

Role of Salbutamol in The Management of Transient Tachypnea of the Newborn: A Comparative Prospective Study

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ABSTRACT

Objective: To compare the outcome of Salbutamol nebulization with normal saline (placebo) in transient tachypnea of the newborn.

Study Design: Comparative prospective study.

Place and Duration of Study: Department of Neonatal Medicine, Military Hospital Rawalpindi, from Jan 2017 to Mar 2018.

Methodology: Sixty term neonates with respiratory rate >60 breaths/min and transient tachypnea of newborn score of ≥ 4 were enrolled. They were randomly allocated to two equal groups. Group-1 received Salbutamol nebulization (0.15 mg/kg) while Group-2 received normal Saline (placebo) nebulization.

Results: The mean gestational age was 38.31 ± 1.28 weeks, while the average birth weight was 2.97 ± 0.27 kg. The mean change in transient tachypnea of newborn score with Salbutamol nebulization was 5.63 ± 1.22 , while 0.63 ± 1.54 with normal Saline nebulization. Likewise, the mean change in respiratory rate with Salbutamol was 9.80 ± 2.05 , while -3.73 ± 2.57 with normal saline.

Conclusion: This study demonstrated nebulized Salbutamol as an effective tool in reversing transient tachypnea of newborns with decreasing respiratory rate compared to normal saline nebulization (placebo).

Keywords: Nebulization, Normal saline, Respiratory rate, Salbutamol, Transient tachypnea of the newborn.

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INTRODUCTION

As many as 7% of all newborns are reported to demonstrate some form of respiratory distress in the neonatal period.¹ In newborns, World Health Organization (WHO) declares tachypnea as a respiratory rate of more than 60/minute.² Transient tachypnea of the newborn (TTN) is a common differential in any newborn who develops respiratory distress immediately after birth at term gestation. One-third of the newborns hospitalized due to respiratory distress are ultimately diagnosed with TTN.³ It results from inadequate or delayed clearance of fetal lung fluid.⁴ It usually sets in at the time of birth or within the first six hours of life.⁵

Although a common entity, pharmacotherapy in TTN remains controversial as various tools have been analyzed in the literature, administration of supplemental oxygen remains the mainstay of therapeutics meant for TTN.⁶ Unnecessary imaging, blood testing, and empirical antibiotic therapy are not the desired choices during TTN management in light of its usual

self-limiting course over the next 72 hours.⁷ There have been attempts in managing TTN with intravenous furosemide-especially predisposing to significant potential for septicemia instead of intravenous cannulation for drug administration.⁸ Nebulized Salbutamol and epinephrine are the other entities engaged in TTN but with limited evidence in their support-especially in our part of hemisphere.⁹

The fact that inhalational salbutamol, a β_2 -adrenergic agonist, has wide utilization in managing bronchopulmonary dysplasia in premature infants steered us towards the hypothesis that Salbutamol can aid in lung fluid absorption in patients with TTN. Therefore, the primary goal of this study is to establish the efficacy of inhalational Salbutamol in reducing respiratory distress in neonates with TTN.

METHODOLOGY

The prospective comparative study was carried out at the Department of Neonatal Medicine (NICU), Military Hospital, Rawalpindi, Pakistan, from January 2017 to March 2018 after permission from the Ethical Review Committee (IERB certificate number A/28/2017). The aim was to compare the outcome of Salbuta-

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mol nebulization with normal saline (placebo) in the treatment of TTN. A sample size of 60 patients was calculated using WHO sample size calculator keeping level of significance=5%, power of the test=90%, population mean=8, test value of population mean=3, SD=3.59.¹⁰ Patients were selected by non-probability consecutive sampling.

Inclusion Criteria: Neonates at term (gestational age \geq 37 weeks) delivered via lower segment caesarean section (LSCS) at the Obstetric Department, having respiratory distress with TTN score of ≥ 4 and respiratory rate >60 breaths/min within six hours of birth were enrolled into the study.

