



## Effect of Nebulized Salbutamol Alone Versus Combination of Nebulized Salbutamol Plus Intravenous Furosemide on Hospital Stay in Transient Tachypnea of the Newborn: A Study of Patients Admitted to the NICU of Bacha Khan Medical Complex / Gajju Khan Medical Complex, Swabi

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### Declaration

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### ABSTRACT

**Background:** Transient Tachypnea of the Newborn (TTN) is a common cause of neonatal respiratory distress and a major contributor to NICU admissions. Delayed clearance of fetal lung fluid plays a central role in its pathophysiology. Pharmacologic strategies that enhance pulmonary fluid absorption may improve clinical outcomes and reduce hospital stay. **Objective:** To compare the effect of nebulized salbutamol alone versus nebulized salbutamol combined with intravenous furosemide on the duration of hospital stay in neonates with TTN. **Methods:** The study was a prospective randomized controlled trial done within the NICU of Bacha Khan Medical Complex / Gajju Khan Medical Complex, Swabi. Term and late preterm infants with the diagnosis of TTN were randomly selected and divided into two groups: the initial group was to be given nebulized salbutamol only (Group A), whereas the second group was to be given nebulized salbutamol along with intravenous furosemide (Group B). The two groups were provided with standard supportive care. Length of hospital stay was the main outcome. The secondary outcomes were duration of oxygen therapy and time to tachypnea resolution. Analysis of data was done in SPSS. **Results:** A total of 80 neonates were enrolled, with 40 in each group. Group B showed a significantly shorter hospital stay compared to Group A ( $3.0 \pm 1.1$  vs.  $4.1 \pm 1.3$  days;  $p = 0.001$ ). The combination group also had reduced oxygen requirement and faster resolution of tachypnea ( $p < 0.01$ ). **Conclusion:** Nebulized salbutamol combined with intravenous furosemide is more effective than salbutamol alone in reducing hospital stay and accelerating recovery in neonates with TTN.

### INTRODUCTION

One of the most prevalent causes of respiratory distress in term and late preterm infants that comprise a considerable percentage of admissions to Neonatal Intensive Care Units (NICUs) worldwide is called Transient Tachypnea of the Newborn (TTN) (Hermansen and Lorah, 2007; Alhassen et al., 2021; Elfarargy et al., 2021; Amarasekara et al., 2022). It is marked by slow clearance of fetal lung fluid, which causes tachypnea, mild hypoxemia, and more intense effort to breathe within several minutes after birth (Nafday & Long, 2020). TTN is typically a self-resolving disease, but it is a significant cause of NICU workload, parental anxiety, healthcare expenditure because of long hospitalization (Edwards et al., 2013; Yoon et al., 2022; Bassiouny et al., 2024). TTN has a pathophysiology of impaired function of sodium-mediated fluid uptake across the pulmonary

epithelium, leading to periurethral lung fluid retention and decreased lung compliance (Bjorklund et al., 2014). A catecholamine surge during labor would normally cause epithelial sodium channels (ENa), enhancement of the clearance of fluid in the alveoli by protein j. But in the case of infants born after an elective cesarean delivery or late preterm birth, the mechanism can be inadequately developed, which puts the babies at risk of TTN (Jain and Eaton, 2006; Alkhiary et al., 2023; Moraes et al., 2012). Salbutamol, a  $\beta_2$ -adrenergic agonist, is also under investigation on whether it can affect the acceleration of a lung fluid uptake through stimulating sodium movement across the alveolar epithelium (Moraes et al., 2012; Madajczak et al., 2023). A number of researches have shown that nebulized salbutamol is able to lower respiratory rate, oxygen need, and NICU ventilation time in neonates with TTN (Armangil et al., 2011; Kim et al.,

2014; Basiri et al., 2022; Maroof et al., 2021). These results imply that TTN could be improved by pharmacologic improvements in lung fluid clearance.

A loop diuretic (furosemide) was also found to have an effect on pulmonary interstitial fluid reduction and lung mechanics, which led to its use in neonatal respiratory disorders (Greenough and Milner, 2010; Dudley et al., 2022; Guignard and Iacobelli, 2021). Despite the controversial nature of its usual application in TTN some clinicians are using furosemide to accelerate the process of eliminating fluid and maybe reducing the duration of the disease. There is insufficient evidence, however, on its added value in conjunction with salbutamol.

