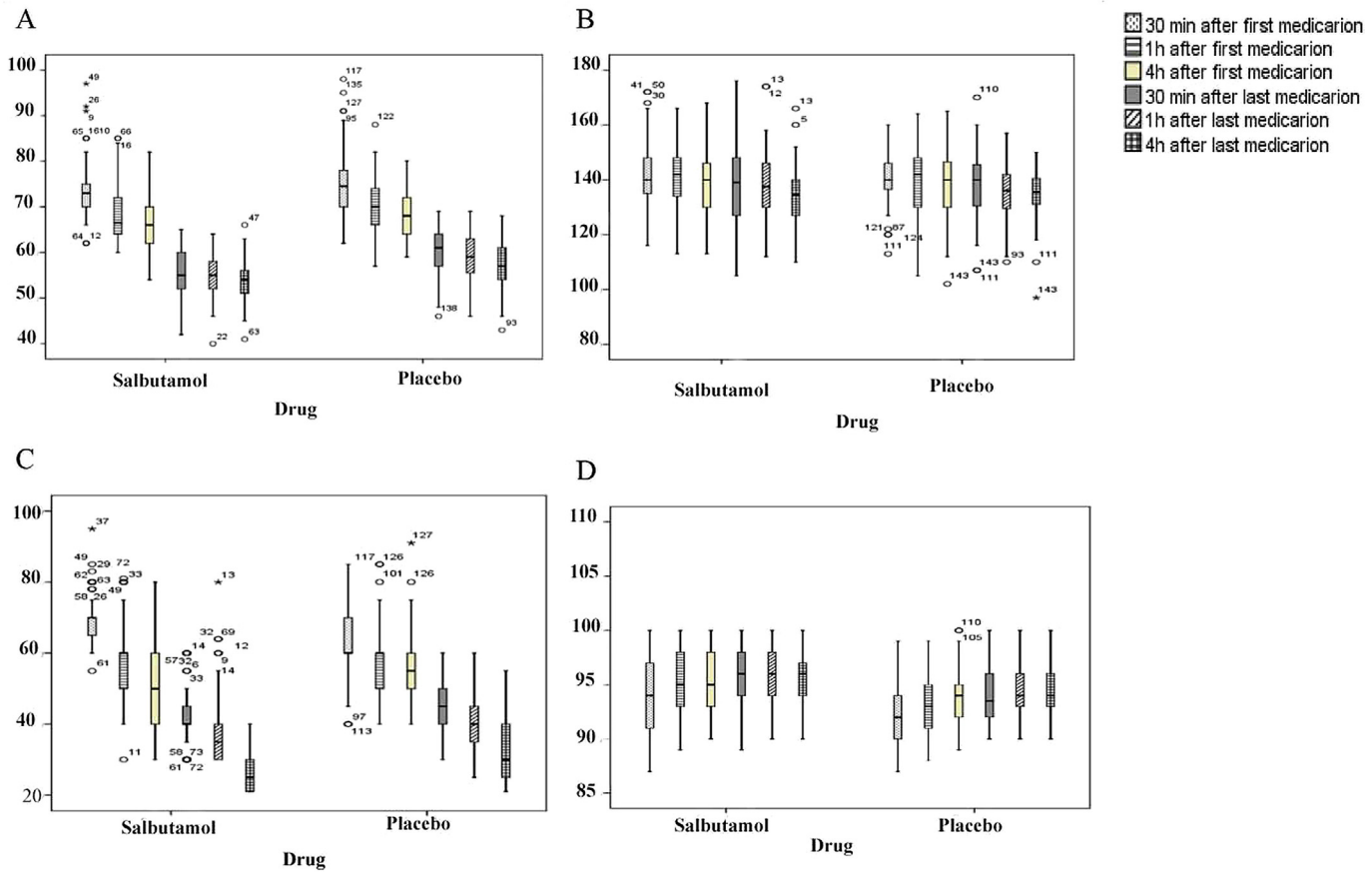

Fig. 3. The trend of some variables in the study groups at different intervals with the first and last doses. A. RR changes; B. HR; C. FIO_2; D. SO_2.

