

## Efficacy of Nebulized L-Epinephrine versus 0.9% NaCl in the Treatment of Bronchiolitis in a Tertiary Care Hospital: A Randomized Controlled Trial

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### ABSTRACT

**Background:** Bronchiolitis is a leading cause of hospitalization in infants bellow 2 years of age. There are multiple modalities used for treatment of bronchiolitis.

**Objectives:** The aim of the study was to compare the efficacy of nebulized epinephrine and 0.9% NaCl in the treatment of bronchiolitis.

**Methods:** This is a randomized controlled trial study was carried out in the Department of Pediatrics, Bangladesh Shishu Hospital and Institute from July 2019 to June 2021. A total 100 patients between ages of 2-months to 1-year admitted with the diagnosis of bronchiolitis, were included in this study. After enrollment, total 100 patients were randomly assigned to group-A were treated with L-Epinephrine nebulization 0.1ml/kg/dose of 1:1000 dilution mixed with normal saline to make a total volume of 3 ml every 8 hourly and children in the group-B were treated with 0.9% NaCl nebulization 3 ml every 8 hourly. Data were collected in the form of age, gender, clinical recovery (MRDAI score and SpO<sub>2</sub>), duration of hospital stay and duration of oxygen therapy. Data were analyzed using computer software SPSS version-24 and p value less than 0.05 was considered as statistically significant.

**Results:** The mean age was 6.26 ±2.16 months in group-A and 6.20± 2.03 in group-B (p value = 0.886). Majority patients were males in both groups. All patients had breathing difficulty and chest indrawing in both groups. Mean MRDAI (Modified Respiratory Distress Assessment Instrument) score at day 1, day 2 and day 3 was statistically significant (p<0.05) when compared between two groups. However, mean MRDAI score at baseline, at 1hour and at day 4 were not statistically significant between two groups. Mean SpO<sub>2</sub> was increased in epinephrine group than normal saline group at 24hrs which was statistically significant. Mean duration of oxygen therapy was 20.1 1±2.1 hours in group-A and 30.51±4.4 hours in group-B with p value 0.006. Mean length of hospital stay was 58.04 2±5.17 hours in group-A and 70.60 2±2.89 hours in group-B with p value 0.010.

**Conclusion:** We concluded that nebulized epinephrine is more effective than nebulized 0.9% NaCl for reduction of clinical severity, duration of oxygen therapy and length of hospital stay in bronchiolitis.

**Keywords:** Bronchiolitis, Epinephrine, 0.9% NaCl, Hospital Stay.

### I. INTRODUCTION

Bronchiolitis is one of the most common lower respiratory tract infections in infants. The American Academy of Pediatrics (AAP) defined bronchiolitis as acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucous production and bronchospasm. It may be defined as the first episode of

wheezing in a child younger than 12 to 24 months who has physical findings of viral respiratory infection and has no other explanation for the wheezing. [1]

It usually occurs in winter from December to March in northern India. [2] It is more common in males as compared to females. Common viral causes of bronchiolitis include respiratory syncytial virus (RSV), parainfluenza virus, influenza virus, human metapneumovirus, adenovirus and rhinovirus. Among them RSV is the most common cause of bronchiolitis and accounts for approximately 60% to 75% of bronchiolitis cases. [3]

Children become infected with RSV by age 2 years with peak incidence being in 2 to 6 months. It has been stated in the literature that bronchiolitis is a cause of hospitalization in 32% of infants and children admitted due to lower respiratory tract disease. [4] Majority of children suffering from bronchiolitis have only mild disease that is self-limiting. But in some cases, the disease can be severe enough to require admission in the intensive care unit. Risk factors associated with bronchiolitis include prematurity, low birth weight, lower socioeconomic group, overcrowded place and underlying cardiopulmonary disease or immunodeficiency. [5]

Pathophysiology is important in order to understand the clinical manifestations and to manage these patients. Viral infection occurs through the upper respiratory tract and spreads to the lower tract within a few days, this results in acute inflammation, edema of the bronchiolar epithelium, necrosis, increased mucus production and peribronchiolar mononuclear infiltration changes that obstruct flow in the small airways leading to hyperinflation, microatelectasis and wheezing.