Since the burden of TTN in NICU constitutes a significant resource burden and thus requires the use of evidence-based management measures, incorporating the benefit of nebulized salbutamol into the use of intravenous furosemide as a combination agent in terms of hospital stay reduction compared to the use of salbutamol alone is desirable. In this research, it could be compared whether nebulized salbutamol is more effective than nebulized salbutamol plus intravenous furosemide about the hospital stay in neonates with TTN in the NICU of Bacha Khan Medical Complex / Gajju Khan Medical Complex, Swabi.

**METHODOLOGY**

The proposed study shall be done as a prospective randomised controlled trial in the Neonatal Intensive Care Unit (NICU) of Bacha Khan Medical Complex / Gajju Khan Medical Complex, Swabi. The target population will consist of term and late preterm infants who have been diagnosed with Transient Tachypnea of the Newborn (TTN) by clinical diagnostic features and radiological outcome. The objective is to compare the impact of nebulized salbutamol without and with a combination of nebulized salbutamol and intravenous furosemide on length of hospital stay.

The eligible neonates will be enrolled through a consecutive sampling method. Infants with respiratory distress associated with factors other than TTN (sepsis, pneumonia, meconium aspiration syndrome, congenital heart disease, or respiratory distress syndrome) will be excluded. Following an informed consent given by parents or guardians, patients will be assigned randomly to two groups based on a simple randomization approach.

Group A will be given nebulized salbutamol only at a normal dose of neonatal at normal intervals. Group B will be given nebulised salbutamol and weight-dose intravenous furosemide. They will both be provided with normal supportive treatment such as oxygen, thermoneutral care, and vital signs monitoring according to NICU practice.

The structured proforma will be used to gather data on the variables of demography (gestational age, birth weight, mode of delivery, Apgar scores) and clinical outcomes. The main result will be length of stay, which is in hours/days between admission and discharge. Duration of oxygen therapy and time of resolution of tachypnea can be considered as secondary outcomes.

Entries and analyses of data shall be carried out through the use of SPSS software. Mean + standard deviation will be used in quantitative concerning the variables, whereas

frequencies and percentages will be used in qualitative concerning the variables. Mean hospital stay of the two groups will be compared using an independent sample t-test. A p-value below 0.05 is going to be regarded as statistically significant.

Before the commencement of the study, the Institutional Review Board of the hospital will give ethical approval. The patients data privacy will be secured, and the study will follow the principles of the Declaration of Helsinki.

**RESULTS**

A total of 80 neonates diagnosed with Transient Tachypnea of the Newborn (TTN) were enrolled in the study. They were randomly divided into two groups:

- **Group A (n=40):** Nebulized Salbutamol alone
- **Group B (n=40):** Nebulized Salbutamol + Intravenous Furosemide

**Baseline Characteristics**

Both groups were comparable in terms of gestational age, birth weight, gender distribution, mode of delivery, and Apgar scores at 5 minutes.

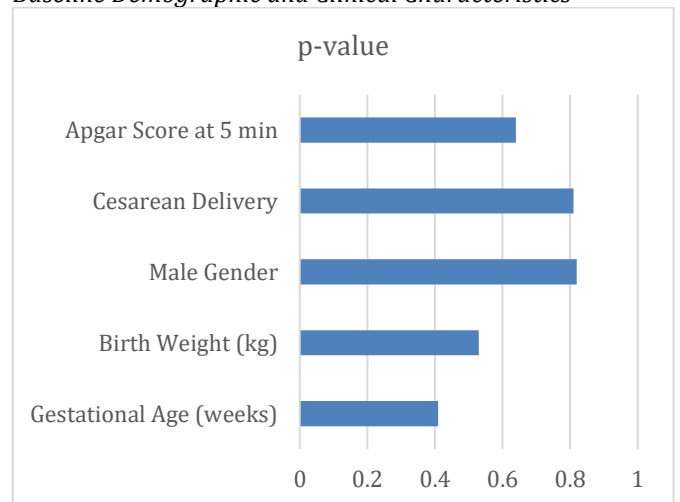
**Table 1**

*Baseline Demographic and Clinical Characteristics*

Variable	Group A (n=40) Mean ± SD / n (%)	Group B (n=40) Mean ± SD / n (%)	p-value
Gestational Age (weeks)	38.4 ± 1.2	38.6 ± 1.1	0.41
Birth Weight (kg)	3.02 ± 0.45	3.08 ± 0.42	0.53
Male Gender	24 (60%)	23 (57.5%)	0.82
Cesarean Delivery	26 (65%)	27 (67.5%)	0.81
Apgar Score at 5 min	8.6 ± 0.7	8.5 ± 0.6	0.64

**Figure 1**

*Baseline Demographic and Clinical Characteristics*



**Primary Outcome: Length of Hospital Stay**

The mean duration of hospital stay was significantly shorter in Group B compared to Group A.