secretion and a delay in the expression of amiloride-dependent sodium channels. These results were consistent with those of other studies.[8,13]

Different studies evaluated the effects of epinephrine and furosemide on TTN and they reported no efficiency for these drugs.[8,15] Stimulation of beta-adrenergic receptors by β2-adrenergic agonists such as salbutamol may result in the expression of epithelial sodium channels on the membranes of alveolar cells by increasing the activity of Na-K-ATPase and ENaC on plasma membranes.[9] The results of the current study on the effect of inhaled salbutamol for the treatment of TTN showed significant differences between the treatment and control groups in favour of the treatment group in RR, FIO_2, oxygen therapy, the duration of hospitalization, and time of oral feeding initiation. The results indicated the efficiency of β2-adrenergic agonists (salbutamol) for the treatment of TTN and the improvement of tachypnea during the treatment course.

The results of a clinical trial by Kim et al. on the effect of inhaled salbutamol on the treatment of TTN showed that the duration of tachypnea and oxygen therapy was shorter in the treatment group compared with that of the control group, and the difference between the groups was significant.[16] In a study by Armangil et al., a significant improvement was observed in patients who received a dose of inhaled salbutamol, compared with the control group in RR, clinical status, and duration of hospitalization.[9] The results of these studies were consistent with those of the current study in regard to the positive effect of salbutamol on the treatment of TTN.

Complicated and diabetic pregnancies have different outcomes in both the foetus and mother, which can be prevented by proper control of blood glucose at pre-gestation, gestation, and even during labour. Although some of the diabetes outcomes had permanent impacts on the foetus, some others were controllable and curable by special care after birth. Newborns of mothers with type 2 diabetes develop TTN 3 times more often than the ones with healthy mothers; the mechanism can be attributed to the reduced clearance of lung fluid in foetus from a diabetic mother. Caesarean section occurs more among such pregnancies and can be considered another contributing factor.

The results of the current study showed that the duration of hospitalization, time of oral feeding initiation, duration of oxygen therapy and CPAP therapy were higher among infants with diabetic mothers, compared to the ones with healthy mothers; however, no significant difference was observed between the groups regarding the mentioned variables.

According to the results of the current study, the duration of oxygen therapy was shorter in the treatment group, compared with the control group, and the difference between the groups was significant; although the differences between the groups were not significant regarding the time of tachypnea initiation, initial RR, O_2 saturation, and FIO_2 at the beginning of hospitalization. It seems that salbutamol reduces the need for

