The Professional Medical Journal
www.theprofesional.com

https://doi.org/10.29309/TPMJ/2021.28.01.4614

ORIGINAL PROF-0-4614

Salbutamol nebulization for management of transient tachypnea of newborn (TTN).

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Article received on:
05/03/2020
Accepted for publication:
23/06/2020

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ABSTRACT… Objective: To compare the mean change in respiratory rate with salbutamol nebulization versus placebo for treatment of transient tacyopnea of newborn. **Study Design:** Randomized Control Trial. **Setting:** Department of Neonatology, Federal Government Polyclinic (PGMI), Islamabad. **Period:** 8th August 2017 to 7th February 2018. **Material & Methods:** 100 neonates fulfilling selection criteria were enrolled in the study. Informed consent was obtained from parents. Demographic information was also noted. All baseline respiratory rate were noted. Neonates were divided into two groups by lottery method. Neonates in Treatment group were nebulized with Salbutamol. Placebo group was nebulized with Normal Saline. Then neonates were followed-up in N.I.C.U after 4 hours of second nebulization. After 4 hours, respiratory rates were assessed and change in respiratory rate was noted. Both groups were compared for mean reduction in respiratory rate by using independent sample t-test. **Results:** In nebulized salbutamol, group, mean respiratory rate was changed from 79.62±8.18bpm to 52.06±4.96bpm. This was a significant decrease ($p<0.05$). In placebo group, mean respiratory rate was changed from 81.88±8.86bpm to 62.50±6.75bpm. This was significant decrease ($p<0.05$). The difference between both groups at baseline was insignificant while after 4 hours was significant. The mean changed in respiratory rate with nebulized salbutamol was 27.56±6.83bpm while with placebo was 19.35±9.83bpm. There was significant difference in mean reduction in respiratory rate ($p<0.05$). **Conclusion:** It has been proved that nebulized salbutamol can be helpful in reducing respiratory rate significantly in neonates with TTN as compared to placebo.

Key words: Placebo, Reduction in Respiratory Rate, Salbutamol Nebulization, Transient Tachypnea of New-Born.

Article Citation: Maroof F, Maqbool T, Irfan HM, Mughal BB, Anwar A, Zia N, Ahsan M. Salbutamol nebulization for management of transient tachypnea of newborn (TTN). Professional Med J 2021; 28(1):52-59. https://doi.org/10.29309/TPMJ/2021.28.01.4614

INTRODUCTION

Transient Tachypnea of the new born (T.T.N) is a parenchymal disorder of the lung in which pulmonary oedema occurs after delayed clearance of foetal fluid of the alveoli.[1] T.T.N is one of the causes of respiratory distress in the neonatal period. The incidence of T.T.N is about 6 in 1000 live births. Normally, there is decrease in the foetal lung liquid in the antenatal period leading to shift of fluid into the interstitium. This process is complete in most normal neonates within several hours after birth. Tachypnea occurs when foetal lung fluid is not adequately or rapidly cleared, for various reasons.[2]

Stimulation of the tissues of the feotal lung by exo-genous β – adrenergics lead to lung fluid absorption both in the human and animal.[3-5] Various studies at different age groups done on the lung physiology of fluid clearance show that Salbutamol helps in clearance of lung fluid.[6]

A study was conducted in India which showed that there is significant decrease in mean respiratory rate in neonates who received Salbutamol nebulization (9.43±1.48bpm) as compared to placebo group (3.6±0.21bpm), the difference is statistically significant with the ($P=0.004$).[7] But another study showed that there were insignificant difference in respiratory rate ($P>0.05$) whether Salbutamol nebulization given or not.[8]

The rationale of this study is to compare the mean reduction in respiratory rate with salbutamol nebulization versus placebo for treatment of TTN. As TTN is a common cause of hospitalization in NICU, a treatment option which can be helpful in decreasing the duration and severity of tacyopnea merits further evaluation. This modality being a cheap intervention has an enormous potential for cost saving, both in developing and developed countries, because it can actually reduce length of hospitalization. Thus, not only will it significantly reduce the hospital economy burden but will also prevent the incidence of hospital acquired infection among neonates and associated anxiety among parents. Literature has showed that salbutamol is more effective in reducing excessive respiratory rate in neonates with tachypnea. But controversial evidence has been noticed in literature. Moreover, no local evidence has been found in literature. We want to conduct this study to confirm the beneficial role of salbutamol. So, that we may be able to implement the results in local settings.

