IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Effects of Salbutamol on the Treatment of Transient Tachypnea of the Newborn

Homa Babaei[1], Shohreh Dabiri[2*], Leila Mohammadi Pirkashani[2], Hadi Mohsenpour[1]

1. Department of Pediatrics, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
2. Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran

ABSTRACT

Background: This study aimed to evaluate the safety and efficacy of inhaled salbutamol for the treatment of Transient Tachypnea of the Newborn (TTN).

Methods: Totally, 80 neonates with TTN were randomly assigned into two groups of treatment and placebo. The treatment and placebo groups received one dose of nebulized salbutamol (dose of 0.15 ml/kg in 2 ml of normal saline) and only 2 ml 0.9% normal saline without salbutamol, respectively. Before starting the study and30, 60 min, and 4 h after nebulization, the respiratory and heart rates, oxygen saturation, a fraction of inspired oxygen, respiratory distress score, the arterial blood gas(after 4 hours), and the time of hospital stay evaluated. The data were analyzed in SPSS software (version 23) through Fisher's exact test, Mann-Whitney U test, and ANOVA.

***Results*:** There were no significant differences between the case and control groups with regard to gender, gestational age, birth weight, mother's history of asthma, type of delivery, first-and fifth-minute Apgar, pneumothorax, and respiratory rates. The duration of tachypnea, hospital stay, oxygen therapy, and the time of initiating enteral feeding were shorter in the case group compared to the control group.

Conclusion: The administration of the salbutamol can significantly improve respiratory distress following 4 h and reduce the duration of hospital stay, tachypnea, and the time of enteral feeding.

Keywords: Neonates, Salbutamol, Transient tachypnea of the newborn

Introduction

Avery described the transient tachypnea of the newborn (TTN) in 1996 as the delay in fetal pulmonary liquid clearance (1). TTN is due to delayed clearance of neonate alveolar fluid (2), which is common in the near term and term neonates (3). The incidence of TTN is 5.7 per1000 live births (2). The prevalence of TTN is more common among male neonates, newborns with perinatal asphyxia or those who are delivered through elective cesarean or whom their mothers are diabetic or asthmatic (4, 5). The clinical manifestations include tachypnea, grunting, nasal flaring, and intercostal retraction immediately following the birth.

These manifestations can be resolved during 48-72 hours after birth; however, it may sometimes extend to 5 days (2). The management of TTN includes oxygen therapy (O2) and conservative interventions (2, 5).The pulmonary liquid absorption during the labor is facilitated through β adrenergic agonist, endogenous steroid, and catecholamines (6). Experiments have demonstrated that pulmonary epithelium secretes Cl^- and fluid throughout gestation; however, it develops the ability to actively reabsorb Na^+ only during late gestation (6).

At birth, the mature lung switches from active Cl- (fluid) secretion to active Na^+ (fluid) absorption in response to circulating catecholamines. Evidence suggests that glucocorticoids play a role in this switch (7). Changes in oxygen tension enhance the Na^+-transporting capacity of the epithelium and increase gene expression for the epithelial Na^+ channel (ENaC).

The inability of the fetal lung immaturity to switch from fluid secretion to fluid absorption mainly results from the immaturity in the expression of ENaC, which can be up-regulated

* *Corresponding author*: Shohreh Dabiri, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. Tel: +989181321038; Email: shohreh_dabiri@yahoo.com

Please cite this paper as:
Babaei H, Dabiri S, Mohammadi Pirkashani L, Mohsenpour H. Effects of Salbutamol on the Treatment of Transient Tachypnea of the Newborn. Iranian Journal of Neonatology. 2019 Mar: 10(1). DOI: 10.22038/ijn.2018.31294.1430

by glucocorticoids and β adrenergic agonist. Glucocorticoids induce lung Na+ reabsorption most likely through the fetal lung alveolar ENaC channel in late gestational age (6-8).Several studies show that pulmonary tissue stimulation by exogen β adrenergic agonist facilitate the pulmonary fluid resorption among animal and human models (9-14).

