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Comparative Efficacy of Nebulised L-Adrenaline Versus Salbutamol in Infants With Bronchiolitis

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Abstract:
Background: *Bronchiolitis is one of the most common lower respiratory infections in infants. There is a wide variation in treatment of bronchiolitis in different institutions and hence there is a need for standardization of existing modalities of treatment.*
Aims:- *To compare the efficacy of nebulised L- adrenaline versus salbutamol in infants admitted with bronchiolitis.*
Settings and Design:- *Tertiary care hospital. Randomized double blind case control trial.*
Method: *70 children in age group of 2 months to 12 months with their 1st episode of wheezing in association with fever and/or coryza were enrolled. Of these, 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);.Three doses of each drug were given, nebulized with oxygen at 20 minutes intervals. Respiratory rate, RDAI score,Heart rate and pulse oxymetry was recorded before intervention and 30 minutes after last dose. Patients who showed significant relief were discharged after an observation period of three hours while those who did not were admitted.*
Results: *Both L-adrenaline and salbutamol caused significant improvement in mean symptom score and oxygenation. However, the adrenaline group showed a significantly better improvement in the study parameters than the salbutamol group. More children in the adrenaline group could be sent home after the emergency treatment.*
Conclusion*: The study concluded that both nebulized salbutamol and l-adrenaline are effective and nebulized l-adrenaline is significantly superior to nebulized salbutamol in infant with bronchiolitis in reliving symptom.*
Keywords: *Nebulized l-adrenaline, nebulized salbutamol, acute bronchiolitis.*

I. Introduction

Acute bronchiolitis is an important cause of morbidity in infants and children. It is the most common cause of hospitalization due to acute lower respiratory tract infection (LRTI) in infants. A number of definitions have been proposed for bronchiolitis: The American Academy of Pediatrics (AAP) defines bronchiolitis as 'acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm [1]; but this definition is of little clinical significance. Another useful definition, which has been used in many clinical studies, is: the first episode of wheezing in a child younger than 12 to 24 months who has physical findings of a viral respiratory infection and has no other explanation for the wheezing, such as pneumonia or atopy [2].

The rate of bronchiolitis related hospitalisation among infants under 1 year of age is 3.1% in developed countries[3]. It accounts for 30.8% of hospitalizations in infants under 1 year of age for lower respiratory infections[3]. Median length of hospital stay among children with bronchiolitis is 2 days[3]. Average cost incurred during treatment for Bronchiolitis was $3799 per hospitalization in united states[4].

75% of bronchiolitis is caused by respiratory syncitial virus (RSV) infection [5].Around 70% of all infants will be infected with RSV in their first year of life and 22% develop symptomatic disease. Other pathogens causing bronchiolitis include adenovirus, human metapneumovirus, influenza virus, and para influenza virus.

Pharmacological interventions used include antibiotics, bronchodilators like β agonists, adrenaline, ipratropium bromide and 3% saline. Other modalities used include corticosteroids, nebulized DNase[6]. Various therapies are being practiced, but most have been shown to be ineffective or having only short term benefits when tested in rigorous clinical trials[7].Nebulisation with L-adrenaline and salbutamol are used as main stay of

pharmacological therapy. Adrenaline has a number of advantages over β_2 adrenergic selective bronchodilators that ensure its efficacy with fewer side effects: (a) α adrenergic vasoconstrictor action that can decongest the mucosa, limit its own absorption, and regulate pulmonary blood flow, with little effect on ventilation–perfusion matching; (b) β_2 adrenergic bronchial muscle relaxant effect; (c) β_2 adrenergic action to suppress release of chemical mediators; (d) physiological antihistamine effect that can reverse histamine effects, such as oedema; and (e) it reduces catarrhal secretions[8].

β_2 Adrenergic bronchodilators have mucosal and pulmonary vasodilator effects. The former increase mucosal absorption rates with resultant direct tachycardic effects, by virtue of the residual inherent β_1 adrenergic activity effects. The latter enhance ventilation–perfusion mismatching which results in hypoxia and hypoxia induced tachyarrhythmia. Airway obstruction increases work of breathing and precipitates hypoxia; both are associated with tachycardia. 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 β_1 adrenergic activity, have more potential to cause tachycardia than adrenaline, which in spite of its potent β_1 adrenergic activity might reduce heart rate[9,10].