Exclusion Criteria: The neonates with a maternal history of premature rupture of membranes (PROM) of significant duration (>18 hours), PIH (pregnancy-induced hypertension), GDM (gestational diabetes mellitus -with fasting plasma glucose >90 mg/dL or oral glucose tolerance test-OGTT with 1-hour plasma glucose >180 mg/dL or 2-hour plasma glucose >150 mg/dL), meconium-stained amniotic fluid, antenatally unbooked mothers or with twin pregnancy were excluded from the study.

The severity of TTN was calibrated against the clinical TTN score, which engaged the variables of respiratory distress and the work of breathing. These include the presence of cyanosis, grunting, chest recessions and nasal flaring as shown in the Table-I.¹⁰ Informed written consent was sought from each parent.

ventilation with continuous SPO2 monitoring. Both groups were observed for the next 4 hours, followed by endorsement of TTN score and respiratory rate on study proforma. The study was double-blinded-as attendants (parents) of the babies and the nurse administering the drug were blinded.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. The independent sample t-test was applied to compare the mean TTN score and respiratory rate between the two groups. The *p*-value of ≤ 0.05 was considered significant.

RESULTS

Among the two Groups, the mean gestational age in Group-1 and 2 were 38.40 ± 1.35 weeks and 38.27 ± 1.23 weeks, respectively. Forty-nine patients (81.67%) were between 37 to 39 weeks of gestational age, as shown in Table-II. 35 (58.33%) of our 60 patients, weighed ≤ 3 kg with an average birth weight in Group-1 of 2.97 ± 0.25 kg, while 2.99 ± 0.27 kg in Group-2 (Table-III). Out of 60 patients, gender distribution in both groups was identical, with 28 (46.67%) males and 32 (53.33%) females.

TTN Score before and 4 hours after treatment with Salbutamol were 8.30 ± 1.37 and 2.67 ± 0.76 , respectively, with the *p*-value of < 0.001 . This showed that the observed mean change in TTN score with nebulized Salbutamol was 5.63 ± 1.22 . In contrast, the average TTN score before and after treatment with normal saline

Table-I: Clinical Scoring of Transient Tachypnea of Newborn (TTN)¹⁰

Score	0 Point	1 Point	2 Points	3 Points
Expiratory Grunting	None	Intermittent	Continuous	0
Supraclavicular Retraction	None	Intermittent (not with every breath)	Continuous (with every breath)	Severe (with both inspiration & expiration)
Subcostal Retraction	None	Intermittent (not with every breath)	Continuous (with every breath)	Severe (with both inspiration & expiration)
Cyanosis	None	At extremities	Central (lips and tongue)	0
Nasal Flaring	None	Mild (occasional)	Moderate (continuous)	Severe (persisting after oxygen inhalation)

A chest X-Ray was done in each case to rule out any congenital pneumonia or pneumothorax and confirm radiological findings consistent with TTN (hyperinflation, prominent perihilar vascular markings and fluid in the fissures). Babies were divided into two equal Groups-Group-1 received Salbutamol nebulization (0.15 mg/kg diluted in 5ml normal saline over 10 min), while Group-2 received normal saline (placebo) nebulization (1 ml/kg). Newborns were kept on CPAP

Table-II: Distribution of Patients According to Gestational Age (GA) and Birth Weight (n=60)

		Group-1, (n=30)	Group-2, (n=30)
		n(%)	n(%)
Gestational age (weeks)	37-39	24(80.00)	25(83.33)
	40-41	06(20.00)	05(16.67)
	Mean \pm SD	38.40 ± 1.35 weeks	38.27 ± 1.23 weeks
Birth weight (kg)	≤ 3	18(60.00)	17(56.67)
	> 3	12(40.00)	13 (43.33)
	Mean \pm SD	2.97 ± 0.25 kg	2.99 ± 0.27 kg

was 8.00 ± 1.23 and 7.33 ± 0.99 , respectively (p -value < 0.001), with a change in TTN score of 0.63 ± 1.54 .