Armangil et al. evaluated the efficacy of inhaled salbutamol on TTN for the first time. They showed a significant decrease in the hospital stay duration among neonates, compared to the placebo group (15). Kim et al. revealed that inhaled salbutamol significantly decreased the time of oxygen therapy. However, it had no significant effect on the tachypnea duration (16). The mentioned studies have reported no kinds of side effects of salbutamol (tachycardia, arrhythmia, hypokalemia, and hyperglycemia (15-17). Due to the lack of reliable evidence in relation to salbutamol effects on TTN, the aim of the present study was to evaluate the safety and efficacy of inhaled salbutamol (β adrenergic agonist) for the treatment of TTN.

Methods

This clinical trial was conducted on all hospitalized neonates diagnosed with TTN in the neonatal intensive care unit (NICU) of Imam Reza Hospital in Kermanshah, Iran, during 2017. Thestudy of Armangil et al. was used to calculate the sample size of this research (15).

The diagnosis of TTN was based on the following criteria: The onset of respiratory distress lower than 6 hours after birth, and typical finding in chest radiography (fluid in minor fissures, hyperaeration, and bilateral perihilar vascular markings).

The inclusion criteria were gestational age of at least 35 weeks and physical examination and radiologic findings suggesting TTN diagnosis.

On the other hand, the newborns with the history of meconium aspiration, respiratory distress syndrome, congenital pneumonia, polycythemia, hypoglycemia, early onset sepsis, cardiac disorders,tachycardia (HR>180 b/min), cardiac arrhythmia, and congenital anomaly were excluded from the study.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{(\mu_2 - \mu_1)^2}$$

Figure 1. The formula used for sample size calculation

Totally, 80 neonates with TTN were randomly assigned into two groups of treatment and control using a random number table. The treatment group received one dose of nebulized salbutamol (Stalin product of Cipla Company of India) by dose of 0.15 ml/kg in 2 ml of normal saline. However, the control group received 2 ml 0.9% normal saline without salbutamol during 20 minutes and the first 6 h of birth. Respiratory rate, heart rate, oxygen saturation, a fraction of inspired oxygen (Fio2), respiratory distress score (according to Anderson-Silverman Retraction Score scale) were evaluated before the treatment, 30 and 60 min, and 4 h after nebulization (Table 1). Moreover, arterial blood gas was measured 4 hours after the intervention. The duration of tachypnea, oxygen therapy, mechanical ventilation, continuous positive airway pressure support (CPAP), hospital stay, and the time of initiating enteral nutrition were observed to assess the efficacy of treatment. In this study, all neonates were monitored for tachycardia and arrhythmia. Tachycardia was defined as heart rate more than 180 beats per minute. The study was also registered in the Iranian Clinical Trials (IRCT2017081414333N80code). The data collection tools consisted of infants' demographic questionnaire and a checklist to record the physiological parameters. The data were analyzed in SPSS software (Version 23) through the Chi-squared test, independent sample t-test, and ANOVA test. P-valueless than <0.05 was statistically significant.

Results

The present study was conducted on 80 neonates with TTN who were randomly assigned into treatment (salbutamol) and control (normal saline) groups. There were no statistically significant differences between the treatment and controlgroups in terms of gender, gestational age, birthweight, mother's history of asthma, type of delivery, and first-and fifth-minute Apgar. The lack of significant differences regarding

Table 1. Anderson-Silverman retraction score scale

Score	Upper chest retraction	Lower chest retraction	Xiphoid retraction	Nasal flaring	Grunt
0	Synchronized	None	None	None	None
1	Lag during inspiration	Just visible	Just visible	Minimal	Audible with Stethoscope
2	See-saw	Marked	Marked	Marked	Audible without Stethoscope

Table 2. Comparison of demographic variables between two groups

Variables		Treatment group N (%)	Control group N (%)	P-value
Gender	Male	24 (60)	29 (72.5)	0.34
	Female	16 (40)	11(27.5	
Type of delivery	Cesarean	37 (92.5)	38 (95)	0.36
	Normal vaginal delivery	3 (7.5)	2(5)	
Variables		Mean ± Sd	Mean ± Sd	P-value
Birth weight(g)		3180.75 ± 696.88	3068.75±576.98	0.2
Gestational age (week)		36.65±1.09	36.30±1.39	0.4
Mother's history of asthma		3.05±0.63	2 ±.0	0.1
First minute APGAR		7.47±0.87	7.52±0.98	0.8
Fifth minute APGAR		8.82±0.81	9.02±0.80	0.2