Bronchiolitis usually occurs by exposure of an infectious agent to an infant with minor respiratory symptoms. Common presenting symptoms include rhinorrhea and cough followed by tachypnea, nasal flaring, accessory respiratory muscles use, and in some children, crackles and wheezing. [6] The clinical hallmarks of bronchiolitis are hyperinflation, microatelectasis of both lung and wheezing. The diagnosis of bronchiolitis is based on history and physical examination. Blood sampling and chest radiography are rarely needed. [7]

The treatment of bronchiolitis mainly supportive, like clearing of the secretions, encouraging feeding, maintenance hydration and oxygen therapy for children presenting with low oxygen saturation. AAP guideline recommend the use of supplemental oxygen if oxygen saturations are less than 90% to avoid hypoxemia but the NICE (National Institute for Health and Care Excellence) guideline recommend that children receive oxygen supplementation when they have oxygen saturation less than 92%. [8] Other treatment strategies include bronchodilators, corticosteroids and nebulized hypertonic saline, although there are no specific recommendations for their use. [9] A randomized controlled trial showed that nebulized L-Epinephrine is more effective than nebulized normal saline in relieving respiratory distress and improving oxygen saturation. [10] Nebulization with 3 to 5 ml of L-Epinephrine is a safe therapy for children with bronchiolitis. Another study showed that infants with bronchiolitis improved significantly earlier in nebulized epinephrine group 5 compared to nebulized placebo group. [11] It was observed in a study that nebulized L-adrenaline was significantly superior to nebulized salbutamol for reduction of respiratory distress and improving oxygen saturation.

## **II. METHODOLOGY**

This Randomized controlled trial study was carried out in the Department of General Pediatrics Bangladesh Shishu (Children) Hospital and Institute Sher-E-Bangla Nagar, Dhaka, Bangladesh during July, 2019 to June, 2021. A total of 100 patients were participated in the study. Among them 50 were Bronchiolitis patients treated with nebulized L-Epinephrine (Group-A) and Bronchiolitis patients treated with nebulized 0.9% NaCl (Group-B). Sample was collected by simple random sampling among the infants of bronchiolitis patients from 2 months to 1 year of age admitted in the Bangladesh Shishu Hospital and Institute. Inclusion criteria were age 2 months to 1 year, both male and female, history of viral prodrome present and first episode of respiratory distress associated with wheezing. Exclusion criteria were history of similar episode of respiratory distress in the past, family history of asthma, congenital heart disease or chronic lung disease, evidence of pneumonia and infants received nebulized salbutamol or corticosteroid in any form in the preceding 72 hours. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

### III. RESULTS

**Table I: Demographic characteristics of the studied patients (n=100)**

Characteristics	Group-A (n=50)	Group-B (n=50)	p-Value
Age (in months) ± SD	6.26±2.16	6.20±2.03	<sup>a</sup> 0.886
Gender			
Male	30 (60%)	28 (56%)	<sup>b</sup> 0.685
Female	20 (40%)	22 (44%)	

Table I shows, the mean age of studied patients was 6.26±2.16 months in group-A and 6.20±2.03 months in group-B. The mean difference was not statistically significant between groups. Majority patients were males in both groups, 30 (60%) in group-A, 28 (56%) in group-B and females were 20 (40%) in group-A, 22 (44%) in group-B. The difference was not statistically significant.

**Table II: Frequency of bronchiolitis patients with different clinical and radiological findings on admission in both groups**

Variables	Group-A (n=50)	Group-B (n=50)	p-Value
Difficulty in breathing	50 (100%)	50 (100%)	1.0
Cough	47 (94%)	49 (98%)	0.307
Fever	39 (78%)	35 (70%)	0.362
Wheeze	40 (80%)	42 (84%)	0.603
Ronchi	46 (92%)	47 (94%)	0.695
Chest Indrawing	50 (100%)	50 (100%)	1.0
Runny nose	37 (74%)	39 (78%)	0.640
Tachypnoea	44 (88%)	45 (90%)	0.749
Feeding difficulty	48 (96%)	50 (100%)	0.153
Hyperinflation	48 (96%)	45 (90%)	0.240
Hypertranslucency	50 (100%)	47 (94%)	<b>0.079</b>

