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Evaluation of the Effect of Inhaled Salbutamol in the Treatment of Neonates with a Diagnosis of TTN

Hasan Vahedi-Zarch[1], Mohamad Hosein Lookzadeh[2], Mahmood Noorishadkam[2], Seyed Reza Mirjalili[2*], Mohammadreza Gholami Banadkoki[1], Farimah Shamsi[3]

[1] Student Research Committee, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Mother and Newborn Health Research Center, Comprehensive Research Institute for Maternal and Child Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Biostatistics and Epidemiology, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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Corresponding author:
Seyed Reza Mirjalili

Email:
dr_sr_mirjalili@yahoo.com

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ABSTRACT

Background: Transient tachypnea of the newborn (TTN), the most common cause of transient respiratory distress in neonates, occurs due to insufficient or delayed absorption of fetal alveolar fluid immediately after birth. Given the limited number of studies evaluating the effectiveness of inhaled salbutamol in TTN patients, this study aimed to assess the therapeutic effects of inhaled salbutamol and to investigate its potential side effects.

Methods: This study was a double-blind randomized clinical trial involving 100 infants with a gestational age of at least 35 weeks, who were diagnosed with TTN. The infants were randomly assigned into two groups. Within the first 6 hours after birth, the intervention group received inhaled salbutamol, while the control group received normal saline, both administered nebulization. The effectiveness of salbutamol on clinical and laboratory parameters, as well as its potential side effects, was examined in infants with TTN.

Results: The TTN score decreased significantly in the salbutamol group at 1 and 6 hours after the intervention compared with the control group. Additionally, the time required to initiate oral feeding was longer in the group receiving salbutamol. However, regarding the length of hospitalization, duration of oxygen therapy, and other clinical parameters, no significant difference was observed between the two groups.

Conclusion: Since no significant differences were observed in major clinical outcomes between the groups, inhaled salbutamol may be considered a safe and potentially effective therapeutic option for infants with TTN.

Introduction

Transient tachypnea of the newborn (TTN) is the leading cause of respiratory distress in neonates and results from insufficient or delayed absorption of fetal alveolar fluid immediately after birth, particularly in term and near-term infants. The reported frequency of TTN ranges from 4 to 5.7% in term infants and reaches approximately 10% among preterm infants. [1–4] Several risk factors for TTN have been identified, including prematurity, high birth weight, male sex, meconium-stained amniotic fluid, elective cesarean delivery, maternal diabetes, maternal chorioamnionitis, and maternal asthma. [5]

The diagnosis of TTN is based on clinical manifestations and radiological findings during the first 6 hours after birth. The most prominent clinical feature is the early onset of tachypnea (>60 breaths per minute). Affected infants may also exhibit signs such as chest retractions, grunting, and nasal flaring. Chest X-ray (CXR) findings include prominent perihilar vascular markings, fluid in the interlobar fissures, particularly the transverse fissure, and mild pleural effusion.

TTN is generally a benign, self-limiting disorder in most affected infants. [1,6] However, in some infants, TTN may progress to severe tachypnea, leading to respiratory failure characterized by hypoxia, dyspnea, and acidosis, which may require intubation and mechanical ventilation. Moreover, a small proportion of affected infants may develop

pneumothorax or pneumomediastinum. These complications are higher in neonates treated with continuous positive airway pressure (CPAP). Pulmonary hypertension may develop in some cases, a condition sometimes referred to as malignant TTN. [7,8] Management of TTN primarily involves supportive care, including hyperbaric oxygen therapy, fluid therapy, and, in some cases, antibiotic therapy. [1,7,9]

Regarding the pathogenesis of TTN, previous studies have identified impaired fluid clearance and disturbances in sodium ion transport processes in pulmonary epithelial cells of the fetal lung as the main mechanisms underlying TTN. [1,10] In addition, mechanical forces applied during birth along with Starling forces, also contribute to this process. [1,5] Previous research indicates that fluid clearance from the fetal lungs primarily depends on activation of sodium reabsorption, mediated by epithelial sodium channels (ENaC) and the Na^+/K^+-ATPase membrane pump. [10] Therefore, the disruption of this regulatory pathway—caused by insufficient sodium transport, a reduced number of transporters, or transporter inactivation—may lead to fluid retention within the alveolar space. [11,12]

Beta-2 adrenergic receptors are widely distributed in pulmonary tissue, including the alveolar epithelium. Activation of these receptors enhances sodium transport through epithelial sodium channels (ENaC) and Na^+/K^+-ATPase pumps, thereby increasing the activity of both systems. [13–15]

Previous studies have shown that beta-2 agonists facilitate alveolar fluid clearance and may be effective in the treatment of pulmonary edema. This effect is mediated through increased the activity of key epithelial ion transport.

proteins. [5,14,16,17] In this context, several studies have evaluated the efficacy of oral or injectable furosemide, inhaled epinephrine, and inhaled salbutamol in the treatment of TTN. While epinephrine and furosemide have demonstrated limited or no efficacy, inhaled salbutamol has been reported to reduce disease duration; however, further well-designed studies are required to confirm its effectiveness. [7,14,15] Therefore, the present study aimed to evaluate the effects of inhaled salbutamol compared with a control group in neonates with TTN and to assess the potential side effects of beta-2 agonist therapy.