Table 3. The means of respiratory rate in treatment and control groups at different time periods

Time	Group	Number	Mean	Std.
Before the intervention	Treatment	40	83.10	6.16
	Control	40	83.75	6.97
30 minafter intervention	Treatment	40	79.35	5.30
	Control	40	81.67	6.87
60 min after intervention	Treatment	40	75.42	4.67
	Control	40	79.17	6.40
4 h after intervention	Treatment	40	73.27	12.84
	Control	40	76.55	5.79

Time * Group ⟶ P-value =0.215

Table 4. The means of heart rate (beats/min) in treatment and control groups at different time periods

Time	Group	Number	Mean	Std.
Before the intervention	Treatment	40	149.95	8.37
	Control	40	153.42	10.31
30 min after intervention	Treatment	40	147.62	8.38
	Control	40	151.82	9.22
60 min after intervention	Treatment	40	144.82	8.27
	Control	40	149.57	8.86
4 h after intervention	Treatment	40	140.75	9.98
	Control	40	146.27	7.90

Time * Group ⟶ P-value =0.257

Table 5. The means of Fio2(%) in treatment and control groups at different time periods

Time	Group	Number	Mean	Std.
Before the intervention	Treatment	40	94.00	9.00
	Control	40	93.50	10.26
30 min after intervention	Treatment	40	72.75	9.86
	Control	40	80.87	10.12
60 min after intervention	Treatment	40	54.25	9.30
	Control	40	67.00	11.14
4 h after intervention	Treatment	40	35.90	10.30
	Control	40	49.87	12.93

Time * Group ⟶ P-value < 0.001

demographic variables between the two groups could be the evidence of the true randomization process (Table 2).

With regard to the quantitative nature of the data and their normal distribution, the repeated measure ANOVA was used to compare the means of respiratory and heart rates, Fio2, O2 saturation, and distress scores between the treatment and control groups at different time periods.

In addition, tables3-7 demonstrate the means of respiratory and heart rates, Fio2, O2 saturation, and distress scores between treatment and control groups at different time periods.

According to the results, there were significant differences between the two groups at different time periods in terms of the meanFio2, O2 saturation, and distress scores ($P<0.05$).

However, no statistically significant differences were observed between the two groups at different time periods regarding the respiratory and heart rate ($P>0.05$, figures 2-6).

The results of independent-samples t-test

Table 6. The means of O2 saturation intreatment and control groups at different time periods

Time	Group	Number	Mean	Std.
Before the intervention	Treatment	40	82.12	4.40
	Control	40	83.22	5.14
30 min after intervention	Treatment	40	87.37	3.54
	Control	40	85.87	4.43
60 min after intervention	Treatment	40	90.90	1.79
	Control	40	88.57	3.34
4 h after intervention	Treatment	40	93.30	2.32
	Control	40	90.72	1.61

Time * Group ⟶ P-value < 0.001

Table 7. The means of distress score in treatment and control groups at different time periods

Time	Group	Number	Mean	Sd.
Before the intervention	Treatment	40	7.87	0.72
	Control	40	7.40	0.98
30 min after intervention	Treatment	40	7.02	0.62
	Control	40	7.27	1.06
60 min after intervention	Treatment	40	6.12	0.79
	Control	40	6.47	0.90
4 h after intervention	Treatment	40	5.22	0.57
	Control	40	6.20	0.96