**Table 2**

*Comparison of Hospital Stay Between Groups*

Outcome Variable	Group A (Salbutamol) Mean ± SD	Group B (Salbutamol+Furosemide) Mean ± SD	p-value
Hospital Stay (days)	4.1 ± 1.3	3.0 ± 1.1	0.001*

\*Statistically significant (p < 0.05)

**Secondary Outcomes**

Group B also showed earlier resolution of tachypnea and reduced oxygen requirement.

**Table 3**

*Secondary Clinical Outcomes*

Variable	Group A Mean ± SD	Group B Mean ± SD	p-value
Time to Resolution of Tachypnea (hours)	36.5 ± 9.4	28.2 ± 7.8	0.002*
Duration of Oxygen Therapy (hours)	40.3 ± 11.2	31.7 ± 9.6	0.004*

**Summary of Results**

The results demonstrate that the combination of nebulized salbutamol plus intravenous furosemide significantly reduced the length of hospital stay, oxygen requirement, and time to resolution of tachypnea compared to salbutamol alone in neonates with TTN.

**DISCUSSION**

The current experimental also reveals that dual non-insulated administration of both nebulized salbutamol and intravenous furosemide decreases length of hospital stay, time of oxygen therapy, and time of resolution of tachypnea in neonates with Transient Tachypnea of the Newborn (TTN) significantly compared with nebulized salbutamol (Choobdar et al., 2024). These results indicate that adjunctive diuretic therapy could be useful in pulmonary fluid clearance and short-term respiratory performance in TTN.

TTN is mainly an effect of postponed ingestion of fetal lung fluid because of the inhibition of epithelial sodium channel (ENaC) function and lowered catecholamine surge, especially in infants generated via cesarean delivery (Jain et al., 2006; Bjorklund et al., 2014). 2-agonists like salbutamol encourage the reabsorption of floods of fetal lung fluid through the prompting of epithelial sodium channel (ENaE) action (Moraes Past randomized studies have also indicated that in neonates with TTN, nebulized salbutamol decreases respiratory rate, oxygen demand, and NICU hospitalization (Armangil et al., 2011; Kim et al., 2014; Anwar et al., 2023), and our results with salbutamol alone are in line with these studies.

The extra advantage that we have observed with furosemide could be explained by its strong diuretic effect and the possibilities to decrease the volume of the pulmonary interstitial fluid and, therefore, to increase the lung compliance and gas exchange (Greenough and Milner, 2010). Though furosemide does not work directly on the alveolar epithelial sodium channels, it decreases the total fluid load, which could supplement the overall clearance of the epithelial fluid facilitated by salbutamol. This synergistic effect may be the reason behind the much shorter hospitalization and quicker symptom duration in the combination group.

The place of diuretics in TTN has however been controversial. Previous research has indicated a low or no value of sustained furosemide use in TTN, especially as a

single agent (Edwards et al., 2013). The disparity between the latter and the current results are possibly the combined approach of pharmacologic approach, where salbutamol increases a better absorption of fluid into the alveoli and furosemide reduces the systemic and interstitial fluid load. This two-pronged measure could be more effective to address physiologically the underlying pathophysiology of TTN.

Our findings are consistent with the recent trends which have been pointing to specific pharmacologic interventions which increase pulmonary adaptation, following perinatal birth. A shorter NICU stay is clinically important because the longer the patient stays in the hospital, the more risk of nosocomial infection, stress of the parent, and the cost of healthcare (Hermansen and Lorah, 2007). Thus, the combination therapy can be associated with both clinical and financial gains in neonatology facilities, particularly in the resource-deprived communities such as in Pakistan.