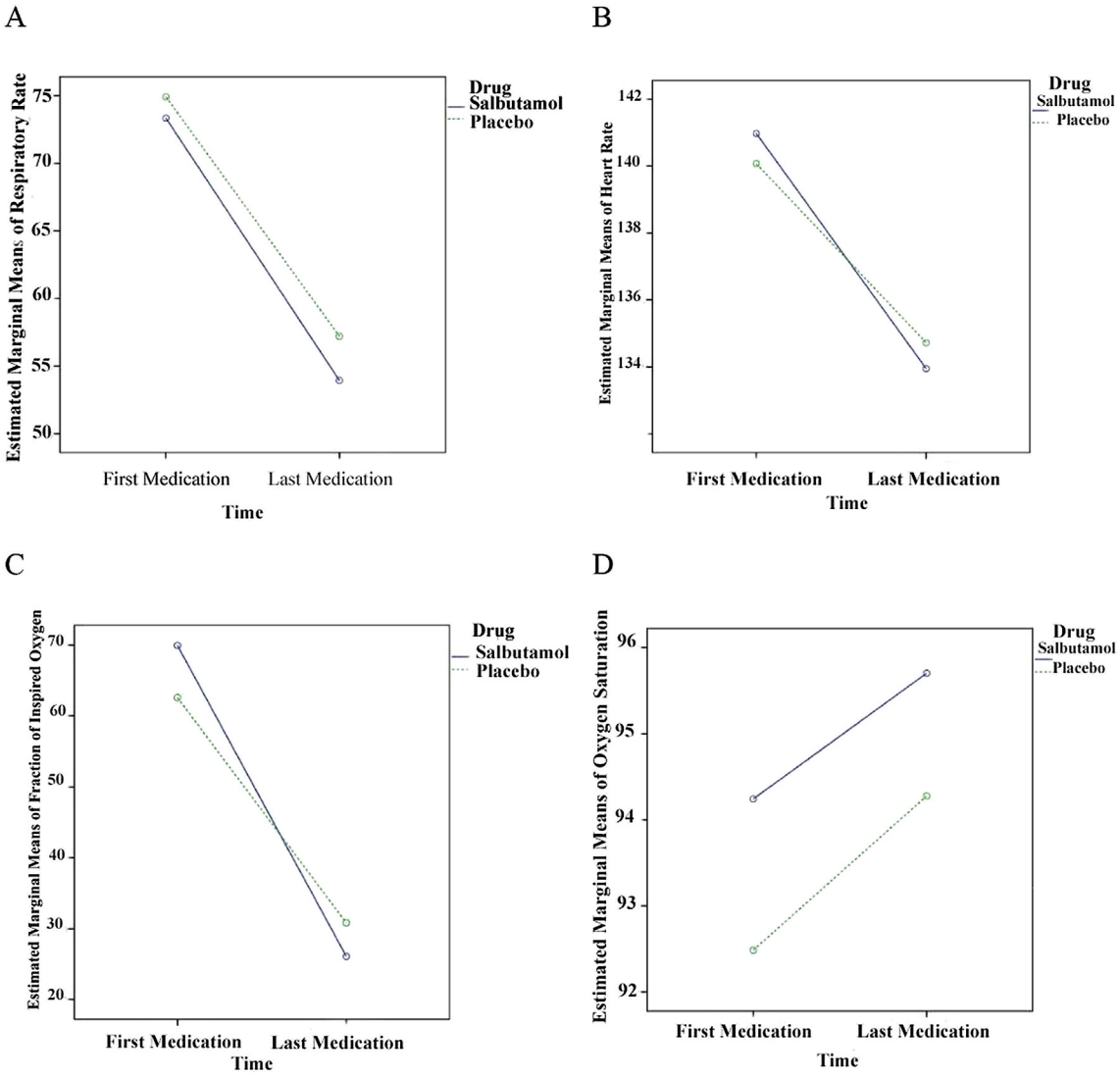

Fig. 4. Trend of changes in the study groups on the first and last doses. A. RR changes; B. HR; C. FIO_2; D. SO_2.

oxygen as adjuvant therapy during TTN treatment. The results of a similar study in Korea also showed a significant difference between the groups in the duration of oxygen therapy, which was consistent with the current study.[16]

In the current study, the duration of CPAP therapy in the treatment group was shorter than that of the control group, and the difference between the groups was significant. In addition, 2 subjects in the control group required mechanical ventilation, while no respiratory failure and need for ventilation were reported in the treatment group. The number of patients who required CPAP therapy in the treatment group was less than in the control group, although the difference was not significant. Since CPAP causes a functional residual capacity (FRC) and affects lung fluid clearance via positive pressure respiration, the difference between the groups was in favour of the effect of salbutamol on the clearance of fluid from alveoli and treatment progression. It seems that inhaled salbutamol reduced the level of respiratory support in patients with TTN.

In the control group of the current study, 2 subjects underwent mechanical ventilation to support respiration, which may be attributed to the exacerbation of malignant TTN and increase of pulmonary arterial pressure. Although the number of patients who required mechanical ventilation was not significant, medical treatment may prevent malignant TTN; however, to confirm the results, further investigations are required.