MATERIAL & METHODS

This randomized control trial was done at the Neonatology Department, Federal Government Polyclinic (PGMI), Islamabad, in six months after the approval of the synopsis i.e. from 8th August 2017 to 7th February 2018. Objective of the study was to compare the mean change in respiratory rate with salbutamol nebulization versus placebo for treatment of transient tacyopnea of newborn. Alternate Hypothesis for this study was that there is a difference in mean change in respiratory rate with salbutamol nebulization versus placebo for treatment of TTN. Transient Tacyopnea of Newborn was defined as neonates presenting with Respiratory Rate >60breaths/min within 6 hours after birth, respiratory distress of <6 hours after birth and Silverman-Anderson score of >5 (T.T.N score). Change in respiratory rate was measured as change in respiratory rate after 4 hours of nebulization in terms of breaths per minute.

TTN scoring system

100 cases were collected using non-probability consecutive sampling (50 cases in each group) Sample size was calculated using WHO sample size calculator taking Confidence Interval: 95%, Power of test: 80% and expected magnitude of mean reduction in respiratory rate i.e. 9.43±1.48bpm with salbutamol and 3.6±0.21bpm with placebo for TTN.

All neonates born of either genders at gestational age >37weeks (accessed on antenatal record) meeting the operational deflation of Transient Tachypnea of Newborn were included in the study. While patients with meconium aspiration syndrome (on history), neonatal respiratory distress syndrome (on medical record), Neonates with medical record of Congenital Heart Disease, Congenital Pneumonia, Persistent Pulmonary Hypertension, Early Onset Neonatal Sepsis/DIC, Hypoglycaemia were excluded from the study.

Demographic information (name, age, sex, birth weight) was also noted. All baseline respiratory rates were noted. Neonates were divided into two groups by lottery method. Neonates in Treatment group were nebulized with Salbutamol at dose of 0.15mg/kg/dose in 2ml of 0.9% Normal Saline over duration of 10 minutes. Placebo group was nebulized with 2 ml of 0.9% Normal Saline. A total of two nebulization was done with an interval of 4 hours between both nebulizations. Both the groups were provided with standard therapy as per N.I.C.U protocol i.e. Oxygen inhalation, intravenous fluids and intravenous antibiotics.

Score	0 Point	1 Point	2 Points	3 Points
Expiratory Grunting	None	Intermittent	Continuous	_
Supraclavicular Retraction	None	Mild	Moderate	Severe
Subcostal Retraction	None	Mild	Moderate	Severe
Cyanosis	None	At Extremities	Central	_
Nasal Flaring	None	Mild	Moderate	Severe

Then neonates were followed-up after 4 hours of second nebulization. After 4 hours, respiratory rate was assessed and change in respiratory rate was noted (as per operational definition).

Data was entered and analysed using SPSS 21.0. Frequency and percentages for qualitative variables like gender, and mean with SD for quantitative variables like gestational age, birth weight, respiratory rate at baseline and after 4 hours and change in respiratory rate was calculated. Both groups were compared for mean change in respiratory rate by using independent sample t-test. P-value≤0.05 was taken as significant. Confounder e.g. Gender, Weight, Gestation at birth, Hours of life, were controlled through stratification. Post stratification independent sample t-test was applied and P ≤0.05 was taken as significant.

