Original Article

A Comparative Study on Nebulised Levosalbutamol *versus* Adrenaline in Wheeze Associated Condition of Children Between 1 Month to 6 Months of Age Admitted in Paediatric Ward of a Tertiary Medical College during COVID-19 Pandemic

Subhadipa Das[1], Subhasis Sardar[2], Rajarshi Basu[3], Tapan kumar Sinha Mahapatra[4]

Background : It is seen that most wheezing episodes in infancy during the COVID-19 pandemic are of viral origin commonly diagnosed as Acute Viral Bronchiolitis, Pneumonia or Wheeze associated Respiratory Tract Infection. Previous trials have provided conflicting evidence regarding the benefit of bronchodilators like β2 agonists, adrenaline, ipratropium bromide etc. It is proved that levosalbutamol is much safer alternative than salbutamol, but no clinical trial till date has assessed it's efficacy to nebulised adrenaline in wheezing episodes in infants. Thus this study will attempt to verify the efficacy of bronchodilators in wheeze associated respiratory conditions and assess the benefits of a β-2 specific agonist *versus* combined α and β (non-specific) agonist among the first time wheezing infants during this COVID-19 pandemic.

Materials and Methods : The study was conducted with 60 infants aged 1 month to 6 months of age attending the Paediatric Medicine Emergency Department of NRS medical college in Kolkata with first time wheeze. The study period was 1.4 years from March, 2020 to July, 2021. Of these 30 received nebulised levosalbutamol (0.1mg/kg/dose) (Group A) and remaining 30 were given adrenaline nebulisation (0.1mg/kg/dose in1:10,000 solution) (Group B) maintaining CDC COVID-19 protocol. In 3 doses of each drug were given along with O_2 at 15 mins interval. Respiratory rate, Respiratory Distress Assessment Index (RDAI) score, heart rate and pulse oximetry were recorded before intervention, just after 2nd dose, 30 mins after last dose and 1 hour after last dose.

Results : Both adrenaline and levosalbutamol caused significant improvement in mean respiratory rate, RDAI score and oxygenation. However, the adrenaline group showed a significantly better improvement in study parameters than levosalbutamol group.

Conclusion : The study concluded that nebulised adrenaline is signifantly superior to levosalbutamol in reliving symptoms in infants with wheeze.

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Key words **: Nebulised Levosalbutamol, Nebulised Adrenaline, Wheeze, COVID-19.**

Editor's Comment :

- This study on children of age 1 month to 6 months who presented with acute respiratory distress. 30 children were given nebulisation with levosalbutamol and the other half were treated with adrenaline.
- The children who were treated with adrenaline nebulisation showed better outcome than the children with levosalbutamol nebulisation.

Wheeze associated respiratory conditions is an extremely common problem in under 5 children with reported attack rates in the western literature being as high as 11.4 per 100 children in the first year and 6 per 100 children below 6 months of age[1]. True wheezing is particularly troublesome manifestation of obstructive lower respiratory tract disease of children. The site of obstruction may be anywhere from the intra thoracic trachea to the small bronchi or large bronchioles and the wheeze is produced due to turbulant airflow that collapse with forced expiration. Children younger than 6 months are specially prone to wheezing because bronchospasm, mucosal edema and accumulation of excessive secretions have a relatively greater obstructive effect on their smaller airways. In addition, the compliant airways in young children collapse more easily with active expiration[2]. Bronchiolitis, pneumonia and wheeze associated Respiratory Tract Infection are common diagnosis in such infants[3].

In addition to anatomic factors related to the Lung

Department of Paediatric Medicine, Nilratan Sircar Medical College and Hospital, Kolkata 700014
[1]MBBS, MD, Senior Resident and Corresponding Author
[2]MBBS, MD, Senior Resident
[3]MBBS, DCH, MD, Associate Professor, Murshidabad Medical College and Hospital, Berhampore, West Bengal 742101
[4]MBBS, DCH, MD, Professor and Head