Time * Group ⟶ P-value < 0.001

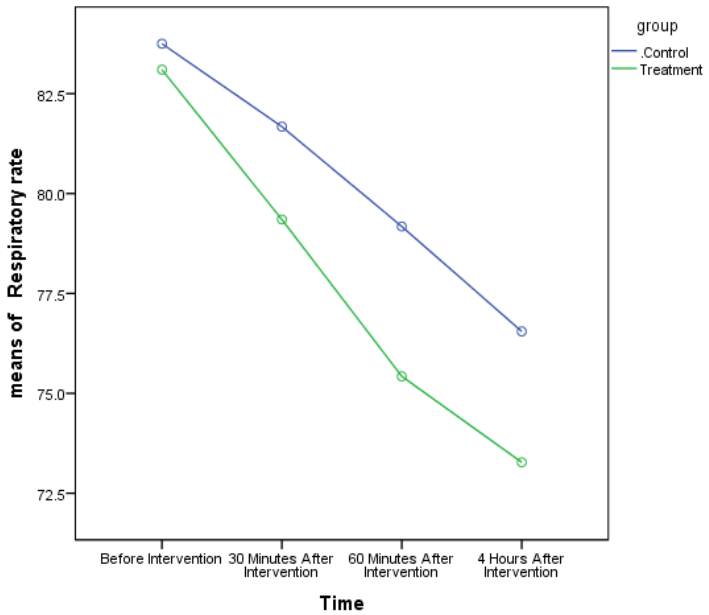

Figure 2. The means of respiratory rate in treatment and control groups at different time periods

showed statistically significant differences regarding the mean scores of tachypnea and oxygen therapy duration, time of initiating enteral feeding, the partial pressure of oxygen (Pao2), and the partial pressure of carbon dioxide (Paco2) after a 4-hour intervention between the two groups (P<0.05).

However, no statistically significant differences were observed in terms of the mean of other variables (i.e., mechanical ventilation, duration of mechanical ventilation, the need for CPAP, CPAP duration, pneumothorax, Pao2, and Paco2 (4 hours after intervention) between the two groups(P>0.05, table 8).

No kinds of side effects of salbutamol were observed among the neonates since they were checked daily in terms of the Na/K and blood sugar.

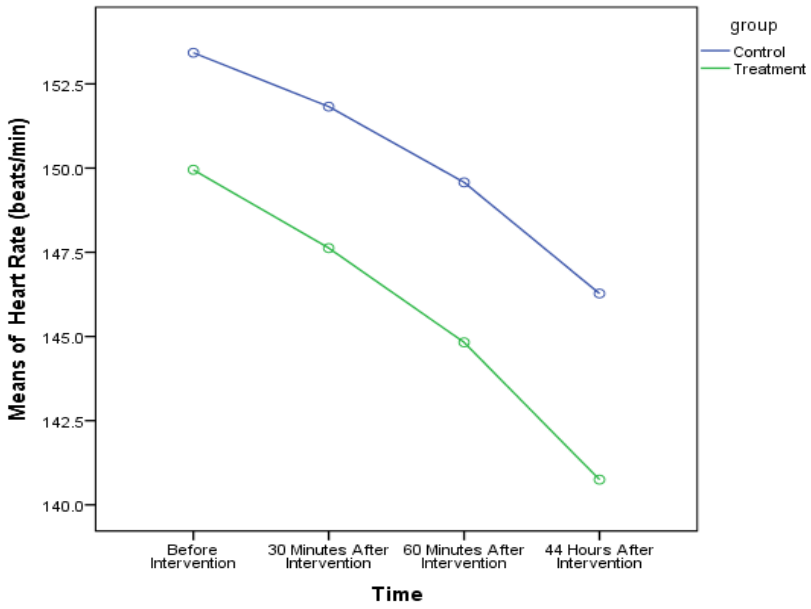

Figure 3. The means of heart rate (beats/min) in treatment and control groups at different time periods

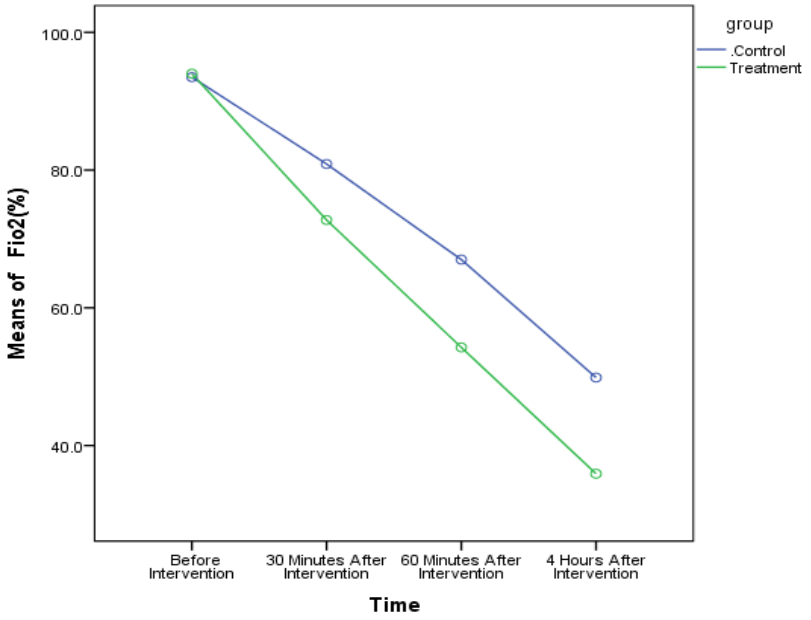

Figure 4. The means of Fio2 (%) in treatment and control groups at different time periods