RESULTS

In this study, the mean age of neonates in nebulized salbutamol group was 3.26±1.59 hours and the mean age of neonates in placebo group was 3.14±1.68hours. There were 26 (52.0%) male and 24 (48.0%) female neonates in nebulized salbutamol group and there were 26 (52.0%) male and 24 (48.0%) female neonates in placebo group. The mean weight of neonates in study with nebulized salbutamol group was 2963.36±282.79 grams and the mean weight of neonates in placebo group was 3034.86±273.64grams. In this study, the mean gestational age of neonates was 39.90±1.43weeks in nebulized salbutamol group and the mean gestational age of neonates in placebo group was 40.00±1.46 week.

At baseline, the mean respiratory rate of neonates in nebulized salbutamol group was 79.62±8.18bpm and the mean respiratory rate of neonates in placebo group was 81.88±8.86bpm. The difference was insignificant (p>0.05). Table-I

After 4 hours of treatment, the mean respiratory rate of neonates in nebulized salbutamol group was 52.06±4.96bpm and the mean respiratory rate of neonates in placebo group was 62.50±6.75bpm. The difference was significant (p<0.05). Table-II

The mean respiratory rate of all neonates, included in this study, at baseline was 80.75±8.56bpm which was changed to 57.28±7.89bpm. There was significant reduction in respiratory rate (p<0.05). Table-III

In nebulized salbutamol, group, mean respiratory rate was changed from 79.62±8.18bpm to 52.06±4.96bpm. This was significant decrease (p<0.05). In placebo group, mean respiratory rate was changed from 81.88±8.86bpm to 62.50±6.75bpm. This was significant decrease (p<0.05). The difference between both groups at baseline was insignificant while after 4 hours was significant. Table-IV

The mean reduction in respiratory rate with nebulized salbutamol was 27.56±6.83bpm while with placebo was 19.35±9.83bpm. There was significant difference in mean change in respiratory rate (p<0.05). Table-V

Data was stratified for age of neonates. Among neonates 1-3hours old, mean reduction in respiratory rate was 27.07±7.29bpm with nebulized salbutamol and 18.90±9.78bpm with placebo. Among neonates 4-6hours old, mean change in respiratory rate was 28.24±6.24bpm with nebulized salbutamol and 20.16±10.12bpm with placebo. The difference was significant between both groups in each strata (p<0.05). Table-VI

Data was stratified for gender of neonates. Among male neonates, mean change in respiratory rate was 27.46±6.81bpm with nebulized salbutamol and 17.62±9.25bpm with placebo. Among female neonates, mean changed in respiratory rate was 27.67±6.99bpm with nebulized salbutamol and 21.29±10.27bpm with placebo. The difference was significant between both groups in each strata (p<0.05). Table-VII

Data was stratified for birth weight of neonates. Among neonates with 2500-3000grams weight, mean change in respiratory rate was 28.18±6.90bpm with nebulized salbutamol and 19.71±9.93bpm with placebo. Among neonates with 3100-3500 grams weight, mean changed

in respiratory rate was 26.77±6.80bpm with nebulized salbutamol and 19.14±9.92bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$). Table-VIII

Data was stratified for gestational age at birth. Among neonates born at 38-40weeks, mean change in respiratory rate was 27.81±7.01bpm with nebulized salbutamol and 18.26±10.53bpm with placebo. Among neonates with born at 40-41weeks, mean change in respiratory rate was 27.11±6.66bpm with nebulized salbutamol and 20.70±8.98bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$). Table-IX

A Comparison of All variables between Nebulized Salbutamol group and Placebo Group is shown in Table-X.