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and Chest wall, immunologic and molecular influences wheezing in infants in comparison to older children[4]. The obstruction to flow is affected by the airway caliber and compliance of the infant's lung. Resistance (R) to airflow through a tube is inversely related to the radius (r) of the tube to the 4th power.In children less than 5 years old, small caliber peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing with mucosal edema and inflammation can cause further flow limitation and subsequent wheeze[5]. With the very compliant newborn chest wall, the inward pressure produced in expiration subjects the intrathoracic airways to collapse. Flow limitation is further affected by the differences in tracheal cartilage composition and airway smooth muscle tone causing further increase in airway compliance in infants compared to older children. All of these mechanisms combine to make the infant more susceptible to airway collapse, increased resistance, and subsequent wheezing. Many of these conditions are outgrown by the 1st year of life by normal growth and muscular development[6]. As already stated that immunologic and molecular influences can contribute to the infant's propensity to wheeze, they have higher levels of lymphocytes and neutrophils, rather than mast cells and eosinophils in broncho alveolar lavage fluid as compared to older children. A variety of inflammatory mediators have also been implicated in the wheezing infant such as histamine and leukotrienes. Fetal and/ or early postnatal "programming" in which the structure and function of the lung are affected by factors including fetal nutrition and fetal and neonatal exposure to maternal smoking may also occur[7]. Available literature by different authors are reviewed to have a comprehensive idea. Pharmacological interventions used in wheeze associated respiratory conditions include antibiotics, bronchodilators like β2 agonists, adrenaline, ipratropium bromide and 3% saline. Other modalities used include corticosteroids[8] but nebulisation with adrenaline and salbutamol are the main stay of pharmacological therapy. Levosalbutamol, though superior to salbutamol, has not been used in clinical trials before. Various other therapies are being practiced, but most have been shown to be ineffective or having only short term benefits when tested in rigorous clinical trials[9]. A variety of agents ranging from parenteral epinephrine to nebulised racemic epinephrine, albuterol, salbutamol are routinely available[10,11]. The interest in epinephrine (α+ β non-specific action) has been significant due to: (a) α - adrenergic vasoconstrictor action that decongest the respiratory mucosa, limit its own absorption and regulate pulmonary blood flow, with little effect on ventilation-perfusion matching (b) β2 adrenergic bronchial muscle relaxant effect (c) β2 adrenergic action suppress release of chemical mediators. (d) Physiological antihistamine effect that reverse histamine effects like edema (e) It also reduces catarrhal secretions[3]. β2 adrenergic bronchodilators have mucosal and pulmonary vasodilator effects by increased cAMP secretion in bronchial smooth muscle cells. The former increase mucosal absorption rates with resultant direct cardiac effects, by virtue of the residual inherent β1 adrenergic activity effects of tachycardia. The latter enhance ventilation perfusion mismatching with resulting hypoxia and hypoxia induced tachyarrhythmia. Airway obstruction increases work of breathing and precipitates hypoxia; both of which are associated with tachycardia. Thus the vasoconstrictor and bronchodilator activities of adrenaline protect against its direct as well as hypoxia induced arrhythmogenicity. It is therefore not surprising that in clinical studies, drugs such as salbutamol, with minimal residual β1 adrenergic activity, have more potential to cause tachycardia than adrenaline, which in spite of its potent β1 adrenergic activity might reduce heart rate[12,13]. This tachycardiac side effect is much lesser in levosalbutamol as compared to salbutamol. Thus, we conducted a cross-sectional observational study to examine the effect of nebulised levosalbutamol versus adrenaline in children with wheeze associated respiratory conditions using clinical parameters where no previous study using levosalbutamol was done.

Materials and Methods

The study was carried out in children who were admitted in Paediatrics Department of our institution through emergency between March, 2020 to September, 2021. Children between the ages of 1 month to 6 months admitted with first time wheeze were included in the study. Children needing nebulisation were selected on the basis of nasal discharge, wheezy cough in the presence of fine inspiratory crackles and/or high pitched expiratory wheeze. Signs of respiratory distress taken into consideration were increase in respiratory rate, tachycardia, increased work of breathing, chest retractions, fine crackles and wheeze. Infants who were below 1 month and above 6 months, infants who required mechanical ventilation or non-invasive ventilation in the past, infants suffering from any