The results of the FIO_2 assessment in the current study are shown in Tables 3–5. Significant differences were observed between the groups regarding pH, PaO_2, and $PaCO_2$, which indicates the effect of treatment on the level of FIO_2 in favour of the treatment group; lung fluid clearance produced improvement in the exchange and regulation of ABG. The results were consistent with those of Armangil et al.[9]

Several side effects were reported for salbutamol including hypokalaemia, tachycardia, chills, and arrhythmia, which is supraventricular tachycardia and particularly occurs following salbutamol infusion. The inhaled form of salbutamol reaches the lungs more effectively and has less systemic side effects. Although salbutamol was used as a bronchodilator in premature infants to treat bronchopulmonary dysplasia and was also

Table 4
Comparison of the effects of administered drugs based on the intervals and regulation of variables.

Parameter	Times	Treatment Group	Control Group	p[a]
RR				0.17
	Time 1	73.3 ± 6.3	75.1 ± 7.9	
	Time 2	53.9 ± 4.1	57.1 ± 5.4	
HR				0.17
	Time 1	140.9 ± 12.1	139.9 ± 9.2	
	Time 2	133.9 ± 9.9	134.7 ± 9.4	
FIO2				<0.0001
	Time 1	69.9 ± 6.6	63.1 ± 10.8	
	Time 2	26.1 ± 5.1	30.8 ± 8.3	
SO_2				0.03
	Time 1	94.2 ± 3.4	92.6 ± 2.9	
	Time 2	95.7 ± 1.9	94.2 ± 2.0	

[a] The p value was calculated based on the regulation of variables such as duration of hospital stay, PO, need for oxygen therapy, CPAP, and dose number at the intervals of 30 min after giving the first dose (Time1) as well as 1 h and 4 h after giving the last dose (Time 2).

administered in the treatment of hyperkalemia and recently to treat TTN, there are still concerns about potential side effects of this drug, especially on HR. Hence, monitoring of HR during treatment with salbutamol was recommended.[17] In the current study, patients were monitored for serum glucose and potassium levels at regular intervals during the treatment and controlled for RR after receiving each dose of the drug due to the potential side effects of salbutamol. However, tachycardia, hypokalaemia, hyperglycaemia, and evidence of arrhythmia were not observed in any of the study subjects following the administration of inhaled salbutamol. Both studies by Armangil in Turkey[9] and Kim[16] in Korea used a single dose of inhaled salbutamol for the treatment of TTN and none of them reported arrhythmia, hypokalaemia, and hyperglycaemia. The results of their studies were in agreement with those of the current study regarding the safety of inhaled salbutamol for infants. In addition, since the administration of salbutamol was continued for 72 h after the onset of treatment in patients with prolonged respiratory distress and most of the subjects received several doses of the medicine, the safety of inhaled salbutamol in infants is more acceptable.

The vital signs were assessed after the administration of each dose of drug/placebo in intervals of 30 min as well as 1 h and 4 h in both groups. The results showed a significant difference between the groups in favour of the treatment group regarding the reduction of RR during the treatment course. The results indicated the efficiency of inhaled salbutamol on the improvement of tachypnea symptoms and the duration of tachypnea in patients with TTN. Shortening the duration of tachypnea shortens the duration of oxygen and antibiotic therapy and finally results in shorter hospitalization as well as lower costs imposed on the patient and health system. The results of 2 aforementioned studies conducted in Turkey and Korea[9,16] also indicated a shorter tachypnea duration in the treatment group, compared with the control group, which was consistent with the results of the current study regarding the positive effect of salbutamol on the reduction of the severity and duration of tachypnea.

Various studies have indicated a significant difference between the first and last doses in the treatment and control groups regarding FIO2. In addition, a number of infants in the treatment and control groups who underwent oxygen therapy ($FIO_2 < 30\%$) with the final dose of salbutamol was 23 and 40, respectively; although the difference between the groups was not significant, the results supported the therapeutic role of salbutamol in clinical improvement and the reduced need for oxygen therapy.