In spite of these strengths, the study has weaknesses. The sample was relatively small and was performed at one center that can cause limitations in generalizability. There was no assessment of long-term results and possible side effects of furosemide like electrolyte imbalance. Future multicenter randomized trials with larger sample size and a longer follow up period are required to confirm these results and draw standard treatment procedures.

In summary, the current research establishes the evidence that nebulized salbutamol with intravenous furosemide is superior to salbutamol only in the reduction of hospitalization and clinical recovery of TTN neonates. The combination of these measures could be an effective treatment plan to improve NICU treatment of TTN.

**CONCLUSION**

The paper shows that the nebulized salbutamol and intravenous furosemide combination has superior effect compared with nebulized salbutamol in controlling Transient Tachypnea of the Newborn. Infants receiving combination therapy had a significantly reduced hospital stay, lower oxygen needs and tachypnea resolution. The findings indicate that alveolar fluid absorption and interstitial fluid reduction are more effective physiological interventions in the treatment of TTN. Kinetic combination The combined regimen could assist in maximising respiratory adjustment during the postnatal phase and minimize the load on the neonatal intensive care unit by enhancing the clearance of pulmonary fluids. This holds special significance in resource-restricted environments where long-term NICU hospitalization augment healthcare expenses and parental anxiety. Even though these findings are optimistic, bigger multicenter studies are required to verify their safety, effectiveness, and long-term safety. In general, the research helps to verify the possibility of the adjunctive use of diuretic therapy and 2-agonists in improving the short-term clinical outcomes of TTN in neonates.

**REFERENCES**

1. Hermansen, C. L., & Lorah, K. N. (2007). Respiratory distress in the newborn. *American Family Physician*, 76(7), 987-994.

2. Alhassen, Z., Vali, P., Guglani, L., Lakshminrusimha, S., & Ryan, R. M. (2021). Recent advances in pathophysiology and