Many recent studies have reported on the efficacy of inhaled L-adrenaline (epinephrine) in the treatment of bronchiolitis, but were subject to criticism over patient selection and study design,in particular the use of bronchodilators for comparison. The study was conducted to understand the comperative efficacy of nebulized salbutamol versus nebulized L-adrenaline in reliving in acute bronchiolitis.

II. Materials &Methods

Randomized double blind case control trial comparing nebulisation of levo adrenaline with nebulisation with the control i.e. salbutamol in children requiring emergency department visit for bronchiolitis in a tertiary care hospital. The study was carried out in children who visited Pediatrics Department of our institution via. ED between January 2016 –April 2016. Children between the ages of two months and twelve months sent by the emergency physician with the clinical diagnosis of bronchiolitis were included in the study. Diagnosis of acute bronchiolitis was considered in an infant with nasal discharge and a wheezy cough, in the presence of fine inspiratory crackles and/or high pitched expiratory wheeze. Signs of respiratory infection taken into consideration were increase in respiratory rate, tachycardia, increased work of breathing, fine crackles and wheeze. Patients were excluded from the study for a variety of reasons including previous wheezing, Previous history of any atopic diseases, regular use of bronchodilator or anti inflammatory medications, any pre existing lung disease , chronic lung disease of prematurity/ bronchopulmonary dysplasia, or cystic fibrosis; congenital anomalies of the chest, lung or heart . No case was repeated. Ethical committee clearance was taken from the institutional ethical committee. Randomization was done by simple random sampling with the prospective cases being allotted serial numbers in cards. The cards were shuffled and picked to enter Group I or Group II alternatively (35 children in each group). A written informed consent was taken for each child from the parent/caregiver. An X-ray was taken for each to exclude consolidation.

Each parent/caregiver also answered a predetermined questionnaire. Each child received 3 doses of salbutamol 0.1 mg/kg/dose with 3 ml saline (group I)or adrenaline (0.1ml/kg/dose in 1;10,000 solution made up to 3 ml with saline (group II) via nebuliser (Pulmomist) with Oxygen of 6 litres/min and the children were assessed pre-treatment and half hour after third dose according to heart rate (HR), respiratory rate(RR), respiratory distress assessment instrument(RDAI) score and oxygen saturation by pulse oximetry (SpO2).Continuous oxygen saturation monitoring was done by Oximax N 560 & 3 values were taken pretreatment,. Just after 2nd dose & 30 minutes after 3rd dose. A comparison between observations before and after intervention in the given groups and between the two groups was done. Data was recorded on a predetermined proforma and analysed using IBM SSPS(ver.22) statistical software employing appropriate statistical tests like paired and unpaired student t test.

III. Results

A total of 70 children were enrolled in the study, out of which 35 were included in the salbutamol group and 35 in the adrenaline group. There was no significant difference in age or sex among the two groups.

Both the groups were shown improvement in the respiratory rates as the numbers of doses have been increased. The mean respiratory rate had fallen from 72.94 breaths per minute at admission to 51.34breaths per minute in the L-adrenaline group. In the salbutamol group the mean respiratory rate had fallen from 73.11breaths per minute at admission to 61.09 breaths per minute after 30 minutes of 3rd dose.

Post intervention heart rate was significantly higher in adrenaline group (Mean-151.97 to 174.49) as compared to salbutamol group(Mean-151.94 to 161.31).

Both the groups were shown improvement in the RDAI as the numbers of doses were increased. The mean RDAI had fallen from 13.8 at admission to 5.17 breaths in the adrenaline group. In the salbutamol group the mean RDAI had fallen from 13.2 at admission to 7.20 post intervention.

There was significant improvement in SpO2 in adrenaline group(Mean-90.4 to 98) as compared to salbutamol group(Mean-91.20 to 94.40) post intervention i.e. 30 minutes after 3 rd dose.