Materials and Methods

This study was a double-blind, randomized clinical trial Including 100 infants with a minimum gestational age of 35 weeks, whose physical examinations and radiological

findings were consistent with a diagnosis of TTN. The infants were randomly divided into two groups. Within the first 6 hours after birth, the intervention group received inhaled salbutamol (Cipla, India) at a dose of 0.15 mL/kg, diluted with 0.9% normal saline to a total volume of 2 mL for nebulization. The control group received inhaled 0.9% normal saline (Iran Injection and Pharmaceutical Products Company) at a dose of 0.15 mL/kg, adjusted to a total volume of 2 mL for nebulization.

In this study, we evaluated indicators such as respiratory and heart rate, peripheral oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), need for surfactant administration, and TTN severity score (according to based on the Silverman–Andersen scoring system). These parameters were assessed before therapeutic intervention and at 1 and 6 hours after treatment. Pulmonary artery pressure was also evaluated in both groups six hours after intervention. Finally, the average length of receiving oxygen therapy, length of stay in hospital, and the time to start oral feeding were recorded for each patient. Given that the potential side effects of this therapeutic intervention include tachycardia, hypokalemia, and hypoglycemia, relevant parameters were evaluated before the intervention and 6 hours afterward. All study data were analyzed in SPSS software using Chi-square, independent samples T-test, and ANOVA.

We excluded newborns with a prior history of meconium aspiration, polycythemia, respiratory distress syndrome, congenital pneumonia, hypoglycemia, early-onset sepsis, cardiac disorders, cardiac arrhythmia, tachycardia (heart rate> 180 bpm), and congenital abnormalities.

Results

In this research, 100 infants diagnosed with TTN were included. Fifty individuals were randomly assigned to the inhaled salbutamol intervention group, and the others were in the control group. Each group included 25 female and 25 male infants, with no significant difference in sex distribution (P = 0.927). Thirty-three people in the salbutamol group and 30 people in the control group were delivered by cesarean section, with no statistically significant difference between the groups (P = 0.534). Thus, the two groups were comparable with respect to sex and mode of delivery.

According to Table 1, the mean infant ages were 2.35 ± 2.62 days in the salbutamol group and 2.57 ± 2.96 days in the control group. This difference was not statistically significant (P = 0.493). The mean Apgar scores at the first and fifth minutes in the salbutamol group were 8.3 ± 0.83 and 9.78 ± 0.46, and in the control group, were 8.10 ± 0.95 and 9.82 ± 0.38, respectively. Comparing the Apgar scores of the two groups at 1 and 5 minutes showed no statistically significant difference between the groups (P = 0.26 and P = 0.64, respectively; Table 1)

Table1. Comparison of demographic and clinical variables between the two group (In this table, the average of variables between the two groups has been compared)

Variables	Participants		P
	Target group	Control group	
Age (day)	2.35 ± 2.62	2.57 ± 2.96	0.493
Gestational age (week)	37.3 ± 1.63	37 ± 1.63	0.583
Apgar Score (first minute)	8.3 ± 0.83	8.10 ± 0.95	0.268
Apgar Score (fifth minute)	9.78 ± 0.46	9.82 ± 0.38	0.641
The time required to start oral feeding (day)	2.88 ± 1.00	2.14 ± 0.85	<0.001
Duration of hospitalization (day)	7.54 ± 1.79	7.04 ± 1.69	0.155
Duration of oxygen therapy (day)	4.04 ± 1.64	3.70 ± 1.52	0.286

The average gestational age in the salbutamol group was 37.3 ± 1.63 and in the control group was 37 ± 1.63 weeks (P = 0.583; Table 1). On the other hand, there was no significant difference between these groups in length of hospital stay (P = 0.155; Table 1).

Similarly, the length of oxygen therapy between the two groups was not significantly different (P = 0.286; Table 1). A significant difference was observed between the salbutamol group and the control group in the time of initiation of oral feeding (P < 0.001). It was higher in the salbutamol group than in the control group (Table 1).

