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Role of Salbutamol in the Management of Transient Tachypnea of the New Born

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ABSTRACT

Background: Transient tachypnea of the newborn (TTN) is a common respiratory disorder in the early neonatal period due to delayed clearance of fetal lung fluid. Salbutamol, a β2-adrenergic agonist, may enhance lung fluid clearance through stimulation of epithelial sodium channels and Na-K-ATPase. However, the therapeutic role of Salbutamol in TTN management remains controversial with limited clinical evidence, necessitating further investigation. **Objective:** To compare the mean change in transient tachypnea of newborn score with inhaled salbutamol and normal saline. **Study Design:** It was a randomized Controlled Trial. This study has been registered with the ClinicalTrials.gov database under the registration number NCT06921291. **Duration and Place of Study:** This study was conducted between August 2024 and December 2024 in the pediatric department of Khyber Teaching Hospital in Peshawar. **Methodology:** A total of 60 neonates with TTN were randomized into two groups (30 in each group) using blocked randomization. Eligible participants included neonates with gestational age >36 weeks of both genders presenting with TTN. Group A received a single nebulized dose of salbutamol (0.15 mg/kg) in 0.9% saline, while Group B received nebulized 0.9% saline. Both groups also received oxygen and IV fluids. **Results:** The mean gestational age at birth was 39.3 ± 1.32 weeks in Group A and 38.93 ± 1.23 weeks in Group B. Males comprised 46.7% in Group A and 66.7% in Group B, while females accounted for 53.3% and 33.3%. Group A demonstrated a significantly greater mean reduction in TTN scores (5.61 ± 1.22) compared to Group B (0.97 ± 0.73, p = 0.000). **Conclusion:** Inhaled salbutamol significantly improves TTN scores compared to normal saline, demonstrating consistent efficacy.

INTRODUCTION

Transient Tachypnea of the Newborn (TTN) is the most common respiratory issue observed in infants delivered via cesarean section or those born prematurely.[1] This condition is typically marked by rapid breathing, which usually manifests within hours of birth. TTN arises due to the slower-than-expected absorption of lung fluid from the fetus, causing an increased effort required for breathing.[2] TTN is generally self-limiting and often resolves in 24 to 72 hours with no significant sequelae.[3] Although the symptoms of Transient Tachypnea of the Newborn (TTN) are typically not life-threatening, they can cause considerable discomfort and distress, necessitating careful monitoring to rule out more severe respiratory conditions such as neonatal pneumonia or Respiratory Distress Syndrome (RDS).[4] The treatment of TTN is primarily supportive, with most cases requiring little intervention, as the condition often resolves on its own without the need for extensive medical management.[5] Newborns diagnosed with TTN are usually maintained under close observation for the possibility of respiratory distress and are provided oxygen as necessary to maintain appropriate oxygen saturation.[6] In more severe cases, Continuous Positive Airway Pressure (CPAP) may be employed to keep the airways open and thus promote the clearance of fluid from the lungs.[7] However, the general course of TTN is benign, and most infants, with supportive treatment, show significant improvement within a few days.[8]

Salbutamol is a β2-adrenergic agonist that has been tried for the management of TTN, given its bronchodilatory effects.[9] The major pharmacological mechanism through which it acts in bronchodilatation is the relaxation of smooth muscles surrounding the airways, thus improving airflow and easing the work of breathing.[10] In the context of TTN, Salbutamol could theoretically help decrease respiratory distress through the mitigation of bronchospasm and facilitation of fluid reabsorption from the lungs.[11] Though not universally required, Salbutamol can be used in cases where TTN presents with a component of airway obstruction or in cases where other respiratory therapies have not yielded sufficient improvement.[12] A study by Ahmed W et al.[13] revealed that the average alteration in the Transient Tachypnea of

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the Newborn (TTN) score after salbutamol nebulization was 5.63 ± 1.22, in contrast to 0.63 ± 1.54 with normal saline nebulization.[13]

This study is essential for our local population because of the increasing prevalence of respiratory disorders in neonates, especially those with Transient Tachypnea of the Newborn. This study can offer useful insights into the possible benefits of Salbutamol in managing TTN, given the scant studies on its efficacy in the region. The findings could help inform local healthcare practices, improve neonatal care, and optimize treatment protocols in neonatal intensive care units (NICUs), ensuring better outcomes for affected infants. Additionally, the study could serve as a foundation for further research and guide clinical decision-making in similar settings.