RR (Respiratory Rate) before and 4 hours after treatment with Salbutamol were 69.43 ± 4.25 and 59.63 ± 3.45 per minute, respectively, with the p -value of < 0.001 . Thus, the exhibited change in RR with Salbutamol nebulization was 9.80 ± 2.05 . In contrast, RR before and after treatment with normal saline were 68.80 ± 3.91 and 72.50 ± 3.10 per minute, respectively (p -value < 0.001), with a mean change of -3.73 ± 2.57 . Distribution of change in TTN score and RR for gestational age, birth weight and gender were shown in Table-IV & Table-V, respectively.

Table-III: Comparison of Transient Tachypnea of Newborn Score and Respiratory Rate-Baseline and after 4 hours of Intervention (n=60)

		Group -1 (n=30)	Group-2 (n=30)	p - value
		Mean \pm SD	Mean \pm SD	
Transient Tachypnea of Newborn Score	Baseline	8.30 \pm 1.37	8.00 \pm 1.23	0.3758
	After 4 hours	2.67 \pm 0.76	7.33 \pm 0.99	0.0001
	Change	5.63 \pm 1.22	0.63 \pm 1.54	0.0001
Respiratory rate (RR)	Baseline	69.43 \pm 4.25	68.80 \pm 3.91	0.5526
	After 4 hours	59.63 \pm 3.45	72.50 \pm 3.10	0.0001
	Change	9.80 \pm 2.05	-3.73 \pm 2.57	0.0001

Table-IV: Change in Transient Tachypnea of Newborn (TTN) Score with respect to Gestational Age, Birth Weight and Gender (n=60)

		Change in Transient Tachypnea of Newborn (TTN) Score		p - value
		Group-1, (n=30)	Group-2, (n=30)	
		Mean \pm SD	Mean \pm SD	
Gestational age (weeks)	37-39	5.38 \pm 0.77	0.68 \pm 1.49	< 0.001
	40-41	6.67 \pm 2.07	0.40 \pm 1.95	< 0.001
Birth weight (kg)	≤ 3	5.28 \pm 0.90	1.18 \pm 1.43	< 0.001
	> 3	6.17 \pm 1.47	-0.08 \pm 1.44	< 0.001
Gender	Male	5.21 \pm 1.05	0.57 \pm 1.51	< 0.001
	Female	6.00 \pm 1.27	0.69 \pm 1.62	< 0.001

Table-V: Change in Respiratory Rate with respect to Gestational Age, Birth Weight and Gender (n=60)

		Change in Respiratory Rate		p - value
		Group 1 (n=30)	Group 2 (n=30)	
		Mean \pm SD	Mean \pm SD	
Gestational age (weeks)	37-39	9.50 \pm 2.09	-4.2 \pm 2.5	< 0.001
	40-41	11.00 \pm 1.55	-1.4 \pm 1.52	< 0.001
Birth weight (kg)	≤ 3	9.67 \pm 2.47	-4.06 \pm 2.63	< 0.001
	> 3	10.00 \pm 1.28	-3.31 \pm 2.53	< 0.001
Gender	Male	10.21 \pm 1.63	-4.64 \pm 2.44	< 0.001
	Female	9.44 \pm 2.37	-2.94 \pm 2.49	< 0.001

DISCUSSION

Respiratory disorders are the most frequent cause of admission under neonatal teams in term and preterm infants.¹¹ Among these, TTN stands as a benign entity with a self-limiting course.¹² The reported incidence of TTN is 0.5-2.8% of deliveries.¹⁰ TTN is the outcome of inadequate or delayed clearance of fetal lung fluid.¹³ Therefore, any term neonate developing respiratory distress marked with expiratory grunting and radiologically proven wet lungs is considered to have TTN. Radiographic findings suggestive of TTN are hyperinflation, prominent perihilar vascular markings and fluid in the fissures.¹⁴ It usually sets in within 6 hours of life and takes the usual course of spontaneous resolution over 2 to 5 days.⁷

Furthermore, oxygen requirement stays at less than 40% during the course without any requirement for intubation or invasive mechanical ventilation. Apart from supplemental oxygen, other therapeutics are still not agreed upon. Because the initial symptoms of TTN are identical to respiratory distress syndrome (RDS), congenital pneumonia and persistent pulmonary hypertension of the newborn (PPHN), often unnecessary imaging, blood testing and empirical antibiotics are engaged as a result of misdiagnosis.¹⁵ The role of pharmacotherapy in TTN management still stays on the undecided front.