As shown in Table 2, comparison of the fraction of inspired oxygen (FiO_2), before, one hour after, and six hours after receiving the therapeutic intervention, showed no significant difference between the two groups (P > 0.05). However, FiO_2 decreased significantly over time in each group independently.

Comparing blood oxygen saturation (SpO_2) level, at the beginning, one hour after, and six hours after receiving the therapeutic intervention, indicated no significant statistical difference between the groups (P > 0.05). However, SpO_2 decreased significantly with increasing time in each group independently.

Comparison of TTN scores at baseline, 1 hour, and 6 hours after intervention demonstrated a significantly lower mean TTN score in the salbutamol group at both 1 and 6 hours after treatment. Although TTN scores decreased significantly over time in both groups, controlling for the time effects showed consistently lower scores in the salbutamol group (Table 2). Mixed ANOVA test showed no significant statistical differences between the groups in respiratory or heart rate (P > 0.05), indicating no relationship between types of intervention and these indicators (Table 2).

According to Table 3, in the salbutamol group, before treatment, 19 infants and six hours after treatment, only 2 infants needed to receive surfactant. However, in the control group, before treatment, 20 infants and six hours after treatment, 3 infants needed to receive surfactant. Using the chi-square test, no significant statistical difference was detected between the frequency of patients who needed surfactant in the salbutamol groups and the control group at either time point. Comparing the frequency of increased pulmonary pressure in infants of the two groups showed no significant difference between them (P = 0.646).

Table 2. Comparison of Clinical Variables between the Two Groups
(In this table, the average of variables between the two groups has been compared)

Variables		Participants		P
		Target group	Control group	
TTN* Score	baseline status	7.38 ± 1.21	7.20 ± 1.47	0.506
	1-hour post-intervention	5.0 ± 1.60	5.68 ± 1.67	0.043
	6-hour post-intervention	4.24 ± 1.39	4.96 ± 1.67	0.022
Respiratory Rate	baseline status	66.6 ± 5.09	67.9 ± 5.46	0.236
	1-hour post-intervention	63.7 ± 4.70	65.1 ± 4.50	0.139
	6-hour post-intervention	61.1 ± 7.3	62.5 ± 4.20	0.232
Heart Rate	baseline status	137.5 ± 10.40	136.8 ± 8.01	0.708
	1-hour post-intervention	137.0 ± 10.05	135.95 ± 7.57	0.553
	6-hour post-intervention	136.70 ± 9.84	135.7 ± 7.64	0.572
FiO2*	baseline status	68.6 ± 9.95	67.3 ± 13.82	0.591
	1-hour post-intervention	57.60 ± 10.90	58.4 ± 12.00	0.729
	6-hour post-intervention	51.3 ± 13.24	54.2 ± 12.60	0.265
SpO2*	baseline status	92.8 ± 1.80	92.9 ± 2.05	0.720
	1-hour post-intervention	94.7 ± 1.96	94.6 ± 1.82	0.793
	6-hour post-intervention	95.18 ± 2.00	95.2 ± 1.80	0.838

*Abbreviations: FiO2: The fraction of inspired oxygen; SpO2: Oxygen saturation; TTN: Transient tachypnea of the newborn

Table 3. Comparison of Clinical Variables between the Two Groups
(In this table, the frequency of variables between the two groups has been compared)

Variables		Participants Target group (n = 50)	Control group (n = 50)	P
Pulmonary artery pressure (6-hour post-intervention)	within the normal range*	47	48	0.646
	elevated	3	2	
Need to get surfactant	baseline status	19	20	0.838
	6-hour post-intervention	2	3	0.646
	Total	21	23	>0.05

* It should be noted that the normal range of pulmonary artery pressure has been calculated separately for each baby and based on their age.

Table 4. Comparison of Laboratory Variables between the Two Groups
(In this table, the average of variables between the two groups has been compared)

Variables		participants Target group	Control group	P
Serum Potassium level (mEq/L)	baseline status	4.53 ± 0.64	4.47 ± 0.77	0.655
	6-hour post-intervention	4.47 ± 0.77	4.43 ± 0.76	0.815
Serum Glucose level (mg/dL)	baseline status	90.90 ± 23.62	94.98 ± 26.66	0.420
	6-hour post-intervention	100.60 ± 24.90	108.90 ± 25.37	0.103
pH	baseline status	7.32 ± 0.049	7.31 ± 0.046	0.521
	6-hour post-intervention	7.36 ± 0.053	7.38 ± 0.044	0.176

An independent t-test showed no significant difference between the two groups in the serum level of potassium, glucose, and pH before and six hours after therapeutic intervention ($P > 0.05$) (Table 4).