METHODOLOGY

This randomized controlled research was performed in the Department of Pediatrics at KTH Peshawar from August 2024 to December 2024. this study has been registered with the ClinicalTrials.gov database under the registration number NCT06921291. A sample size of 60 participants (30 per group) was determined using a sample size calculation with a 95% confidence level and 80% power. The calculation was based on data from a prior study,[13] which reported a mean change in TTN scores of 5.63 ± 1.22 for the salbutamol nebulization group and 0.63 ± 1.54 for the normal saline nebulization group. The sample size was calculated with the following assumptions: an effect size of 1.3 (Cohen's d), which indicates a large effect, was estimated using the difference in means between the two groups divided by the pooled standard deviation; standard deviations of 1.22 for the salbutamol group and 1.54 for the saline group; a significance level (α) of 0.05, and a study power of 80% to minimize the risk of Type II error. Based on these parameters, the calculated sample size of 60 participants (30 per group).

Eligible participants were neonates with gestational age >36 weeks (based on the last menstrual period) of both genders presenting with TTN as per the operational definition. Transient tachypnea is defined as the onset of respiratory distress (TTN score of ≥4 using the modified Downes score) within 6 hours after birth, accompanied by a chest radiograph showing fluid in minor fissures, hyperaeration, and bilateral perihilar vascular markings. Meconium-stained amniotic fluid, pregnancy-induced hypertension, gestational diabetes mellitus (fasting plasma glucose >90 mg/dL or OGTT results >180 mg/dL at 1 hour or >150 mg/dL at 2 hours), pre-existing renal disease or liver disease, maternal history of premature rupture of membranes >18 hours, and unbooked antenatal status were among the exclusion criteria.

Birth weight, gender, and gestational age at birth were recorded as baseline demographics. Parents gave their written informed consent. Blocked randomization was used for the randomization process. Group B received nebulized 0.9% saline with oxygen and intravenous fluids, while Group A received a single nebulized dose of salbutamol 0.15 mg/kg in 0.9% saline with oxygen and IV fluids. TTN scores were noted prior to treatment and four hours after nebulization.

SPSS version 26.0 was used to analyze the data. For quantitative data, means ± standard deviations or medians (IQR) were given, whereas frequencies and percentages were computed for categorical variables. Data normality was evaluated using the Shapiro-Wilk test. Using t-tests, differences in TTN score changes between groups were examined. To account any imbalance in categorical variables (like gender) on the primary outcome (TTN score) it was adjusted using Analysis of Covariance (ANCOVA).

RESULTS

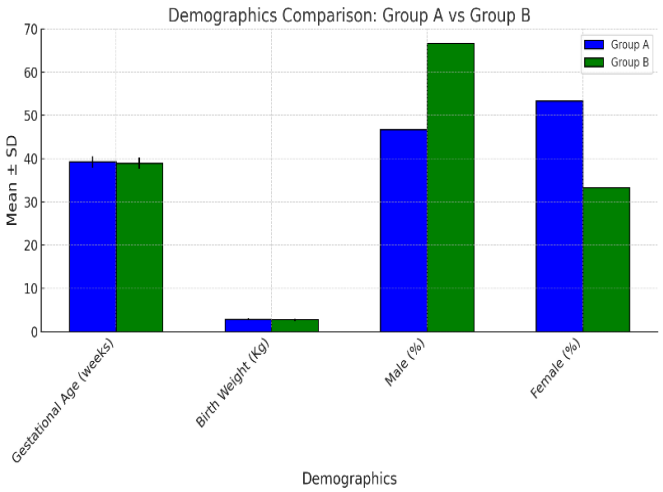
Gestational age at birth was 39.3±1.32 weeks in Group A and 38.93±1.23 weeks in Group B. Birth weights were 2.87±0.28 kg and 2.78±0.23 kg, respectively. Males comprised 46.7% in Group A and 66.7% in Group B, while females accounted for 53.3% and 33.3% (as shown in Table 1).

