

## Effects of Salbutamol and Furosemide in The Treatment of Transient Tachypnea of Newborn - A Randomized Controlled Trial

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### ABSTRACT

**Objective:** To assess and compare the effect of Salbutamol and Furosemide therapy in the management of transient tachypnea of newborn.

**Study Design:** Randomized controlled trial (Registered with Clinical Trials.gov: NCT03208894).

**Place and Duration of Study:** Neonatal Intensive Care Unit of Pakistan Emirates Military Hospital Rawalpindi from Oct 2019 to May 2020.

**Methodology:** A total of 100 newborns were included in the study. They were divided into 4 groups. Group-A received nebulized 0.1ml Salbutamol. Group-B was given single intravenous dose of injection Furosemide at the dose of 2mg per kg. Group-C received both IV Furosemide and nebulized Salbutamol. Control group-D received only supportive care.

**Results:** There were 48 male babies and 52 female babies. The average gestational age was  $38.8 \pm 6.2$  weeks and the average birth weight was  $2558 \pm 620$  grams. Administration of both Salbutamol and IV Furosemide together (group-C) showed significant reduction in the mean duration of oxygen dependency compared to control-group ( $13.40 \pm 3.342$  vs  $83.64 \pm 68.546$  hours respectively ( $p < 0.001$ ), as well as the need for mechanical ventilation. The mean duration of oxygen dependency in other two groups (A and B) were also reduced compared to control group, but the results were not statistically significant.

**Conclusion:** Salbutamol and Furosemide when given together tend to reduce the duration of oxygen dependency and need for invasive mechanical ventilation in babies with transient tachypnea of newborn.

**Keywords:** Furosemide, Mechanical ventilation, Transient tachypnea of newborn, Salbutamol.

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### INTRODUCTION

Transient tachypnea of newborn (TTN) is a common respiratory disorder of neonatal period. Occurring mainly in term and late pre-term babies, it involves inadequate clearance of fetal lung fluid after delivery.<sup>1</sup> It is a common respiratory disorder which occurs in neonatal period.<sup>2,3</sup> Data about the exact prevalence of TTN is scarce in Western literature,<sup>4,5</sup> however, the worldwide incidence of TTN in relation to gestational age shows that almost 10% of infants between 33-34 weeks of gestation, 5% of infants at 35-36 weeks and less than 1% of those more than 37 weeks have clinical features suggestive of TTN.<sup>6,7</sup>

With the onset of labor in the term or later pre-term mother, the fetal lungs begin to clear out fluid. This process is facilitated by the passive diffusion and active transport of sodium in type II alveolar cells. This complex sequence of events allows the fetal lungs to get clear of the excessive amount of fluid in the immediate postnatal period.<sup>8,9</sup>

Clinical features of TTN involve the onset of

tachypnea, grunting, nasal flaring and various degrees of chest retractions.<sup>10</sup> The risk factors, which contribute to the development of TTN, are birth by cesarean section, male gender, maternal history of asthma, prematurity, macrosomia and history of maternal diabetes.

No effective and definitive treatment has been developed so far for TTN. Current treatment mostly relies on administering oxygen therapy. Drugs studied to be effective in relieving symptoms of TTN include diuretic therapy, inhaled racemic Epinephrine, and inhaled beta 2-agonists, however none of the trials have so far been able to identify a definitive treatment option for this condition.<sup>3</sup>

In developing countries like Pakistan, where there are limitation of resources and Neonatal Intensive Care Units (NICUs/nurseries) are overburdened with the number of babies, it is operational necessity to reduce the length of stay. Neonates admitted to NICUs with TTN though generally a benign condition require close observation and supportive treatment for varying periods that might extend up to many days. Therefore, we need to have some definitive and effective management strategy that can reduce the duration of oxygen dependency and/or duration of hospital stay without

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any complication. Therefore we conducted a randomized controlled trial in our set up to assess and compare the role of Salbutamol (a beta 2 agonist) and Furosemide therapy in the management of transient tachypnea of newborn.

## METHODOLOGY

This randomized controlled trial was carried out in the NICU of Pakistan Emirates Military Hospital, Rawalpindi from October 2019 to May 2020. Permission was sought from Hospital Ethical Committee and study was registered with Clinical Trials.gov (NCT 03208894). Consent was sought from the parents of newborns participating in the study.

