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ORIGINAL ARTICLE

Efficacy of Nebulized Hypertonic Saline with Adrenaline Versus Normal Saline with Adrenaline in Children with acute Bronchiolitis

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Abstract:

Background: *Bronchiolitis is the most common cause of lower respiratory tract illness in infancy, and hospital admission rates appear to be increasing both in developed and developing countries around the world. RSV is the principal pathogenic organism. Relieving symptoms is the main aim of management and there is no convincing evidence that any other form of therapy will reliably provide beneficial effects in infants with bronchiolitis. Bronchodilators like salbutamol, anti-cholinergic ipratropium bromide, adrenaline and saline nebulization have been used with varying results. Patients treated with nebulized adrenaline exhibited only short time benefit in case of acute bronchiolitis. But very few randomized control trials with nebulized adrenaline & hypertonic saline solution have so far been done and proven to be better in relieving symptoms and also decreasing hospital stay.*

Objective: *To compare the outcome of acute bronchiolitis treated with normal saline and hypertonic saline solution with adrenaline.*

Methodology: *Forty-eight infants and young children (2-24 months) hospitalized with bronchiolitis (runny nose followed by cough, breathing difficulty, chest indrawing and rhonchi on auscultation) were enrolled in the study. It was a single blind randomized control trial. The study was conducted in Pediatric Pulmonology unit of BSMMU from January 2007 to June 2008. Children were randomized into three groups: (1) group A 1.8% Sodium Chloride solution (2) group B 0.9% Sodium Chloride solution (control) and (3) group C 3.6% Sodium Chloride solution. Each patient received 0.1ml/kg Adrenaline mixed with either group of Sodium chloride solution. Each patient was treated with 3 doses of nebulization after admissions, 08 hours after admissions and 16 hours after admissions. Clinical severity score (wheeze, chest indrawing, respiratory rate) also recorded before and after medication. Outcome of therapy was evaluated by respiratory rate, clinical severity score and O2 saturation before and after therapy.*

Results: *Fever, running nose, respiratory rate, heart rate, chest indrawing and rhonchi were improved after 3rd dose of nebulization in all three groups and the improvement was higher in group C but no significant ($p>0.05$) difference was observed. However, cough, breathing difficulties, hypoxia (SaO2) and CS score were also improved after 3rd dose of nebulization in all three groups and the improvement was significantly($p<0.05$) higher in group C with compared to others two groups.*

Conclusion: *The present study concluded that nebulized normal saline with adrenaline and hypertonic saline with adrenaline were found effective in children with bronchiolitis. Nebulized hypertonic saline with adrenaline was found more effective than normal saline with adrenaline.*

Key Words: *Bronchiolitis,Normal Saline,Hypertonic saline,Adrenaline.*

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Introduction:

Bronchiolitis is the most common cause of lower respiratory tract illness in infancy and hospital admission rates appear to be increasing both in developed and developing countries around the world. More than 70.0% cases are due to respiratory syncytial virus (RSV), other pathogens are parainfluenza virus, adenovirus, rhinovirus, influenza virus and Mycoplasma pneumoniae[1].

Acute Bronchiolitis is characterized by bronchiolar obstruction due to mucosal oedema and accumulation of mucus and cellular debris.

There is no convincing evidence that any other form of therapy will reliably provide beneficial effects in infants with bronchiolitis. Therapies such as bronchodilators, corticosteroids, physiotherapy, palivizumab, ribavirin, antibiotics or anticholinergics have not demonstrated any measurable clinical effect.

Bronchodilators like salbutamol are often used in the treatment of bronchiolitis but rather than beneficial effect bronchodilator may cause harmful effect to the patients. It may be secondary to irritant effect or osmotic effect of nebulizing solution on the airways or bronchodilator may inhibit hypoxia induced pulmonary vaso-constriction resulting in increased intrapulmonary shunting and a decreased in oxygen saturation [2].

