ORIGINAL ARTICLE

INHALED SALBUTAMOL IN TRANSIENT TACHYPNEA OF NEWBORN

MUHAMMAD ANWAR[1], MUNIR AHMAD[2], AFAQ HUSSAIN[3], MUHAMMAD ASGHAR ALI[4], KASHAF WASE[5], MAIRA AHMAD[6]

[1]*Associate Professor (Neonatology),* [2-4]*Senior Registrar(Neonatology),* [5]*Postgraduate Resident,* [6]*Woman Medical Officer*
Quaid -e- Azam Medical College, Bahawalpur, Sadiq Abbasi (Civil) Hospital, Bahawalpur

ABSTRACT

Background: Transient tachypnea in newborn is one of the commonest reasons of respiratory distress in newborn.
Objective: To determine the effectiveness of inhaled salbutamol in neonates.
Method: This open label randomized control trial was conducted at Department of Neonatology, Sir Sadiq Muhammad Khan Abbasi Hospital, Bahawalpur during January 2018 to November 2022. Total 80 neonates with gestational age ≥34 week admitted in NICU with clinical diagnosis of Transient Tachypnea of Newborn, experiencing respiratory distress within 6 hours of birth were included in this study. Demographic data including age, gender, duration of stay, mode of delivery, APGAR score, heart rate, respiratory rate, blood oxygen saturation, (FiO_2), blood potassium level, glucose level and arterial blood gases (PH, partial pressure of arterial oxygen [PaO_2], partial pressure of arterial carbon dioxide [$PaCO_2$]), CXR findings and TTN bedside score were recorded. The neonates were divided into two groups based on salbutamol inhalation: (Group A) consisted of neonates who received supplementary care and (group-B) comprised of neonates who received a single standard dose (0.15 mg/kg) of inhaled salbutamol therapy via ultrasonic nebulizer for 5 minutes, in addition to supplementary care. Data were entered and analyzed in SPSS version 20. Qualitative statistics were presented as mean ± SD, while quantitative statistics were presented in frequency or percentages. Statistical test was performed among dependent and independent variables by Chi square test ($\chi 2$) and where the values in a cell was < 5 Fisher's exact test was applied. A p value ≤ 0·05 was taken significant statistically
Results: TTN bedside clinically respiratory changes i.e., respiratory rate, figures of oxygen saturation, requirement of incremental oxygen, blood gas i.e., PH, PO2, PCO_2 and span of hospitalizing were significantly better in group 2 neonates than in neonates of group 1 ($P > 0.05$) while no mathematical major changes were noted in heart rate, potassium and glucose level ($P > .05$).
Conclusion: Inhaled salbutamol is better as an adjuvant therapy to standard care in newborns with transient tachypnea.

Keywords: Transient tachypnea, Newborn, Salbutamol

How to cite this article: Anwar M, Ahmad M, Hussain A, Ali MA, Wase K, Ahmad M. Inhaled salbutamol in transient tachypnea of newborn. Pak Postgrad Med J 2023;34(1): 28-32

DOI: https://doi.org/10.51642/ppmj.v34i01.541

Correspondence to: *Muhammad Anwar,*
Associate Professor,
Department of Neonatology,
Quaid -e- Azam Medical College, Bahawalpur,
Pakistan.

Email: *hmanwar157@qamc.edu.pk*

INTRODUCTION

Reasons of perinatal dyspnea are countless and one of the commonest reasons is a Transient tachypnea in newborn (TTN) either in the full-term or late preterm neonates[1]. The predictable prevalence ranges from 0.5% to 2.8% of all deliveries[2-4]. Its basic pathology is the slow absorption of fetal lung fluid at birth[5]. Risk factors are male gender, premature,