**Inclusion Criteria:** All the neonates diagnosed to have TTN on the basis of clinical and radiological features by consultant neonatologist were included in the study.

**Exclusion Criteria:** Babies born via vaginal route, having major congenital malformations, history of meconium aspiration, early onset neonatal sepsis and those with congenital heart disease were excluded from the study.

Newborns fulfilling the inclusion criteria were randomly (computer generated) assigned to four groups. Each group contained 25 newborns, making a total study sample size of 100. Group-A received nebulized single dose of 0.2 ml Salbutamol (Ventolin respiratory solution containing 5mg per ml Salbutamol Sulphate) in 2ml of 0.9% normal saline. Group-B was given single intravenous dose of injection Furosemide at the dose of 2mg per kg. Group-C was given a combination of both Furosemide IV and nebulised Salbutamol in above doses. All the newborns in groups A, B and C were given standard treatment including oxygen support, IV fluids and antibiotics according to the unit protocol. Group-D was given neither Salbutamol nebulisation nor Furosemide but received supportive care similar to other three groups. This group served as control group for the rest of the three groups.

On admission, respiratory rate, heart rate, oxygen saturation by pulse oximetry, capillary blood gases, base line investigations (complete blood count, blood sugar and serum electrolytes), chest x-ray, and TTN scores were determined for each baby and at 1-hour, 2-hours, 4-hours and 6-hours post admission. TTN score was ascertained from the respiratory distress assessment instrument (Table-I).<sup>11,12</sup>

The primary outcome measure of the study was total duration of oxygen dependency. Statistical

Package for Social Sciences (SPSS) version 23 was used for the data analysis. Values were measured in terms of mean  $\pm$  SD, frequency and percentages. To compare the categorical variables, chi-square test (Fisher's exact test) was used. For all statistical tests, the *p*-value of  $\leq 0.05$  was considered significant.

## RESULTS

Total 100 newborns were included in the study. All the neonates completed the study protocol. There were 48 male babies and 52 female babies, all were delivered by LSCS out of which 35 were delivered by emergency LSCS and 65 were delivered by elective LSCS. The average gestational age was 38.8  $\pm$  6.2 weeks and the average birth weight was 2558  $\pm$  620 grams. The average TTN score on admission was 4.60  $\pm$  1.40.

Out of 25 patients in group-A (salbutamol-group), 11 (44%) newborns were off the oxygen within 24 hours, 8 (32%) babies remained on oxygen for 24-48 hours, 1 (4%) baby remained on oxygen for 48-96 hours and 5 (20%) babies remained oxygen dependent for more than 96 hours. The mean duration of oxygen dependency (primary outcome measure) was 58.00  $\pm$  53.50. There were no significant differences between the treatment and control groups in the primary outcome measure (58.00  $\pm$  53.50 vs 83.64  $\pm$  68.54 hours respectively), *p*-value=0.283 (Table-II).

**Table-I: Clinical scoring of the transient tachypnea of newborn.**

	0 Point	1 Point	2 Points	3 Points
Expiratory grunting	None	Intermittent	Continuous	
Supraclavicular retractions	None	Mild	Moderate	Severe
Subcostal retractions	None	Mild	Moderate	Severe
Cyanosis	None	At Extremities	Central	
Nasal flaring	None	Mild	Moderate	Severe

**Table-II: Comparison of the intervention groups with control group.**

Study Groups	Primary outcome measure (when off oxygen)	<i>p</i> -value
Group-A (Salbutamol group)	58.00 $\pm$ 53.50	0.283
Control Group	83.64 $\pm$ 68.546	
Group-B (IV Furosemide group)	54.04 $\pm$ 51.560	0.171.
Control Group	83.64 $\pm$ 68.546	
Group-C (IV Furosemide $\pm$ nebulised Salbutamol group)	13.40 $\pm$ 3.342	<0.001
Control Group	83.64 $\pm$ 68.546	

In group-B (IV furosemide group), 14 (56%) newborns were off the oxygen within 24 hours, 3 (12%)

babies remained on oxygen for 24-48 hours, 5 (20%) babies remained on oxygen for 48-96 hours and 3 (12%) babies remained oxygen dependent for than 96 hours. The mean duration of oxygen dependency in this group was  $54.04 \pm 51.56$ . There was statistically no significant difference between the treatment and control groups for the primary outcome measure i.e. duration of oxygen dependency ( $54.04 \pm 51.56$  vs  $83.64 \pm 68.54$  respectively),  $p$ -value=0.171 (Table-II).