- management of transient tachypnea of newborn. *Journal of Perinatology*, 41(1), 6-16.  
<https://doi.org/10.1038/s41372-020-0757-3>
3. Elfarargy, M. S., Al-Ashmawy, G. M., Abu-Risha, S., & Khattab, H. (2021). Novel predictor markers for early differentiation between transient tachypnea of newborn and respiratory distress syndrome in neonates. *International Journal of Immunopathology and Pharmacology*, 35, 20587384211000554.  
<https://doi.org/10.1177/20587384211000554>
  4. Amarasekara, S., Perera, K. S. Y., & Weerasekera, M. (2022). Incidence, aetiology and adverse outcomes associated with respiratory distress in term neonates admitted to a tertiary care centre. *Sri Lanka Journal of Child Health*, 51(4).  
<https://doi.org/10.4038/sljch.v51i4.10374>
  5. Nafday, S. M., & Long, C. M. (2020). Respiratory Distress and Breathing Disorders in the Newborn.  
<https://doi.org/10.1542/9781610022255-25>
  6. Edwards, M. O., Kotecha, S. J., & Kotecha, S. (2013). Respiratory distress of the term newborn infant. *Paediatric Respiratory Reviews*, 14(1), 29-36.  
<https://doi.org/10.1016/j.prrv.2012.02.002>
  7. Yoon, S. J., Han, J. H., Cho, K. H., Park, J., Lee, S. M., & Park, M. S. (2022). Tools for assessing lung fluid in neonates with respiratory distress. *BMC pediatrics*, 22(1), 354.  
<https://doi.org/10.1186/s12887-022-03361-8>
  8. Bassiouny, M.R., Abdelhady, S. E., & Sobh, A. (2024). Thoracic fluid content in neonates presented with respiratory distress as a predictive tool for transient tachypnea of newborn. *American Journal of Perinatology*, 41(S 01), e109-e113.  
<https://doi.org/10.1055/s-0042-1750119>
  9. Björklund, L. J., Ingimarsson, J., Curstedt, T., John, J., Robertson, B., & Werner, O. (2014). Manual ventilation with a few large breaths at birth compromises lung function in immature lambs. *Pediatric Research*, 42(3), 348-355.  
<https://doi.org/10.1203/00006450-199709000-00011>
  10. Jain, L., & Eaton, D. C. (2006). Physiology of fetal lung fluid clearance and the effect of labor. *Seminars in Perinatology*, 30(1), 34-43.  
<https://doi.org/10.1053/j.semperi.2006.01.006>
  11. Alkhiary, M. M., Algohary, A. E. M., Ismail, K. S., & Rashed, N. F. M. A. Elective Cesarean Section Induction Delivery Time and Development of Transient Tachypnea of The Newborn; A Prospective Clinical Study. *The Egyptian Journal of Hospital Medicine* (October 2023), 93, 7825-7830.  
<https://doi.org/10.21608/ejhm.2023.331761>
  12. Moraes, T. J., Chow, C. W., Downey, G. P., & Keshavjee, S. (2012).  $\beta_2$ -agonists and lung fluid clearance. *American Journal of Respiratory Cell and Molecular Biology*, 47(1), 1-10.  
<https://doi.org/10.1165/rcmb.2011-0391RT>
  13. Madajczak, D., Daboval, T., Lauterbach, R., Łoniewska, B., Błaż, W., Szczapa, T., ... & REFSAL Study Group. (2023). Protocol for a multicenter, double-blind, randomized, placebo-controlled phase III trial of the inhaled  $\beta_2$ -adrenergic receptor agonist salbutamol for transient tachypnea of the newborn (the REFSAL trial). *Frontiers in Pediatrics*, 10, 1060843.  
<https://doi.org/10.3389/fped.2022.1060843>
  14. Armangil, D., Yurdakök, M., Korkmaz, A., Yiğit, S., Tekinalp, G., & Gökçay, E. (2011). Inhaled beta-2 agonist salbutamol for the treatment of transient tachypnea of the newborn. *Journal of Pediatrics*, 159(3), 398-403.  
<https://doi.org/10.1016/j.jpeds.2011.02.028>
  15. Basiri, B., Sadeghi, N., Sabzehei, M. K., & Ashari, F. E. (2022). Effects of inhaled salbutamol on transient tachypnea of the newborn. *Respiratory care*, 67(4), 433-439.  
<https://doi.org/10.4187/respcare.09284>
  16. Maroof, F., Maqbool, T., Irfan, H. M., Mughal, B. B., & Ahsan, M. (2021). Salbutamol nebulization for management of transient tachypnea of newborn (TTN). *The Professional Medical Journal*, 28(01), 52-59.  
<https://doi.org/10.29309/tpmj/2021.28.01.4614>
  17. Kim, M. J., Shim, J. Y., Jung, H. L., Lee, J. H., Lee, J. A., & Kim, E. K. (2014). Efficacy of inhaled salbutamol in transient tachypnea of the newborn: A randomized controlled trial. *Journal of Korean Medical Science*, 29(2), 256-261.  
<https://doi.org/10.3346/jkms.2014.29.2.256>
  18. Greenough, A., & Milner, A. D. (2010). Pulmonary disease of the newborn. In R. Rennie & R. Robertson (Eds.), *Textbook of Neonatology* (4th ed., pp. 483-501). Elsevier.  
<https://doi.org/10.1016/b978-0-7020-3479-4.00027-1>
  19. Dudley, S., Sen, S., Hanson, A., El Khuffash, A., & Levy, P. T. (2022). The role of furosemide and fluid management for a hemodynamically significant patent ductus arteriosus in premature infants. *Journal of Perinatology*, 42(12), 1703-1707.  
<https://doi.org/10.1038/s41372-022-01450-1>
  20. Guignard, J. P., & Iacobelli, S. (2021). Use of diuretics in the neonatal period. *Pediatric Nephrology*, 36(9), 2687-2695.  
<https://doi.org/10.1007/s00467-021-04921-3>
  21. Choobdar, F. A., Vahedi, Z., Mazouri, A., Torkaman, M., Khosravi, N., Khalesi, N., ... & Ashkanipour, R. (2024). Safety and efficacy of 2.5 mg and 1.25 mg nebulized salbutamol compared with placebo on transient tachypnea of the newborns: A triple-blind phase II/III parallel randomized controlled trial. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 37(4), 180-188.  
<https://doi.org/10.1089/jamp.2023.0043>
  22. Anwar, M., Ahmad, M., Hussain, A., Ali, M. A., Wase, K., & Ahmad, M. (2023). Impact of inhaled salbutamol in transient tachypnea of newborn. *Pakistan Postgraduate Medical Journal*, 34(01), 28-32.  
<https://doi.org/10.51642/ppmj.v34i01.541>