cesarean section without labor, gestational diabetes, maternal H/O asthma and perinatal asphyxia[6]. It may be the only pathology or it may be a part of other neonatal complaint for example surfactant deficiency[7], neonatal pneumonia[7] and PPHN[8, 9]. It belongs to one major nontrivial cause of admission in neonatal units regardless of its self-limiting nature that need treatment, consist of caring, including incremental oxygen, nothing per oral and intravenous fluids that finally may lead to the vital deployment of health resources[10, 11]. Minimum number of neonates needs ventilator help and or CPAP[12]. Infrequently, few newborns suffered severe hypoxemia corrected with incremental oxygen. Possible management depends upon on knowing the physiology of reabsorption of fluid in lung at birth[1]. Immediately after delivery of baby, levels of natural catecholamines and switching on of β-adrenergic agonist helps respiratory epithelium to switch to absorptive nature than secretory mode. Waking up β-adrenergic receptors while consuming β-2 adrenergic agonists (β2AA) up-regulates sodium transportation by intensifying the action of sodium channels, sodium potassium adenosine triphosphatase and large quantity of protein at plasma membrane[13]. Inhalational salbutamol i.e., a β2-adrenergic agonist used universally in the management of bronchopulmonary dysplasia in premature as well[14-16]. Varieties of medicines are being universally recommended in TTN, but paucity of data is available on this. In this situation, a study was planned to determine the effectiveness of inhaled salbutamol in neonates.

METHODS

This open label randomized control trial was conducted at Department of Neonatology, Sir Sadiq Muhammad Khan Abbasi Hospital, Bahawalpur during January 2018 to November 2022 after approval from the IRB/Ethical Committee of Sir Sadiq Muhammad Khan Abbasi Hospital Bahawalpur, Punjab, Pakistan. Informed written consent was taken from every parent or guardian. Transient tachypnea of newborn (TTN) was defined as any neonates with gestational age ≥34 suffered from respiratory distress i.e., respiratory rate greater than 60/minute (expiratory grunting, nasal flaring or supraclavicular or subcostal retraction and cyanosis), requiring supplemental oxygen to maintain SpO_2 between 90% to 95% and abnormal findings on chest X ray (fluid in minor fissure, some symmetrical hyperaeration, prominent vascular and or perihilar markings). Sample size of 74 newborns on the basis was calculated of the fact that TTN constituted from 0.5% to 2.8% of all deliveries (37 in each group). All neonates with gestational age ≥34 week admitted in NICU with clinical diagnosis of TTN experienced respiratory distress within 6 hours of birth were included in this study. Neonates having APGAR score at 5^{th} minutes ≤ 6, hypocalcemia, hypoglycemia, meconium aspiration, polycythemia, congenital heart disease, neonate who developed tachycardia during nebulization i.e., heart rate >180 beats/min, major congenital malformations, intrauterine growth retardation (IUGR), RDS, emergency cesarean delivery, patients managed on ventilators, need CPAP support and sepsis were excluded.

The neonates were divided into two groups based on salbutamol inhalation: (Group A) consisted of neonates who received supplementary care, supplementary care, incremental oxygen followed by protocol used for TTN and (group-B) comprised of neonates who received a single standard dose (0.15 mg/kg) of inhaled salbutamol therapy via ultrasonic nebulizer for 5 minutes, in addition to supplementary care, supplementary care, incremental oxygen followed by protocol used for TTN. Heart rate/min, respiratory rate/min, blood oxygen saturation (O_2 Sat), fraction of inspired oxygen (FiO_2), blood potassium level and glucose level, arterial blood gases (PH, partial pressure of arterial oxygen [PaO_2], partial pressure of arterial carbon dioxide [$PaCO_2$]), Chest X-rays, serum calcium level were done before nebulization and levels of arterial blood gases and Potassium were also done 3 to 4 hours after salbutamol nebulization whereas C-reactive protein, complete blood counts were determined at 24 hours of age in all cases. A bedside scoring approach for the Respiratory Distress Evaluation being useful an Instrument for bedside evaluation of the TTN bedside clinical score. Demographic data including age, gender, duration of stay, mode of delivery, APGAR score, heart rate, respiratory rate, blood oxygen saturation, (FiO_2), blood potassium level, glucose level and arterial blood gases (PH, partial pressure of arterial oxygen [PaO_2], partial pressure of arterial carbon dioxide [$PaCO_2$]), CXR findings and TTN bedside score were recorded..