IV. Tables

Table 1; Comparison of initial and final parameters in both groups

S. no.	Variable	Group	Before treatment		After treatment		Change (initial value – final value)	
			(Mean ± SD)	t value p value	(Mean ± SD)	t value p value	(Mean ± SD)	t value p value
1	Heart rate	A(n = 35)	151.97 ± 8.923	t = 0.015 p= 0.988	174.49 ± 9.7	t = 6.587 p< 0.001	22.514 ± 3.657	t = 36.421 p < 0.001
		B(n = 35)	151.94 ± 6.403		161.31 ± 6.773		9.371 ± 9.143	t = 6.064 p < 0.001
2	Respiratory rate	A(n = 35)	72.94 ± 4.311	t = 0.121 p= 0.904	51.34 ± 5.357	t = 8.257 p< 0.001	21.6 ± 3.108	t = 41.117 p < 0.001
		B(n = 35)	73.11 ± 7.226		61.09 ± 4.475		12.029 ± 3.699	t = 19.243 p < 0.001
3	RDAI score	A(n = 35)	13.8 ± 1.346	t = 1.610 p= 0.112	5.17 ± 1.581	t = 6.078 p< 0.001	8.629 ± 1.699	t = 30.041 p < 0.001
		B(n = 35)	13.2 ± 1.746		7.20 ± 1.183		6 ± 2.029	t = 17.493 p < 0.001

Table 2- Comparison of serial recording of pulse oxymetry values

Pulse oxymetry	SpO_2 - 1	SpO_2 – 2	SpO_2 - 3	Change (Final – initial)
Group A (n)	(35)	(35)	(35)	(35)
Mean ± S.D.	90.4 ± 0. 497	95.8 ± 1.183	98 ± 0.642	7.60 ± 0.847
Group B (n)	(35)	(35)	(35)	(35)
Mean ± S.D.	91.20 ± 1.183	93.20 ± 0.759	94.40 ± 1.035	3.2 ±1.623
t value	3.688	10.941	17.493	53.075 for group A 11.862 for group B
p value	< 0.001	< 0.001	< 0.001	< 0.001

Table 3- Comparison of outcome of both groups post intervention

Outcome	Group A	Group B	Total	$\chi 2$, df, P value Pearson Chi-Square	Odds ratio 95% Confidence Interval
Early discharge	32	25	57	4.629, 1, 0.031	4.267 (1.060 – 17.168)
Late discharge	3	10	13		
Total	35	35	70		

V. Discussion

The use of bronchodilators has always been controversial. The use of a combined alpha-adrenergic and beta-adrenergic agonist, such as adrenaline was postulated to offer better benefit with its effect of reducing the mucosal oedema and achieving satisfactory bronchodilatation[11].

Analysis of results revealed that the children in both the groups had similar clinical profile at the time of inclusion in the study. After three doses of nebulization, both the adrenaline and salbutamol groups showed significant improvement in mean respiratory rate, RDAI score as well as oxygen saturation. However, these changes were significantly more marked in the adrenaline group as compared to the salbutamol group for all parameters ($p<0.001$ for each parameter). Not only were the mean scores and mean SpO2 levels better in the adrenaline group, but also the oxygen saturation were higher in adrenaline as compared to salbutamol group ($p <0.01$). This benefit in clinicophysiologic profile was also reflected in the need for hospitalization as the admission rate was significantly lower in the adrenaline group (8.6% versus 28.6%; p value = 0.03). Thus, both drugs showed good efficacy with L-adrenaline being better than salbutamol.

Most researchers used the racemic epinephrine but perhaps there is no pharmacological basis for the belief that racemic mixture is safer than L-adrenaline[12,13]. We found two earlier studies that has compared L-adrenaline with salbutamol in bronchiolitis. Study conducted by Menon K et al[14] had concluded that L-adrenaline was more effective though the dose used by authors(3ml of 1 in 1,000 solution per dose) was much higher but another study that was conducted by Madhusmita SRay et al [15] had used the same dose as it is done in our study and concluded that L-adrenaline is more effective than salbutamol. Kristjansson et al(16) compared racemic adrenaline with placebo for the treatment of bronchiolitis and concluded that racemic adrenaline was more efficacious. Wennegren *et al.*[17] in a study of children with wheezy bronchitis, found racemic adrenaline to be more efficacious than nebulized salbutamol. Similarly, Sanchez *et al.*[18] and Reijonen *et al.*[19] also found nebulized racemic epinephrine to be better than nebulized salbutamol for the treatment of bronchiolitis.

VI. Conclusion

Bronchodilators, both specific and non specific are useful in relieving symptoms and improving oxygenation in wheezy infants with clinical diagnosis of Bronchiolitis, who present with respiratory distress and wheezing in association with coryza. However, of the two drugs, L-adrenaline shows a better efficacy in terms of relieving distress and improving oxygenation as well as decreasing the need for admission. Larger, multi centric, double blinded randomized controlled trials are required to confirm these results.

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