congenital anomalies of Chest, Lung or Heart, children on regular use of bronchodilator or steroid use (more than 4 weeks prior to hospital admission), very sick infants needing PICU admission with impending respiratory failure and infants having high grade fever, raised TLC>15,000/mm^3, lobar consolidation on skiagram were excluded from the study. No cases were repeated. Ethical committee clearance was taken from the institutional ethical committee. A total of 60 children were taken. Of these, 30 children who received nebulised levosalbutamol (0.15 mg/kg/dose with 3ml saline)(Group 1) and another 30 children who received adrenaline nebulisation (0.5ml/kg/dose in1:1000 solution with 3ml saline)(Group 2) were enrolled. A written informed consent was taken for each child from the parent/caregiver. An arterial blood gas (ABG) and a chest skiagram were taken for each to exclude respiratory failure and lobar consolidation respectively. Each parent/caregiver had to answer a predetermined questionnaire. In 3 doses of each drug were given at 15 mins interval via nebuliser with O_2 @6lts/min maintaining CDC COVID-19 protocol[14] as a part of treatment process. Heart rate, respiratory rate, oxygen saturation by calibrated multichannel pulse oximeter (SpO2) and Respiratory Distress Assessment Index (RDAI) score were recorded before intervention, just after 2nd dose, 30 minutes after last dose and 1 hour after last dose. A comparison between observations before and after nebulisation in the given groups and between the two groups were done. Data was recorded on a predetermined pro-forma and was analysed using statistical software (SPSS ver. 26). Along with the above, IV fluids (DNS+KCl), humidified oxygen through mask and syrup paracetamol for temperature above 100°F were given in both the groups. Breastfeeding on demand or top feeding whatever the baby was on was continued. Response to treatment was determined by-changes in heart rate, changes in oxygen saturation in room air, changes in respiratory rate and changes in Respiratory Distress Assessment Index (RDAI) score. Data was recorded on a predetermined proforma and analysed using the paired and unpaired Student's t-test. P value <0.05 was taken as significant.

Results

A total of 60 children in the age range of 1 to 6 months of age were included in the study with 30 in each group. The mean age of children was (3.49±1.59) months in Group 1 and (2.66±1.72) months in Group 2. A total of 35% of children in Group 1 and 31.67% of children Group 2 were boys and the rest were girls. The two Groups were comparable with respect to their mean initial HR, RR, SpO2 and RDAI scores. The trends of the various parameters through the initial three nebulisations (based on mean values at 0, just after second dose, 30 minutes after third dose and 1 hour after third dose) in the two groups are shown in Tables 1-4. At the end of three nebulisations, the mean (SD) changes in parameters in both groups are given in Table 5. In Group 1, the post-nebulisation mean heart rate/min increased by (6.276±1.112), the mean respiratory rate/min decreased by (3.267±2.149), the mean SpO_2% increased by (2.967±1.45) and the mean respiratory distress assessment score decreased by (1.733±1.311). In Group 2 also the post-nebulisation mean heart rate/min increased by (6.233±1.775), mean respiratory rate/min falling by 6.633±2.327, mean SpO_2% increasing by (4.633±1.67), mean

Table 1 — *Comparison of serial recording of Heart rate values*

Heart rate (HR)	HR 1	HR 2	HR 3	HR 4
Group 1	138.17±11.35	140.43±11.3	142.27±11.15	144.43±11.09
Group 2	144.43±14.71	146.73±14.60	148.70±14.37	150.67±14.17
t	1.84	1.86	1.93	1.89
p	0.07	0.06	0.05	0.06

Table 2 — *Comparison of serial recording of respiratory rate values*

Respiratory Rate (RR)	RR 1	RR 2	RR 3	RR 4
Group 1	61.93±6.41	61.47±6.19	60±6.20	58.67±5.57
Group 2	64.40±5.73	62.30±5.34	60.27±5.26	57.77±4.96
t	1.56	0.558	0.17	0.66
p	0.12	0.57	0.85	<0.001

Table 3 — *Comparison of serial recording of oxygen saturation values*

Oxygen saturation (Spo2)	SpO_2 1	SpO_2 2	SpO_2 3	SpO_2 4
Group 1	89.17±1.08	89.67±1.02	90.77±1.10	92.13±1.19
Group 2	88.77±1.35	90.00±1.39	91.70±1.50	93.40±1.32
t	1.26	1.05	2.73	3.58
p	0.21	0.29	0.08	<0.001

Table 4 — *Comparison of serial recording of RDAI scores*

RDAI Score	RDAI 1	RDAI 2	RDAI 3	RDAI 4
Group 1	12.93±1.81	12.87±1.81	11.97±1.71	11.20±1.54
Group 2	14.23±1.61	13.03±1.62	11.87±1.63	10.20±1.82
t	2.90	0.37	0.23	2.29
p	0.05	0.70	0.81	<0.001

respiratory distress assessment instrument score falling by (4.033±1.033). All the parameters in both the groups (within the groups) had registered a statistically significant change (p<0.0001). On comparing the two Groups for difference in the change of parameters brought about, it is noticed that there was no significant difference in change of heart rate, there was a significant difference in change in respiratory rate, oxygen saturation and RDAI score favouring adrenaline Group (p<0.0001) (Table 5). There were no significant side effects such as tachyarrythmia, irritability, tremors or facial blanching with either epinephrine /levosalbutamol initially or during subsequent nebulisations.