Data were entered and analyzed in SPSS version 20. Qualitative statistics were presented as mean ± SD, while quantitative statistics were presented in frequency or percentages. Statistical test was performed among dependent and independent variables by Chi square test ($\chi 2$) and where the values in a cell was < 5 Fisher's exact test was applied. A p value ≤ 0·05 was taken significant statistically.

RESULTS

A total 80 neonates with gestational age ≥34 week to 41+6 week admitted in NICU with clinical diagnosis of TTN according to clinical scoring criteria were registered in this study and were distribute randomly into 2 groups. Each group consisted of 40 subjects. Both groups were comparable (P > 0.05) in their demographic data as shown in table1.

The median period of stay in hospital was one day shorter and oxygen inhalation was 17 hours less in the salbutamol group (P > 0.001, P > 0.005 respectively) as compared to control group as shown in table 3. Statistical figures of Oxygen saturation, TTN bedside score, respiratory rate, FiO_2, PaO_2, PCO_2, PH, blood glucose level, and blood potassium level before and 4 hours after management are displayed in Table4.

After successively nebulization with salbutamol, there were notable rectifying numbers in respiratory rate, TTN bedside score, FiO_2, PH, PO_2 and PCO_2 ($P < 0.05$). However no statistically noteworthy changes were noted in glucose and potassium amongst the biochemistry levels and clinically in heart rate ($P > 0.05$)

Table 1. Demographic Data

	Group 1 (n=40)	Group 2 (n=40)	P value
Age (Minutes) at the time admission mean ± SD	35.13 ± 8.35	34.88±7.54	0.8886
Full term (≥ 37 week)	20 (50%)	22 (55%)	0.659
Late Preterm (34 to 36+6 week)	20 (50%)	18 (45%)	0.659
Males	22 (55%)	23 (57.5%)	0.822
Females	18 (45%)	17(42.5%)	0.822
Elective cesarean delivery	16 (40%)	19 (47.5%)	0.499
Spontaneous vaginal delivery	24 (60%)	21 (52.5%)	0.499
Maternal risk factor			
Asthma	3 (7.5%)	3 (7.5%)	0.75
Pneumonia	2 (5%)	3 (7.5%)	0.75
UTI	1 (2.5%)	0	0.75
Birth weight (kg) mean ± SD	2.46 ± 0.59	2.47 ± 0.54	0.9372
White blood cell count mean ± SD	15.05 ± 7.57	16.15 ± 6.94	0.5001
Hemoglobin (g/dL) mean ± SD	15.38 ± 2.5	14.99 ± 3.0	0.5295
Apgar score (5th minute) mean ± SD	7.85 ± 0.70	7.65 ± 0.662	0.1931
O2 saturation at admission mean ± SD	84.73 ± 0.86	84.37 ± 0.868	0.0688
Clinical Score mean ± SD	7.20 ± 0.97	6.98±0.97	0.3136
Mode of respiratory support with supplemental O2 delivery			
Low flow <1 Liter/Minute	18 (45%)	21 (67.5%)	0.50
High flow >1 Liter/Minute	22 (55%)	19 (32.5%)	0.50

Table 2. Criteria for respiratory status assessment and TTN clinical

	Score			
	0 Point	1 Point	2 Point	3 Point
Expiratory grunting	None	Intermittent	Continuous	-
Supraclavicular retraction	None	Mild	Moderate	Moderate
Subcostal retraction	None	Mild	Moderate	-
Cyanosis	None	At extremities	central	Moderate
Nasal Flaring	None	Mild	Moderate	Moderate