Discussion

The aim of this study was to evaluate the safety and efficacy of inhaled salbutamol (β adrenergic agonist) for the treatment of TTN.

The TTN is due to delay in intrapulmonary fluid resorption and it is an important diagnosis with a dilemma of therapy in NICU (18). During the fetal period, the presence of adequate intrapulmonary fluid is necessary for normal growth and developments of fetal pulmonary as well as a successful transition from intrauterine to extrauterine life (19). The most common clinical presentation of TTN is tachypnea, which presents during the first and second hours after birth. The respiratory rate can reach up to 60-120 breath/min (18). Persistent tachypnea can lead to the increase in hospital stay duration, antibiotic therapy, and parent anxiety (20). This study showed that the duration of tachypnea, hospital

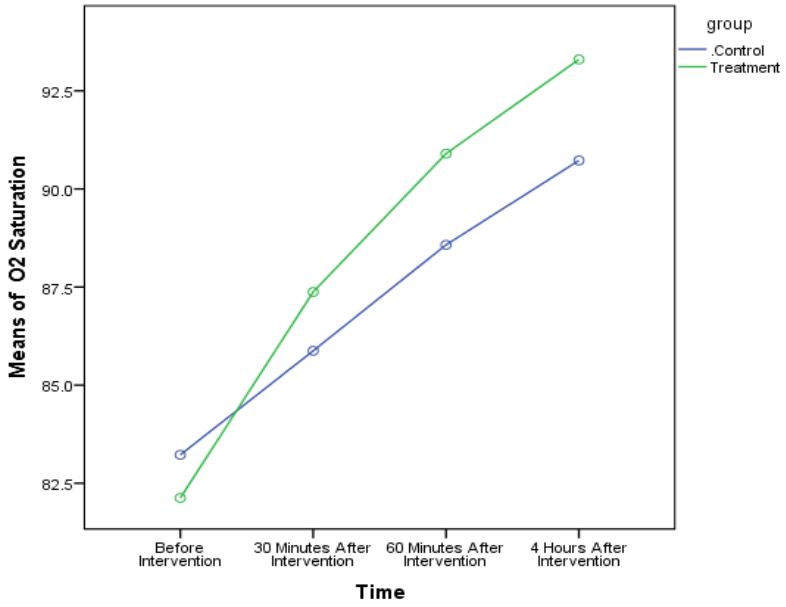

Figure 5. The means of O2 saturation in treatment and control groups at different time periods

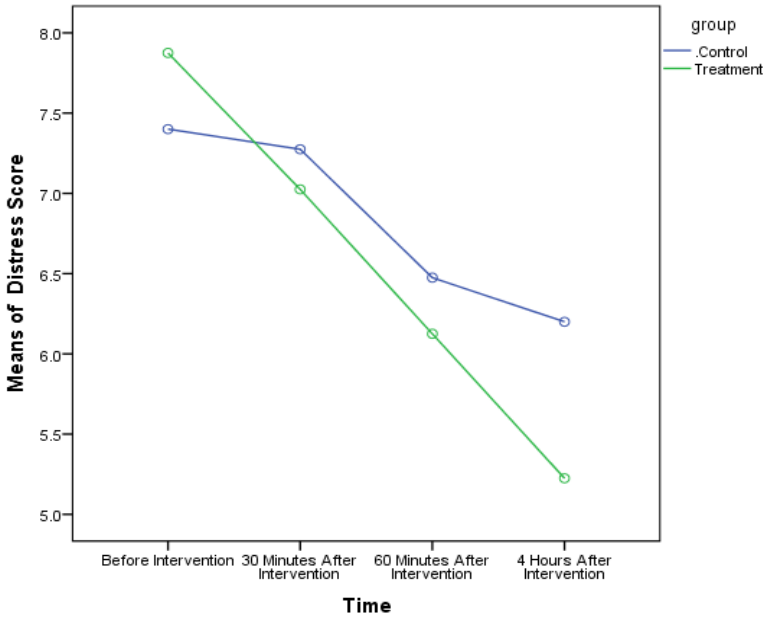

Figure 6. The means of distress score in treatment and control groups at different time periods

stay, oxygen therapy, and the time of initiating enteral feeding were shorter in the salbutamol group than the control group.