Table II shows all the cases in both groups presented with difficulty in breathing and chest indrawing. Cough was 47(94%) in group-A and 49(98%) in group-B. Feeding difficulty was 48(96%) in group-A and 50(100%) in group-B. Fever was 39(78%) in group-A and 35(70%) in group-B. Wheezing was a presenting feature of 40(80%) in group-A and 42(84%) in group-B. Tachypnoea was present 44(88%) and 45(90%) in group A & B accordingly. 46(92%) cases in group-A and 47(94%) in group-B presented with rhonchi. Hypertranslucency was present 50(100%) in group-A and 47(94%) in group-B whereas hyperinflation 48(96%) in group-A and 45(90%) in group-B. According to clinical presentation and radiological findings both groups are same.

**Table III: Comparison of clinical recovery by MRDAI score between two groups**

Variables	Group-A (n=50)	Group-B (n=50)	p-Value
At Baseline (without nebulization)	6.14±1.65	6.06±1.57	0.805
At 1 Hour (After nebulization)	5.38±1.65	5.72±1.46	0.278
Day 1 (After nebulization)	3.96±1.54	4.58±1.36	0.036*
Day 2 (After nebulization)	2.70±1.63	3.38±1.52	0.036*
Day 3 (After nebulization)	2.39±1.16	2.97±0.86	0.038*
Day 4 (After nebulization)	1.64±0.84	1.87±0.69	0.380

Table III shows total MRDAI score at baseline, at 1hour and day 4 were not statistically significant when compared between groups (p>0.05). However, changes of total MRDAI score at day 1, day 2 and day 3 were significantly lower in group-A than group-B (p<0.05).

**Table IV: Comparison of SpO2 between two groups**

Variables	Group-A (n=50)	Group-B (n=50)	p-Value
SpO2 At Admission	92.7±3.4	92.9±3.4	0.839
SpO2 After 24 hours	96.3±1.6	95.5±1.8	0.013*

Table IV shows mean SpO<sub>2</sub> during admission  $92.7 \pm 3.4$  in group-A and  $92.9 \pm 3.4$  in group-B, which was not statistically significant whereas changes of SpO<sub>2</sub> was higher in group-A ( $96.3 \pm 1.6$ ) than group-B ( $95.5 \pm 1.8$ ) at 24 hours after first nebulization ( $p < 0.05$ ).

**Table V: Comparison of duration of oxygen therapy and length of hospital stay between groups**

Variables	Group-A (n=50)	Group-B (n=50)	p-Value
Duration of oxygen therapy (in hours)	20.1±12.1	30.5±14.4	0.006*
Length of hospital stay (in hours)	58.04±25.17	70.60±22.89	0.010*

Table V shows the patients of group-A on an average required 20.1±12.1 hours of oxygen therapy, while the patients of group-B required 30.5±14.4 hours of oxygen therapy. Duration of oxygen therapy significantly lower in group-A compared to group-B ( $p < 0.05$ ).

**Table VI: Comparison of heart rate between two groups**

Variables	Group-A (n=50)	Group-B (n=50)	p-Value
Heart rate at Admission	140.7±16.7	138.6±10.2	0.607
Heart rate at 24 hours	138.9±17.1	136.4±10.01	0.292

Table VI shows at admission and at 24 hours after first nebulization mean heart rate was not statistically significant when compared between two groups.

#### IV. DISCUSSION

This prospective, randomized controlled trial study was carried out in department of Pediatrics of Bangladesh Shishu (Children) Hospital and Institute, Dhaka. Hundred patients of 2 to 12 months of age with acute bronchiolitis were included in this study.

In current study the mean age was  $6.26 \pm 2.16$  months in epinephrine group and  $6.20 \pm 2.03$  months in 0.9% NaCl group. The mean age difference was not statistically significant between groups. Similar to our study, John et al. showed mean age  $6.67 \pm 3.01$  months in epinephrine group and  $6.73 \pm 2.95$  months in salbutamol group. [12] In present study we observed that the majority patients were males, 30(60%) in epinephrine group and 28(56%) in 0.9% NaCl group. Females were 20(40%) in epinephrine group and 22(44%) in 0.9% NaCl group. The difference was not statistically significant between groups. Usman and Islam also showed similar findings in their study. [13, 14] The high incidence of bronchiolitis in males as compared to females may be attributed to presence of XX chromosomes which provide greater genetic diversity to the female immunologic defenses.