Table 3. Duration of hospitalization and oxygen inhalation (Hours)

Parameters	Group 1 (n=40)	Group 2 (n=40)	P value
Timespan of hospitalization (Hours)	64.38 ± 10.15	43.13 ± 16.33	0.001
Duration of oxygen inhalation (Hours)	42.63 ± 8.87	25.60 ± 10.98	0.005

DISCUSSION

In our study, newborns with established TTN were managed with incremental oxygen alone were compared with TTN newborns who received single-dose inhaled salbutamol via ultrasonic nebulizer in addition to traditional treatment. Breakthrough in respiratory rate, TTN bedside score, FiO_2, PH, PO_2, PCO_2 ($P < 0.05$), duration of hospitalization and timespan of oxygen inhalation were trivial in the salbutamol group as compared to control group. Aslan and his colleagues showed an amity among TTN and polymorphisms of β-adrenergic receptor (ADRB 1-2) in alveolar type II cells that trigger sodium potassium adenosine triphosphatase (Na+K+-ATPase) by multiplying appearance of ENaC, subsequently facilitating absorption of trans-epithelial sodium.[17-19] Animal model and human studies[20-23] combined has shown that intravenous administration of albuterol (salbutamol) stimulates lung tissue in ex vivo environment led to increase absorption of lung fluid. As constriction of fetal lung fluid is dependent on catecholamine levels and Greennough, Lagercrantz and their colleagues[24] had observed the abnormal levels of natural catecholamine in newborns established TTN. Based on available data and numerous studies have suggested

the usefulness of inhaled salbutamol in TTN, the management modus operandi in established TTN was transformed in way that single-dose of inhaled salbutamol via ultrasonic nebulizer was brought in established TTN. Similar observations had been made in numerous studies conducted in various countries like Turkey[1], Korea[14], Egypt[25-27] and Iran[28-31]. All these observations advocated that β2AA is a new useful treatment approach for downsizing the natural proceeding of TTN and resolves the urgency of dyspnea over time[1]. We took aid from bedside scoring approach for evaluation of respiratory distress for totaling TTN bedside clinical score and this bedside scoring methodology was favored considering that we had found it a very simple, helpful without difficulty and noninvasive tool with minimally inter-observer variability which matches the observations noted by Esengul Keles[1] and his colleagues.

No side effects had been noted after administration of a single inhaled salbutamol via ultrasonic nebulizer which is similar to studied conducted by Armangil et al[32] and Mohammad zadeh et al[30].

In our study, a significant taper off in bedside clinical score and biochemistry values suggests the successful application of inhale salbutamol in neonates. Small number of patients comprises of limitations of this study. However, more advance prospective research papers on larger scale are compulsory to document the usefulness of inhaled salbutamol as a beneficial interference for routine protocol for this frequently observing disorder.

Table 4. Figures before and 4 hours after inhaled Salbutamol via ultrasonic nebulizer