Moreover, the Fio2 and Pco2 decreased; however, O2 saturation and Pao2 increased over time in the salbutamol group.

Armangil et al. (15) showed that salbutamol can decrease hospital stay duration among neonates diagnosed with TTN and the results are consistent with the findings of this study (P<0.05). The same results have been found by Armangil et al. in relation to salbutamol effects on respiratory rates; however, in this study, no statistically significant differences were observed in this regard (P>0.05) (15).

Mohammadzadeh et al. (21) showed that inhaled salbutamol can significantly decrease the time of oxygen therapy, initiation of enteric feeding and hospital stay duration. The obtained results are in line with the findings of the present

Table 8. The means of different variables in treatment and control groups

Variable	Group	N	Mean	Sd.	P-value
Duration of Tachypnea (Hour)	Treatment	40	34.45	8.74	<0.001
	Control	40	51.12	16.09	
Duration of oxygen therapy (Hour)	Treatment	40	41.80	7.77	<0.001
	Control	40	60.05	18.15	
Mechanical ventilation	Treatment	40	1.95	0.22	0.4
	Control	40	1.90	0.30	
Duration of mechanical ventilation (Day)	Treatment	40	0.30	1.89	0.11
	Control	40	1.92	6.06	
The need for continuous positive airway pressure	Treatment	40	2.42	7.08	0.33
	Control	40	1.32	0.47	
Continuous positive airway pressure duration (Hour)	Treatment	40	23.92	18.15	0.17
	Control	40	30.50	24.49	
Time of initiating enteral feeding (Day)	Treatment	40	2.22	0.42	0.01
	Control	40	3.55	3.28	
Duration of hospital stay(Day)	Treatment	40	4.92	0.82	<0.001
	Control	40	6.52	1.06	
Pneumothorax	Treatment	40	2.10	0.98	0.29
	Control	40	1.92	0.34	
The partial pressure of oxygen (4 h after intervention)	Treatment	40	89.82	7.19	<0.001
	Control	40	77.92	11.70	
The partial pressure of dioxide carbon (4 h after intervention)	Treatment	40	41.89	3.97	<0.001
	Control	40	47.70	5.59	

study (P<0.05). As the previous studies showed no neonates experienced any kinds of salbutamol side effects (15, 16). Kim et al. (16) stated that inhaled salbutamol can result in shorter duration of tachypnea and subsequently shorter duration of oxygen and antibiotic therapy.

However, no significant reduction in the time of hospital stay duration was observed (16). In the present study, a significant decrease was observed in the time of hospital stay duration in the case group (P<0.001). Mousavi et al. (22) showed that administration of salbutamol can result in the significant reduction of respiratory distress score which was consistent with the results obtained from this study (P<0.05). In the aforementioned study, the final amount of Pco_2 in the case group increased; however, it was not significant. In the present study, this amount had significantly decreased in the case group (P<0.05). Due to the small sample size, it is not possible to rely on the results of the need for CPAP. In addition, with regard to the limited studies in relation to salbutamol and its effects on different aspects of TTN management and evaluation, the present study can be considered a unique one.

Conclusion

The administration of salbutamol can significantly improve respiratory distress following 4 hours, reduce the time of hospital stay, the day of enteric feeding initiation, and the duration of tachypnea and heart rate.

Acknowledgments

This work was performed in partial fulfillment of the requirements for Pediatrics Specialty of Shohreh Dabiri, Faculty of Science, Kermanshah University of Medical Sciences, Kermanshah, Iran. The authors appreciate the experts in Clinical Research Development Center of Imam Reza Hospital for their advice on the preparation of this study.

Conflicts of interests

None.