The results of a study in Turkey also indicated a significant difference between the treatment and control groups regarding the reduced need for FIO2.

The duration of hospitalization in the treatment group was shorter than that of the control group in the current study, and the difference between the groups was significant. It seems that the positive effect of salbutamol on the reduction of tachypnea severity and the need for oxygen therapy shortened the duration of hospitalization. In addition, a similar study conducted in Turkey also showed a significant difference between the treatment and control groups regarding the duration of hospitalization. Another study in Korea also indicated shorter hospitalization in the treatment group, compared with the control group, although the difference was not significant.[16]

Table 5
Comparison of the results of the current study with two similar studies.

Results With Significant Differences	Drug Prescription Pattern	Number of Subjects		Reference
		Treatment Group	Control Group	
1. Reduction in the duration of oxygen therapy 2. Reduction in the duration of antibiotic therapy 3. Maximum RR reduction during 72 h	A single and similar dose of drug/placebo	28	12	18
1. Reduction in hospital stay 2. Improvement in TTN clinical score after the treatment 3. Reduction in RR after treatment 4. Improvement in PaO_2, PCO_2, FIO_2, and pH	A single and similar dose of drug/placebo	22	32	9
1. Reduction in the duration of oxygen therapy 2. Reduction in hospital stay 3. Reduction in need for CPAP therapy 4. Shortening the time of oral feeding initiation 5. Improvement in RR and FIO2 in the last dose of medication	Several, but similar, doses of drug/placebo	74	74	The current study

In the current study, a drug/placebo was given to the subjects in different doses; it was started 6 h after birth and continued for a maximum of 72 h in the case of prolonged respiratory distress and the need for oxygen therapy. Although no significant difference was observed between the treatment and control groups regarding the average time of receiving the drug/placebo, the number of subjects who received less than 4 doses in the treatment group was less than in the control group and the difference between the groups was significant; however, it seems that the prescription of 4 doses of salbutamol had the maximum efficiency and there was no increased efficiency with more doses. Studies conducted in Korea and Turkey[9,16] used a single dose of inhaled salbutamol that was inconsistent with the protocol of the current study; there was also a difference between the two studies and the present one in drug/placebo dose numbers.

Overall, the results of the current study were similar to those of the studies conducted in 2010 and 2014, as summarized in Table 5.[9,16]

The differences between the current study and two aforementioned studies regarding some variables can be attributed to different sample sizes, dose numbers, and types of populations.

Although, despite developments in perinatology and neonatology, TTN is still common and considered a major cause of morbidity from prolonged treatment in infants; employment of new remedies to reduce the severity and duration of illness is of great importance. The current study indicated that the prescription of inhaled salbutamol improved the treatment of TTN.

In addition, since few studies have evaluated the effects of salbutamol on the treatment of TTN, it was possible to compare the results of the current study with nationwide data sets. Hence, it seems that to have a more acceptable conclusion further studies are needed.

The results of the current study indicated that improvement in the clinical parameters, as well as the initiation of oral feeding, a faster reduction in the need for oxygen therapy, a reduction in the need for advanced respiratory support and the duration of hospitalization, and an improvement in the level of blood gases, were the positive effects of salbutamol in the treatment of TTN.

However, better improvement of disease symptoms and shorter hospital stays resulted in the reduction of treatment costs and parents' anxieties, which may produce proper mental and economic outcomes. Although drug prescription was continued for 72 h in the current study, a maximum of 4 doses may have the maximum efficiency and there would be no further effect from additional doses.

Acknowledgments

This manuscript was part of a Specialty Thesis in Pediatrics. The authors express their gratitude to the deputy vice-chancellor for research at Ahvaz Jundishapur University of Medical Sciences for supporting the study.

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