Parameters		Group 1 (n=40)	Group 2 (n=40)
TTN clinical score	Before treatment	7.20 ± 0.96	6.98±0.97
	After treatment	6.88± 0.68	4.95± 0.75
	p value	0.09	0.0001
Respiratory rate	Before treatment	73.20 ± 7.67	72.03 ± 6.43
(breaths/min)	After treatment	72.20 ± 7.44	69.30 ± 5.67
	p value	0.555	0.047
Heart rate (beats/min)	Before treatment	140.88 ± 12.61	144.38 ± 18.16
	After treatment	142.73 ± 11.91	137.33 ± 18.07
	p value	0.50	0.085
FiO2 (%)	Before treatment	53.00 ± 6.86	55.88 ±3.90
	After treatment	59.13 ± 1.92	54.00 ± 4.11
	p value	0.0001	0.039
Oxygen saturation	Before treatment	86.60 ± 1.42	84.50 ± 1.10
	After treatment	88.73 ± 1.39	91.03 ± 0.97
	p value	0.0001	0.0001
PaO2 (mm Hg)	Before treatment	52.83 ± 2.39	49.20 ± 1.43
	After treatment	57.35 ± 3.06	61.18 ± 1.89
	p value	0.0001	0.0001
PaCO2 (mm Hg)	Before treatment	43.53 ± 1.93	42.98 ± 1.52
	After treatment	43.52 ± 1.92	42.09 ± 1.82
	p value	0.96	0.02
PH	Before treatment	7.3345 ± 0.09	7.3175 ± 0.10
	After treatment	7.2640 ± 0.53	7.35 ± 0.043
	p value	0.4149	0.0214
Serum potassium level	Before treatment	4.2825 ± 0.61	4.2525 ± 0.54
(mEq/L)	After treatment	4.3775 ± 0.61	4.1975 ± 0.49
	p value	0.51	0.60
Serum glucose level (mg/dL)	Before treatment	76.65 ± 18.30	72.50 ± 18.06
	After treatment	79.63 ± 17.68	73.75 v 18.02
	p value	0.46	0.75

CONCLUSION

Inhaled salbutamol is better as an adjuvant therapy to standard care in newborns with transient tachypnea.

ETHICAL APPROVAL

The study was approved by the Department of Medical Education, Quaid-e-Azam Medical College, Bahawalpur, vide reference No. 465/DME/QAMC Dated 26.09.2018.