References

1. Avery ME, Gatewood OB, Brumley G. Transient tachypnea of newborn. Possible delayed resorption of fluid at birth. Am J Dis Children. 1966; 111(4): 380-5.
2. Crowley MA. Neonatal respiratory disorders. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant. 10th ed. St. Louis: Elsevier Mosby; 2015. P. 1113-33.
3. Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. J Perinatol. 2005; 25(4):251-7.
4. Takaya A, Igarashi M, Nakajima M, Miyake H, Shima Y, Suzuki S. Risk factors for transient tachypnea of the newborn in infants delivered vaginally at 37 weeks or later. J Nippon Med Sch. 2008; 75(5):

269-73.
5. Lewis V, Whitelaw A. Furosemide for transient tachypnea of the newborn. Cochrane Database Syst Rev. 2002; 1:CD003064.
6. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Semin Perinatol. 2006; 30:34-43.
7. Richardson BS, Czikk MJ, daSilva O, Natale R. The impact of labor at term on measures of neonatal outcome. Am J Obstet Gynecol. 2005; 192(1):219-26.
8. Zanardo V, Simbi AK, Franzoi M, Soldà G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. Acta Paediatr. 2004; 93(5):643-7.
9. Sakuma T, Tuchihara C, Ishigaki M, Osanai K, Nambu Y, Toga H, et al. Denopamine, a beta (1)-adrenergic agonist, increases alveolar fluid clearance in ex vivo rat and guinea pig lungs. J Appl Physiol. 2001; 90(1):10-6.
10. Sakuma T, Folkesson HG, Suzuki S, Okaniwa G, Fujimura S, Matthay MA. Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med. 1997; 155(2):506-12.
11. Mutlu GM, Factor P. Alveolar epithelial beta2-adrenergic receptors. Am J Respir Cell Mol Biol. 2008; 38(2):127-34.
12. Irestedt L, Lagercrantz H, Hjemdahl P, Hägnevik K, Belfrage P. Fetal and maternal plasma catecholamine levels at elective cesarean section under general or epidural anesthesia versus vaginal delivery. Am J Obstet Gynecol. 1982; 142(8):1004-10.
13. Ronca AE, Abel RA, Ronan PJ, Renner KJ, Alberts JR. Effects of labor contractions on catecholamine release and breathing frequency in newborn rats. Behav Neurosci. 2006; 120(6):1308-14.
14. Smith DE, Otulakowski G, Yeger H, Post M, Cutz E, O'Brodovich HM. Epithelial Na(+) channel (ENaC) expression in the developing normal and abnormal human perinatal lung. Am J Respir Crit Care Med. 2000; 161(4 Pt 1):1322-31.
15. Armangil D, Yurdakök M, Korkmaz A, Yiğit Ş, Tekinalp G. Inhaled beta-2 agonist salbutamol for the treatment of transient tachypnea of the newborn. J Pediatr. 2011; 159(3):398-403.
16. Kim MJ, Yoo JH, Jung JA, Byun SY. The effects of inhaled albuterol in transient tachypnea of the newborn. Allergy Asthma Immunol Res. 2014; 6(2):126-30.
17. Kao B, Stewart de Ramirez S, Belfort MB, Hansen A. Inhaled epinephrine for the treatment of transient tachypnea of the newborn. J Perinatol. 2008; 28(3):205-10.
18. Moresco L, Bruschettini M, Cohen A, Gaiero A, Calevo MG. Salbutamol for transient tachypnea of the newborn. Cochrane Library. 2016; 5:CD011878.
19. Guglani L, Lakshminrusimha S, Ryan RM. Transient tachypnea of the newborn. Pediatr Rev. 2008; 29(11):59-65.
20. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. J Appl Physiol. 1996; 81(1):209-24.
21. Mohammadzadeh I, Akbarian-Rad Z, Heidari F, Zahedpasha Y, Haghshenas-Mojaveri M. et al. The effect of inhaled salbutamol in transient of tachypnea of the newborn: a randomized clinical trial. Iran J Pediatr. 2017; 27(5):e9633.
22. Mussavi M, Asadollahi K, Kayvan M, Sadeghvand S. Effects of nebulized albuterol in transient tachypnea of the newborn a clinical trial. Iran J Pediatr. 2017; 27(3):e8211.