Discussion

Transient tachypnea of the newborn (TTN), the most common cause of transient respiratory distress in the newborn, which occurs as a result of insufficient or delayed absorption of the fetal alveolar fluid after birth. [1,18,19] Previous studies have suggested that this disease can be a result of dysfunction in the ENaC channel and the Na^+/K^+-ATPase pump in fetal alveolar epithelial cells, leading to the secretion of chloride and fluids into this space instead of actively absorbing sodium and fluids from the alveolar space. [1,18,20]

Although beta-2 agonists are widely used to treat neonatal respiratory diseases and chronic lung disease in preterm infants, data on the optimal dose, treatment duration, and efficacy of their inhaled administration remain limited. Current studies investigating the effectiveness of intravenous albuterol (salbutamol) on in-vitro and in-vivo pulmonary edema models confirm that salbutamol can be an effective drug in patients with acute respiratory distress syndrome. Furthermore, the protective effect of salbutamol on the active sodium transport across the alveolar membrane in normal and affected lungs indicates that the administration of beta-2 agonists accelerates the clearance of alveolar fluid in transient tachypnea of the newborn. [7,14,21]

The main goal of this research was to evaluate the effectiveness of inhaled salbutamol on clinical and laboratory parameters in infants with TTN and to investigate its potential side effects. In this study, 100 newborns were examined, matched in gender and type of delivery. The results demonstrated that in the salbutamol group compared to the control group, the TTN score decreased significantly in the first and sixth hours after receiving the treatment. Additionally, the time required to initiate oral feeding was longer in the salbutamol group than in the control group. However, no significant difference was observed between the two groups in other parameters such as length of hospitalization and duration of oxygen therapy.

Several studies have reported that salbutamol can decrease the respiratory rate, FiO_2 requirements, and duration of oxygen therapy in infants with TTN. [22,23] In line with the present study, two studies have shown that salbutamol can reduce the symptoms of respiratory distress in infants. However, unlike the study by Babaei et al., the present study did not show a change in the length of care in a hospital and a reduction in the time to initiation of oral feeding. [21]

Babaei et al. showed that salbutamol can reduce the fraction of inspired oxygen (FiO2) compared to the control group. [21] However, in the present study, despite the FiO_2 being reduced over time, no significant relationship was observed for the salbutamol group.

In line with Babaei et al. study, a study by Mohammadzadeh et al. showed that the use of inhaled salbutamol in the treatment of TTN can reduce the duration of hospitalization. [5,21] Conversely, Kim et al. did not report a significant difference in this parameter. [3]

Given that beta-2 agonists may cause tachycardia, dysrhythmias, and electrolyte disorders, in this study, the highest heart rate, changes in electrolyte levels, and biochemical blood changes in infants were investigated. The results showed no significant change in the heart rate during the treatment, and no significant difference between infants' heart rates before and after receiving salbutamol, consistent with findings in the research by Babaei et al. and Kim et al. [3,22]

Additionally, serum potassium levels before and six hours after receiving the intervention did not change significantly in either of the two groups. Blood glucose and pH levels increased significantly six hours after receiving the intervention in both groups. Since there was no significant difference between the two salbutamol and control groups, it can be concluded that salbutamol played a minimal role in these biochemical changes.

In this study, we had some limitations. Future investigations with larger sample sizes and multicenter designs are recommended to improve the generalizability of the results. Additionally, the lack of measurement of pulmonary artery pressure at the beginning of the study is another limitation of this study.

Conclusion

The results of the present study showed that the use of inhaled salbutamol can significantly reduce the TTN score compared to the control group. However, it should be noted that infants treated with inhaled salbutamol can initiate oral feeding later than the control group.

Infants with TTN treated with inhaled salbutamol did not differ significantly from the control group in treatment complications. Considering the other results of this study, it can be concluded that inhaled salbutamol may be an effective and safe option for treating infants with TTN.

Conflict of Interest

The authors declare no conflicts of interest regarding the study.

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Ethical Considerations

The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (Code: IR.SSU.MEDICINE.REC.1400.014).

Author's Contribution

Conceptualization, S.R.M. and H.V-Z.; Methodology, F.Sh. and S.R.M.; Conducting the data collection and performing the analyses, H.V-Z., and F.Sh.; Writing- original draft preparation, M.G.B; Assisting in interpreting the results and reviewing the literature, F.Sh., M.H.L, and M.N.; Providing critical revisions and oversight throughout the study, S.R.M.; Reviewing and approving the final manuscript, S.R.M.

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