Table 1

Mean ± SD of Patients According to Demographics in Both Groups (n=60)

Demographics	Group A n=30 Mean ± SD	Group B n=30 Mean ± SD
Gestational Age at Birth (weeks)	39.300±1.32	38.933±1.23
Birth Weight (Kg)	2.871±0.28	2.779±0.23
Gender	n (%)	n (%)
Male	14 (46.7)	20 (66.7)
Female	16 (53.3)	10 (33.3)

Figure 1



The mean reduction in TTN scores was significantly greater in Group A (5.61±1.22) than in Group B (0.97±0.73), with a p-value of 0.000 (as shown in Table 2).

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Table 2

Comparison of Mean Change in Transient Tachypnea of New Born Score in Both Groups (n=60)

	Group A n=30	Group B n=30	t	P-value
Change in transient tachypnea of new born score	5.611±1.22	0.969±0.73	17.914	0.000

Stratified analyses revealed consistent findings across gestational age, gender, and birth weight. For gestational age <40 weeks, mean TTN score reductions were 5.77±1.26 in Group A and 0.89±0.74 in Group B (p=0.000). For gestational age ≥40 weeks, reductions were 5.39±1.17 and 1.11±0.70, respectively (p=0.000). Among males, Group A had a mean reduction of 5.34±1.18, compared to 1.01±0.66 in Group B, while females showed reductions of 5.85±1.23 and 0.87±0.87 (p=0.000). For birth weight <3 kg, reductions were 5.76±1.21 in Group A and 0.99±0.78 in Group B; for ≥3 kg, reductions were 5.35±1.24 and 0.86±0.44, respectively (p=0.000) (as shown in Table 3).

Table 3

Stratification of Mean Change in Transient Tachypnea of New Born Score with Respect to Gestational Age at Birth, Gender and Birth Weight in Both Groups

Stratification Factor	Subgroup	Group (n)	Mean ± SD (TTN Score)	p-Value
Gestational Age at birth (weeks)	< 40	A (17)	5.774 ± 1.26	0.000
		B (20)	0.897 ± 0.74	
	≥ 40	A (13)	5.397 ± 1.17	0.000
		B (10)	1.113 ± 0.70	
Gender	Male	A (14)	5.337 ± 1.18	0.000
		B (20)	1.018 ± 0.66	
	Female	A (16)	5.850 ± 1.23	0.000
		B (10)	0.871 ± 0.87	
Birth Weight (Kg)	< 3	A (19)	5.763 ± 1.21	0.000
		B (24)	0.996 ± 0.78	
	≥ 3	A (11)	5.349 ± 1.24	0.000
		B (6)	0.858 ± 0.44	

The effect of gender on changes in transient tachypnea of newborn scores was analyzed using univariate analysis. The results revealed that there was no statistically significant difference between genders ($F(1,58) = 3.055$, $p = 0.086$) as shown in Table 4.

Table 4

Effect of Gender on Change in Transient Tachypnea of Newborn Score (Analysis of Covariance (ANCOVA))