We conducted this study to compare the outcome of Salbutamol nebulization with normal saline (placebo) in the treatment of TTN. The mean gestational age in Group-1 and 2 were 38.40 ± 1.35 weeks and 38.27 ± 1.23 weeks, respectively, with 81.67% between 37 to 39 weeks of gestation and average birth weight in Group-1 of 2.97 ± 0.25 kg, while 2.99 ± 0.27 kg in Group-2. Gender distribution was identified as male to female ratio was 1:1.1. Dehdashtian *et al.* also failed to identify any gender preference for TTN.¹⁶ On the other hand, Mussavi *et al.* While conducting a study on TTN, identified equal gender distribution (male 51.7%) with an average birth weight of 2.70kg and mean gestational age of 36.9 weeks.¹⁷ On the contrary, Kaur *et al.* in India found a male predominance as 65% of their studied newborns were male.¹⁸

In our patients, TTN scores before and 4 hours after treatment with Salbutamol were 8.30 ± 1.37 and 2.67 ± 0.76 , respectively, with an observed mean change of 5.63 ± 1.22 . In contrast, the average TTN score before and after treatment with normal saline was 8.00 ± 1.23 and 7.33 ± 0.99 , respectively, with a change of 0.63 ± 1.54 .

In a randomized controlled trial conducted in Iran, Mussavi *et al.* also managed 60 neonates with TTN on CPAP and improvement was witnessed with albuterol nebulization (0.15 mg/kg) as respiratory distress score improved from 5.6 to 1.7, in contrast to 5.6 to 3.9 in the placebo group (saline nebulization).¹⁷ However, in India, Basiri *et al.* while managing 100 newborns with TTN on nasal prong oxygen at the gestational age of 35-41 weeks, failed to identify any improvement in TTN Score before and 4 hours after Salbutamol (0.15 mg/kg) nebulization as the reported scores were 5.7 and 5.4 respectively.¹⁸

In our study group, RR (respiratory rate) was 69.43±4.25 per minute before Salbutamol administration, with the exhibited change of 9.80±2.05 post salbutamol. In contrast, RR before and after treatment with normal saline were 68.80 ± 3.91 and 72.50 ± 3.10 per minute, respectively, with a mean deterioration of -3.73 ± 2.57. Another study, however, documented no improvement as RR before and 4 hours post Salbutamol nebulization were 73.4 and 72.2, respectively.¹⁸

Our study exhibited considerable improvement in the respiratory distress of neonates with nebulized salbutamol. During labor, levels of β-adrenergic agonists such as endogenous steroids and catecholamines rise with the rapid clearing of fetal lung fluid as sodium moves from the alveoli into the interstitium thereby removing Na⁺ and fluid.¹³ Stimulating lung tissue with an exogenous β-adrenergic agonist via the above-postulated pathway can be pivotal in stimulating lung fluid absorption in TTN.

LIMITATIONS OF STUDY

The limitation of our study was that the sample size was not large, which could have enabled us for a more accurate comparison. Furthermore, response in terms of ABGs changes is not recorded, however, in future trials, it may be done for validation of results.

CONCLUSION

This study has demonstrated nebulized Salbutamol as a more effective tool than normal saline in reversing TTN in terms of TTN score and respiratory rate after four hours of inhalation. This directs us to recommend that Salbutamol via nebulization (0.15 mg/kg) should be used as a primary method of treatment in every term infant presenting with transient tachypnea of newborn in order to turn tides towards a better outcome.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

WA: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

AMT: Conception, study design, drafting the manuscript, approval of the final version to be published.

FAS & ZA: Data analysis, data interpretation, critical review, approval of the final version to be published.

AS & HJ: Data acquisition, Critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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