In our study cough, fast breathing and wheezing were present in most of the children. Cough was a presenting feature of 47(94%) in epinephrine group and 49(98%) in 0.9% NaCl group. Fast breathing was 44(88%) in epinephrine group and 45(90%) in 0.9% NaCl group. Wheezing was 40 (80%) in epinephrine group and 42 (84%) in 0.9% NaCl group. The difference was not statistically significant between groups. Similar results also found in studies by Islam et al. [15] In current study shows that predominant radiological findings are hyperinflation and hypertranslucency in both groups. Hypertranslucency was present 50(100%) in epinephrine group and 47(94%) in 0.9% NaCl group whereas hyperinflation was 48(96%) in epinephrine group and 45(90%) in 0.9% NaCl group. Kabir also showed that hypertranslucency was the most predominant radiological findings in their study which is similar to our study. [16, 17] At admission mean SpO<sub>2</sub> was  $92.7 \pm 3.4$  in epinephrine group and  $92.9 \pm 3.4$  in 0.9% NaCl group, difference was not statistically significant. In present study mean SpO<sub>2</sub> after 24 hours was  $96.3 \pm 1.6$  in epinephrine group and  $95.5 \pm 1.8$  in 0.9% NaCl group. SpO<sub>2</sub> was increased in epinephrine group than normal saline group, which was statistically significant.

In this study at admission mean heart rate was  $140.7 \pm 16.7$  in epinephrine group and  $138.6 \pm 10.2$  in 0.9% NaCl group which was not statistically significant when compared between two groups. At 24 hours mean heart rate was decreased in two groups but it was not statistically significant when compared between groups. Similar to our results, Usman et al. and John et al. found no significant change of heart rate in patients treated with nebulized epinephrine compared to nebulized salbutamol. [13, 16] Herilanto et al. also showed no significant change of heart in patients nebulized with epinephrine, salbutamol or normal saline. [18] As respiratory distress decreased after nebulization and patient become quite so heart rate decreased in both groups. Unlike our results, Wainwright et al.; Morshed and Amin found a significance increase in heart rate after treatment with nebulized epinephrine ( $p < 0.05$ ). [19, 20]

Similar to our study, John showed that duration of oxygen therapy in epinephrine group  $54.71 \pm 5.89$  hours and salbutamol group  $59.64 \pm 5.92$  hours which was statistically significant ( $p < 0.05$ ). [12] Koley and Koley observed that adrenaline group required a shorter duration in their study which was also similar to this study. [21] Usman showed no significant difference between adrenaline and salbutamol group ( $p > 0.05$ ), which were not similar to our study. [13]

In current study mean hospital stay was  $58.04 \pm 25.17$  hours in epinephrine group and  $70.60 \pm 22.89$  hours in 0.9% NaCl group. Length of hospital stay was reduced in epinephrine group in compared to normal saline group, which was statistically significant ( $p < 0.05$ ). Koley and Koley reported length of hospital stay in adrenaline and salbutamol groups were  $96.07 \pm 6.13$  hours and  $106.86 \pm 6.65$  hours respectively, which was statistically significant ( $p < 0.05$ ) and it was similar to present study. [21] Usman observed a mean duration of hospital stay of  $3.9 \pm 1$  and  $4.2 \pm 0.96$  days in adrenaline and salbutamol groups respectively ( $p = 0.016$ ). [13] Modaresi also reported shorter duration of stay in epinephrine group in their study which was similar to our study. [4] Hartling et al. revealed that epinephrine may be favorable compared to placebo. It reduces duration of oxygen therapy and also reduces the length of hospital stay as evidenced by the findings of the present study. [22]

### **Limitations of the study**

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the entire country and bronchiolitis was diagnosed clinically isolation of virus could not be done.

## **V. CONCLUSION**

Nebulization with epinephrine is more effective than nebulization with 0.9% NaCl for reduction of clinical severity, length of hospital stays and duration of oxygen therapy in case of bronchiolitis.

## **VI. RECOMMENDATION**

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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