Variable	Mean Square	F	P value
Gender	19.101	3.055	0.086

DISCUSSION

Recent molecular studies highlight salbutamol role beyond bronchodilation. Salbutamol has been shown to reduce inflammatory cytokine release and may enhance surfactant production, both of which could contribute to improved respiratory function in TTN by reducing pulmonary edema and promoting alveolar stability. The study demonstrated a significantly greater reduction in transient tachypnea of the newborn (TTN) scores with inhaled salbutamol compared to normal saline. Salbutamol, a β2-adrenergic agonist, likely accelerated fluid clearance from the alveoli by stimulating sodium-potassium ATPase and epithelial sodium channels, which are crucial for resorbing lung fluid during neonatal adaptation to extrauterine life. The consistent efficacy across stratifications—gestational age, gender, and birth weight—supports its robustness, highlighting salbutamol's physiological role in enhancing pulmonary adaptation regardless of demographic or birth characteristics. These findings emphasize salbutamol as a promising intervention for TTN management. The findings of our study align with those of other studies in demonstrating the efficacy of inhaled salbutamol in improving clinical outcomes for transient tachypnea of the newborn (TTN). Our study reported a significant reduction in TTN scores in Group A (salbutamol) compared to Group B (placebo) across all stratifications, including gestational age, gender, and birth weight. The mean reduction in TTN scores was 5.61±1.22 in Group A and 0.97±0.73 in Group B, consistent with findings from Dalia M. Al Lahonya et al.[14] , who also reported significant improvements in TTN scores and respiratory rates with salbutamol.

In comparison to Ahmed Noaman et al.[15] our study corroborates their findings of reduced Downe's scores and shorter hospital stays in the salbutamol group. Both studies underscore salbutamol's efficacy and safety. Similarly, our results align with the findings of Waqas Ahmed et al.[13] who demonstrated a comparable reduction in TTN scores (5.63±1.22) with salbutamol nebulization, affirming the drug's effectiveness.

Our findings also support those of Homa Babaei et al.[16] who demonstrated significant reductions in tachypnea duration, hospital stays, and oxygen therapy with salbutamol. Both studies highlight salbutamol's role in reducing TTN symptoms and improving clinical outcomes without adverse effects. However, Babaei et al.[16] did not specifically report detailed stratified analyses by gestational age, gender, or birth weight, as in our study, which adds to the robustness of our findings.

Differences were observed in the baseline characteristics and study outcomes. For example, the gestational ages and birth weights in our study (39.3±1.32 weeks and 2.87±0.28 kg for Group A) are slightly higher than those reported by Arshad Khushdil et al.[17] (average gestational age 38.8±6.2 weeks and birth weight 2.56±0.62 kg). These variations may be attributed to different inclusion criteria or geographic population differences, potentially influencing baseline severity and responsiveness to treatment.

While the Cochrane Review by Moresco et al.[18] highlighted inconsistent results across studies and low-

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certainty evidence regarding salbutamol's benefits, our study provides robust evidence with statistically significant findings across all stratifications. The consistent reduction in TTN scores across gestational age, gender, and birth weight in our study offers stronger support for salbutamol's efficacy compared to the broader and more heterogeneous dataset reviewed by Moresco et al.[18]

Lastly, Behnaz Basiri et al.[19] reported shorter respiratory support duration and reduced TTN scores with salbutamol, which parallels our findings. However, the lack of significant differences in hospital stays in Basiri's study differs from our results, potentially due to different study designs or endpoints measured. These differences emphasize the need for standardized methodologies in future research.

These findings collectively highlight the consistent efficacy of salbutamol in improving clinical outcomes for TTN, as demonstrated across multiple studies, including ours. While variations in methodologies and population characteristics exist, the overall evidence supports the role of salbutamol as a promising therapeutic intervention. Future research should focus on addressing limitations in evidence quality, particularly through larger, multicenter trials with standardized protocols, to further validate these outcomes and refine treatment strategies for TTN.

While this study demonstrates the efficacy of salbutamol nebulization in neonates with TTN, several limitations should be considered. The small sample size (60 participants) and single-center design may limit the generalizability of the findings. A larger, multi-center trial would strengthen the external validity and provide more robust evidence. Additionally, although we adjusted for gender imbalance in the analysis, the unequal distribution between groups may still influence the results.

CONCLUSION

In conclusion, our study demonstrates that inhaled salbutamol significantly improves clinical outcomes in neonates with transient tachypnea of the newborn by reducing TTN scores, respiratory rates, and oxygen dependency across all stratifications of gestational age, gender, and birth weight. The consistent efficacy observed reinforces salbutamol's role as a safe and effective therapeutic option for TTN management.

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