REFERENCES

1. Keleş E, Gebeşçe A, Demirdöven M, Yazgan H, Baştürk B, Tonbul A. The effects of inhaled β-adrenergic agonists in transient tachypnea of the newborn. Global pediatric health. 2016; 3:2333794X16645258.
2. 2.Agrawal V, David RJ, Harris VJ. Classification of acute respiratory disorders of all newborns in a tertiary care center. J Natl Med Assoc. 2003; 95:585-595.
3. 3.Tutdibi E, Gries K, Bücheler M, Misselwitz B, Schlosser RL, Gortner L. Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. Pediatrics. 2010;125(3): e577-e83.
4. 4.Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. Journal of Perinatology. 2005;25(4):251-257.
5. 5.Avery ME, Gatewood OB, Brumley G. Transient tachypnea of newborn: possible delayed resorption of fluid at birth. Am J Dis Child. 1966;111(4):380-385.
6. 6.Dani C, Reali MF, Bertini G, Wiechmann L, Spagnolo A, Tangucci M et al (1999) Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Eur Respir J 14:155-159
7. 7.Haney PJ, Bohlman M, Sun CC. Radiographic findings in neonatal pneumonia. AJR Am J Roentgenol 1984; 143(1): 23-6.
8. 8.Heritage CK, Cunningham MD. Association of elective repeat cesarean delivery and persistent pulmonary hypertension of the newborn. Am J Obstet Gynecol 1985; 152(6 Part 1): 627-9.
9. 9.Bucciarelli RL, Egan EA, Gessner IH, Eitzman DV. Persistence of fetal cardiopulmonary circulation: one manifestation of transient tachypnea of the newborn. Pediatrics 1976; 58(2): 192-197.
10. 10.Cloherty JP, Eichenwald EC, Stark AR, editors. Manual of neonatal care. Lippincott Williams & Wilkins; 2008.
11. 11.Hack M, Fanaroff AA, Klaus MH, Mendelawitz BD, Merkatz IR. Neonatal respiratory distress following elective delivery. A preventable disease? Am J Obstet Gynecol. 1976; 126:43-47.
12. 12.Tudehope DI, Smyth MH. Is 'transient tachypnoea of the newborn' always a benign disease? Report of 6 babies requiring mechanical ventilation. Aust Paediatr J 1979; 15(3): 160-165.
13. 13.Aslan E, Tutdibi E, Martens S, Han Y, Monz D, Gortner L. Transient tachypnea of the newborn: a role for polymorphisms in the beta-adrenergic receptor (ADRB) encoding genes? Acta Paediatr. 2008; 97:1346-50.
14. 14.Kim MJ, Yoo JH, Jung JA, Byun SY. The effects of inhaled albuterol in transient tachypnea of the newborn. Allergy, asthma & immunology research. 2014;6(2):126-130.
15. 15.Stroustrup A, Trasande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. J Pediatr. 2012; 160:38-43.
16. 16.Wiswell TE, Rawlings JS, Smith RE, Goo ED. Effect of furosemide on the clinical course of transient tachypnea of the newborn. Pediatrics. 1985; 75:908-10.
17. 17.Karabayir N. Intravenous furosemide therapy in transient tachypnea of the newborn. Pediatr Int. 2010; 52:851.
18. 18.Walters_DV, Olver_RE. The role of catecholamines in lung liquid absorption at birth. Pediatric Research 1978;12(3):239-242.
19. 19.Barker PM, Olver RE. Invited review: clearance of lung liquid during the perinatal period. J Appl Physiol 2002; 93(4): 1542-1548.
20. 20.Sakuma T, Tuchihara C, Ishigaki M, Osanai K, Nambu Y, Toga H, Takahashi K, et al. Denopamine, a beta (1)-adrenergic agonist, increases alveolar fluid clearance in ex vivo rat and guinea pig lungs. Appl Physiol 2001; 90:10-16.
21. 21.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. American journal of respiratory and critical care medicine. 1997;155(2):506-512.
22. 22.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; 120:1308-14.
23. 23.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; 161:1322-31.
24. 24.Greennough A, Lagercrantz H. Catecholamine abnormalities in transient tachypnea of the premature newborn. J Perinat Med. 1992; 20:223-226.
25. 25.Nawar F, Aly HA, Helmy S, Abd El Monaem M. Is Salbutamol and Adrenalin Inhalation Effective in Management of Transient Tachypnia of Newborn? Journal of Advances in Medicine and Medical Research. 2016:1-8.
26. 26.Talaat AA, Abohashish MM, Farid TM, Salah MM. Evaluation of inhaled beta-2 agonist in management of transient tachypnea of the newborn. Bulletin of the National Research Centre. 2020;44(1):12.
27. Bakry AR, Atia AA, Hablas HR, Abd el aziz AF. The role of inhaled β2-adrenergic agonists in treatment of transient tachypnea of the newborn. Al-Azhar J Pediatr. 2019;22(1):57-74.
28. Babaei H, Dabiri S, Mohammadi Pirkashani L, Mohsenpour H. Effects of Salbutamol on the Treatment of Transient Tachypnea of the Newborn. Iran J Neonatol. 2019;10(1):42-49.
29. 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.
30. Mohammadzadeh I, Akbarian-Rad Z, Heidari F, Zahedpasha Y, Haghshenas-Mojaveri M. The effect of inhaled salbutamol in transient of tachypnea of the newborn: a randomized clinical trial Iran J Pediatr. 2017;27(5).e9633.
31. Malakian A, Dehdashtian M, Aramesh MR, Aletayeb MH, Heidari S. The effect of inhaled salbutamol on the outcomes of transient tachypnea of the newborn. Journal of the Chinese Medical Association. 2018 1;81(11):990-997.
32. 31.Armangil D, Yurdakok M, Korkmaz A, Yigit S, Tekinalp G. Inhaled beta-2 agonist salbutamol for the treatment of transient tachypnea of the newborn. J Pediatr. 2011; 159(3):398-403.

AUTHOR'S CONTRIBUTIONS

MA: Manuscript writing, data collection, data interpretation, research work
MA, MAA: Data collection, literature research work
AH: Data collection, data interpretation, literature research work
KW, MA: Data collection, research work