In group-C (IV Furosemide + nebulised Salbutamol-group), 24 (96%) newborns were off the oxygen within 24 hours, 1 (4%) baby remained on oxygen for 24-48 hours and none of the babies in this group was on oxygen for more than 48 hours. The mean duration of oxygen dependency in this group was  $13.40 \pm 3.342$ . There was statistically significant difference between the treatment and control groups in the primary outcome measure ( $13.40 \pm 3.34$  vs  $83.64 \pm 68.54$  hours respectively),  $p$ -value <0.001.

Among the control group (group-D), 8 (32%) newborns were off the oxygen within 24 hours, 6 (24%) babies remained on oxygen for 24-48 hours, 3 (12%) baby remained on oxygen for 48-96 hours and 8 (32%) babies remained oxygen dependent for more than 96 hours.

## DISCUSSION

Almost 33% newborns admitted to the neonatal intensive care units with respiratory problems are diagnosed to have TTN.<sup>13,14,15</sup> The incidence of TTN in Pakistan was found to be 14.1%.<sup>16,17</sup> At birth, the release of catecholamines, steroids and vasopressin affect the balance of fluid in the alveoli from fluid secretion to fluid absorption, thereby facilitating the adaptation to ex-utero environment.<sup>18,19</sup>

NICUs in developing countries like Pakistan have limited resources and are overburdened with neonates diagnosed with TTN. Trained NICU staff is also required to manage such babies in NICU, some of which require mechanical ventilation if appropriate treatment is not provided timely, therefore some definitive treatment should be available to reduce the duration of oxygen dependency and the duration of NICU stay.

Study conducted by Mussavi *et al*, showed considerable reduction in the respiratory distress after inhalation of nebulized albuterol. The need for positive pressure ventilation was decreased in those babies who were given Salbutamol inhalation.<sup>17</sup> Similarly, another study conducted by Armangil *et al*, on the possible effects of Salbutamol inhalation on 54 infants with

TTN revealed reduced need for oxygen support and mechanical ventilation after the initial 30 minutes of Salbutamol inhalation.<sup>20</sup> A Korean study evaluated the effects of inhaled Salbutamol in TTN demonstrated reduction of tachypnea in the infants receiving Salbutamol intervention and also the duration of supplemental oxygen requirement.<sup>10</sup> However, we were unable to demonstrate this effect in our study population who just received inhaled Salbutamol. Our study also showed that role of Furosemide in TTN management is insignificant. Similar results were shown by Wiswell and colleagues on 50 infants,<sup>21</sup> and by Karabayir *et al*, in 2006.<sup>22</sup>

Group-C received both IV Furosemide and nebulized Salbutamol. Majority of neonates in this group were off the oxygen within first 24 hours, only one baby remained oxygen dependent up to 48 hours, however, none of the babies required mechanical ventilation. This suggests that combined diuretic effect of Furosemide and the beta 2 agonist function of Salbutamol substantially reduce the lung fluid volume responsible for the respiratory insufficiency caused by TTN in newborns. Both drugs act synergistically to reduce the work of breathing and hasten patient recovery.

So far, we have not been able to identify any local study looking at the effects of using both drugs simultaneously. Our study was the first to suggest the usefulness of combining inhaled Salbutamol and intravenous Furosemide in the management of TTN.

## LIMITATIONS OF STUDY

The main limitation of our study was the small sample size in each study group. Large multi-center randomized controlled trials are need to be conducted in order to confirm or refute our findings.

## RECOMMENDATION

On the basis of our results, we recommend that babies with clinical and radiological features suggestive of TTN, should be treated with a single dose of IV Furosemide (2mg per kg) and nebulisation with Salbutamol (0.2ml in 02ml NS).

## CONCLUSION

Salbutamol and Furosemide when given together decrease the work of breathing hence reducing the duration of supplemental oxygen requirement and the need for invasive mechanical ventilation.

**Conflict of Interest:** None.

## Authors' Contribution

ZA: Conceived the idea, collected and organized the data and helped refining the final draft, AK: Collected and organized the data, wrote main manuscript, MA: Writing of initial

manuscript and refining the final draft, SN: Writing of initial manuscript and refining the final draft, MY: Organized the data writing of initial manuscript and refining the final draft, FA: Collected data organized the data and wrote the initial manuscript.

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