Table 5 — *Comparison of initial and final parameters in both groups*

	Mean ± SD change in parameters			
	Heart Rate (HR)	Respiratory Rate (RR)	Oxygen saturation (SpO_2)	RDAI Score
Group 1	6.276±1.112 t = 30.864 p <0.001	3.267±2.149 t =8.328 p<0.001	2.967±1.45 t = 11.207 p<0.001	1.733±1.311 t = 7.24 p<0.001
Group 2	6.233±1.775 t = 19.235 p<0.001	6.633±2.327 t = 15.617 p<0.001	4.633±1.67 t = 15.188 p<0.001	4.033±1.033 t =21.378 p<0.001
t	1.89	0.660	3.58	2.29
p	Not significant	<0.001	<0.001	<0.001

Discussion

The main aim of our study was to determine efficacy between nebulised levosalbutamol and nebulised adrenaline in wheeze associated conditions of children between 1 month and 6 months of age according to clinical parameters.

In a study done by Sireesha S, *et al* on comparison of nebulized Salbutamol *versus* Adrenaline in the treatment of wheeze associated Respiratory Tract Infection between 2 months to 2 years of age mainly focussing on Bronchiolitis showed a total of 30 children were enrolled. 22 (73.3) were in age Group of 2 months to 1 year and 8 (26.7%) were in age Group of 1-2 years and they found no added advantage of decreasing the respiratory rates, wheezing and retractions of one over the other groups[15].

In another study done by Syama Prasad Sit, *et al* on Comparative Efficacy of Nebulised L-Adrenaline Versus Salbutamol in Infants with Bronchiolitis between 2 months to 12 months of age with bronchiolitis showed a total of 70 children were enrolled. 35 received L-adrenaline (0.1ml/kg/dose in 1 in 10,000 solution) (Group A) and 35 received salbutamol (0.1mg/kg/dose)(Group B).Both L-adrenaline and salbutamol caused significant improvement in mean symptom score and oxygenation[16].

In another study done by Gayti Koley, *et al* on Comparison of Salbutamol to Adrenaline nebulisation in Acute Severe Bronchiolitis showed a total of 21 infants in the age Group of 1 month-1 year were enrolled in the study. They received salbutamol (0.15 mg/kg with saline to a total of 3 ml) through nebuliser with Oxygen or adrenaline 1:10000 (0.5 ml/kg subject to a maximum of 2.5 ml with saline to make it 3 ml). The study showed that respiratory status was better with significant improvement in RR, RDAI score and SpO2, decreased oxygen requirement and shorter hospital stay in the adrenaline group[17].

All of these studies came up with varied results and conclusion. Also all these studies had used salbutamol in infants presenting with wheeze. It is well established that levosalbutamol to be more efficacious than salbutamol in terms of improvement in respiratory and cardiac parameters. Again these studies used 0.1ml/kg of 1:10000 epinephrine which is much lesser than the recommended useful dose. In our study a total of 60 children in the age range of 1 to 6 months were included with 30 children in each Group. Each children who received either levosalbutamol (0.15mg/kg with 3ml saline) or epinephrine (1:1000, 0.5ml/kg with 3 ml saline) for wheeze were enrolled. Each of them were given 3 doses of each drug at 15 mins interval via nebuliser with O_2 @6lt/min maintaining COVID-19 CDC protocol. The mean age of children (mean ± SD) was (3.49±1.59) months in Group 1 and (2.66±1.72) months in Group 2. A total of 35% of children in Group 1 and 31.67% of children Group 2 were boys and the rest were Girls. The two Groups were comparable with respect to their mean pretreatment heart rate, respiratory rate, RDAI and oxygen saturation. Most of the cases had viral pneumonia with 40% of total patients; 33.33% of total patients had wheeze associated Lower Respiratory Tract Infection and rest others had bronchiolitis (26.67%). The major limitation of our study is that it is a cross-sectional observational study with no control group for comparison, the observations were done at a single point of time with no follow-up. However, comparison of various statistical variables helped us to draw some conclusion against major outcomes.

Conclusion

Both adrenaline and levosalbutamol caused significant improvement in mean symptom score and oxygenation. On comparing the two groups for difference in the change of parameters brought about, it was noticed that there was no significant difference in change of Heart rate but there was a significant difference in change in Respiratory rate, Oxygen saturation and RDAI score favouring epinephrine group. Larger, multi centric, double blinded randomized controlled trials are required to confirm these results.

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