		Group	
		Nebulized Salbutamol	Placebo
Respiratory Rate (bpm)	N	50	50
	Mean	79.62	81.88
	SD	8.18	8.86

Table-I. Comparison of respiratory rate (bpm) at baseline in both groups
Independent samples t-test = 1.325, p-value 0.188 (Insignificant)

		Group	
		Nebulized Salbutamol	Placebo
Respiratory Rate (bpm)	N	50	50
	Mean	52.06	62.50
	SD	4.96	6.75

Table-II. Comparison of respiratory rate (bpm) at 4hours in both groups
Independent samples t-test = 8.809, p-value 0.000 (Significant)

		Follow-up	
		Baseline	After 4 Hours
Respiratory Rate (bpm)	N	50	50
	Mean	80.75	57.28
	SD	8.56	7.89

Table-III. Comparison of respiratory rate (bpm) at follow-up
Paired sample t-test = 25.055; p-value 0.000 (Significant)

		Group		P-Value (Independent Samples)
		Nebulized Salbutamol	Placebo	
Respiratory Rate (bpm)	N	50	50	
	Baseline	79.62±8.18	81.88±8.86	0.188
	After 4hours	52.06±4.96	62.50±6.75	0.000
p-value (paired sample)		0.000	0.000	

Table-IV. Comparison of respiratory rate (bpm) at follow-up in both groups

		Group	
		Nebulized Salbutamol	Placebo
Change	N	50	50
	Mean	27.56	19.38
	SD	6.83	9.83

Table-V. Comparison of change in respiratory rate in both groups
Independent samples t-test = 4.834; p-value 0.000 (Significant)

Age (hours)	Change	Group		P-Value
		Nebulized Salbutamol	Placebo	
1-3	N	29	31	0.001
	Mean±SD	27.07±7.29	18.90±9.78	
4-6	N	21	19	0.004
	Mean±SD	28.24±6.24	20.16±10.12	

Table-VI. Comparison of change in respiratory rate in both groups stratified for age

Gender	Change	Group		P-Value
		Nebulized Salbutamol	Placebo	
Male	N	26	26	0.000
	Mean±SD	27.46±6.81	17.62±9.25	
Female	N	24	24	0.015
	Mean±SD	27.67±6.99	21.29±10.27	

Table-VII. Comparison of change in respiratory rate in both groups stratified for gender

Weight (Grams)	Change	Group		P-Value
		Nebulized Salbutamol	Placebo	
2500-3000	N	28	21	0.001
	Mean±SD	28.18±6.90	19.71±9.93	
3100-3500	N	22	29	0.002
	Mean±SD	26.77±6.80	19.14±9.92	

Table-VIII. Comparison of change in respiratory rate in both groups stratified for weight

Gestation (Weeks)	Change	Group		P-Value
		Nebulized Salbutamol	Placebo	
38-40	N	32	27	0.000
	Mean±SD	27.81±7.01	18.26±10.53	
41-42	N	18	23	0.015
	Mean±SD	27.11±6.66	20.70±8.98	

Table-IX. Comparison of change in respiratory rate in both groups stratified for gestational age

	Salbutamol Group	Normal Saline Group
No. of patients n(%)	50	50
Age (hours of life)	3.26 hours	3.14 hours
Gender Male Female	 26 (52.0%) 24 (48.0%)	 26 (52.0%) 24 (48.0%)
Gestational Age (weeks) (mean ± SD)	39.90±1.4 wks	40.00±1.4 wks
Birth weight in kgs (mean±SD)	2.9±0.2	3.0±0.2
Respiratory Rate / Baseline Respiratory Rate at admission (mean± SD)	79.62 ± 8.18	81.88 ± 8.86
Respiratory Rate / Respiratory Rate at 4 hours	52.06 ± 4.96	62.50 ± 6.75
Comparison of Reduction in Respiratory Rate	27.56 ± 6.83	19.38 ± 9.83

Table-X. Comparison of All variables between nebulized salbutamol group and placebo group

DISCUSSION

TTN shows increasing incidence with increase in caesarean sections for maternal ease and the anxiety with the changing life-style. It is supposed to be due to result from delayed fluid resorption from the neonatal lungs, an important diagnostic dilemma in NICU.[9]

In our trial, the mean respiratory rate of neonates at baseline was 80.75±8.56bpm which was reduced to 57.28±7.89bpm. There was a significant change in respiratory rate ($p<0.05$). In nebulized salbutamol group, the mean respiratory rate was changed from 79.62±8.18bpm to 52.06±4.96bpm. This was significant decrease ($p<0.05$). In placebo group, mean respiratory rate was changed from 81.88±8.86bpm to 62.50±6.75bpm. This was a significant decrease ($p<0.05$). The difference between both groups at baseline was insignificant while after 4 hours was significant. Thus the mean change in terms of reduction in respiratory rate with nebulized salbutamol was 27.56±6.83bpm while with placebo was 19.35±9.83bpm. There was significant difference in mean reduction in respiratory rate ($p<0.05$).

A study was conducted in India which showed that there is significant decrease in mean respiratory rate in neonates who received Salbutamol nebulization (9.43±1.48bpm) as compared to placebo group (3.6±0.21bpm), the difference is statistically significant with the ($P=0.004$).[7] But another study showed that there were insignificant difference in respiratory rate ($P>0.05$) whether Salbutamol nebulization given or not.[8]

A review was conducted, including 140 infants comparing nebulized salbutamol with placebo; one of three trials had newborns into two different doses of the intervention. We found differences in oxygen therapy duration but no differences in need for CPAP) or for mechanical ventilation. Among the secondary outcomes of these studies, there was no difference in terms of duration of hospital stay and tachypnea. It was concluded in this met analysis that currently there is insufficient evidence regarding the efficacy and safety of salbutamol in management of TTN. This was because of paucity of included trials, small sample size.[10] Not much has been done in literature. And our study also supported the nebulized salbutamol for TTN.

In this study, the mean age of neonates in nebulized salbutamol group was 3.26±1.59hours and the mean age of neonates in placebo group was 3.14±1.68hours. Data was stratified for age of neonates. Among neonates 1-3hours old, mean reduction in respiratory rate was 27.07±7.29bpm with nebulized salbutamol and 18.90±9.78bpm with placebo. Among neonates 4-6hours old, mean reduction in respiratory rate was 28.24±6.24bpm with nebulized salbutamol and 20.16±10.12bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$). Table-X

In study, we had 26 (52.0%) male and 24 (48.0%) female neonates in nebulized salbutamol group and there were 26 (52.0%) male and 24 (48.0%) female neonates in placebo group. Data was stratified for gender of neonates. Among male neonates, mean reduction in respiratory rate was 27.46±6.81bpm with nebulized salbutamol and 17.62±9.25bpm with placebo. Among female neonates, mean reduction in respiratory rate was 27.67±6.99bpm with nebulized salbutamol and 21.29±10.27bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$).

In this study, the mean weight of neonates in nebulized salbutamol group was 2963.36±282.79grams and the mean weight of neonates in placebo group was 3034.86±273.64grams. Data was stratified for birth weight of neonates. Among neonates with 2500-3000grams weight, mean reduction in respiratory rate was 28.18±6.90bpm with nebulized salbutamol and 19.71±9.93bpm with placebo. Among neonates with 3001-350grams weight, mean reduction in respiratory rate was 26.77±6.80bpm with nebulized salbutamol and 19.14±9.92bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$).

The mean gestational age of neonates in nebulized salbutamol group was 39.90±1.43weeks in this study and the mean gestational age of neonates in placebo group was 40.00±1.46week. Data was stratified for gestational age at birth. Among neonates born at 38-40weeks, mean reduction in respiratory rate was 27.81±7.01bpm with nebulized salbutamol and 18.26±10.53bpm with placebo. Among neonates with born at 40-41weeks, mean change in respiratory rate was 27.11±6.66bpm with nebulized salbutamol and 20.70±8.98bpm with placebo. The difference was significant between both groups in each strata ($p<0.05$).

CONCLUSION

It has been proved that nebulized salbutamol can be helpful in changing and reducing respiratory rate significantly in neonates with TTN as compared to placebo. Now the controversy resolved and salbutamol found to be effective in controlling respiratory rate of neonates. And we have also got local evidence. Now we will implement the nebulized salbutamol for neonates presenting with TTN in local setting.

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