Recent evidence has suggested that adrenaline may offer some clinical benefit. Although different nebulized solutions such as Salbutamol, Ipratropium bromide and Adrenaline are being used, research and there by guidelines to date support nebulized Adrenaline as drug of choice[3]. Study shows L- Adrenaline (1:1000 soln. Adrenaline, 0.1ml/kg) are more effective than that of salbutamol in case acute bronchiolitis. Study reveal that Adrenaline is not only effective but also inexpensive and relatively safe alternative[4]. With comparison to salbutamol nebulized Adrenaline also showed promising results due its unique mechanism of action in infants with bronchiolitis. It can decongest mucosa with alpha adrenergic vasoconstriction and this may in addition lead to decreased systemic absorption resulting in less tachycardia than salbutamol.

But more recent studies simply substituting normal saline with hypertonic saline solution with adrenaline has shown promising results in case of bronchiolitis by improving clinical severity score and decreasing hospital stay[5].Recently relatively low concentration (<3.0%) hypertonic solution is designed to use in order to decrease the possible negative effect of a higher concentrations (>7.0%) on the cilliary beat frequency and thus hypertonic solution was used in conjunction adrenaline solution in order to avoid any possible bronchoconstriction effect for the treatment of acute bronchiolitis[6]. So, from recent observations and studies, it is expected that nebulized adrenaline with normal or hypertonic saline may act effectively for the treatment of acute bronchiolitis.

Materials and Method

A randomized controlled clinical trial was conducted in the Pulmonology Unit of Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University Dhaka from January 2007 to June 2008. To determine the sample size, the following formula is used;

$$n = \frac{10.51[(R+1) - p_2 (R^2+1)]}{p_2 (1-R)^2}$$

Each group the estimated sample size was 16, therefore 3X16=48 sample was collected.

Children up to 2 years of age, children having preceding/existing runny nose with cough, problem of Breathing difficulty (as perceived by the caregiver), lower chest in-drawing, rhonchi on auscultation were marked as inclusion criteria.

Child with atopic conditions (asthma, allergic rhinitis, allergic conjunctivitis, atopic eczema), history of similar previous attacks, children with congenital heart disease and tuberculosis, children with chronic lung disease were in exclusion criteria. Patients, admitted into Paediatric Pulmonology Department after applying inclusion and exclusion criteria, were enrolled in the study. Children's are randomized into three groups. (i) Group A: 1.8% Sodium Chloride solution,

(ii) Group B: 0.9% Sodium Chloride solution and (iii) Group C: 3.6% Sodium Chloride solution.

The protocol of the study was approved by the Ethical Committee, Department of Paediatrics.

A structured questionnaire was filled up through a face-to-face interview with the caregivers at the very outset. Detailed history was taken and through physical examination was done. The children were randomized into any of the three groups. The random number had the respective group of 1.8% Nacl (A), 0.9% Nacl (B) and 3.6% Nacl (C). Then as per random number table each patient was chronologically categorized without remainder approach. Thus, out of 48 each 16 patients with male 12 & female 04, in group A were nebulized with 1.8% saline plus adrenaline, 16 children with male 10 & female 06, nebulized with 0.9% saline plus adrenaline in group B and 16 children with male 09, female 07, in group C nebulized with 3.6% saline plus adrenaline. Each patient received 0.1 ml/kg Adrenaline mixed with the solution of a container (either 4.0ml of either normal saline or 1.8% NaCl solution or 3.6% NaCl solution) by air driven nebulizer with face mask, according to random table number. Total three doses were given.1st dose (7:00 A.M) was given to patients after admission, 2nd dose was (3:00 P.M) 8 hours after admission and 3rd dose was given 16 hours (11:00 P.M) after admission. $Sa0^2$ prior to therapy and 30 minutes after nebulization and also clinical severity score was evaluated simultaneously after 1st, 2nd and 3rd dose i.e. after admission, 08 hours and 16 hours of admission period. Parameters was measured and recorded before and after therapy as per clinical severity score [11]. Feeding was allowed as usual like breast feeding and other milk formula feeding which the baby was getting before hospitalization. IV fluid with 20% restriction was given when oral feeding was not possible because of severe respiratory distress. Routine investigations like Hb%, TWBC, differentials, chest X-ray were done.

Statistical analysis

As we had taken three groups of which group B i.e. 0.9% Naci solution was taken as control group. So, at first step we compared group A and group B, then at second step compared group B and group C and at third step group C and group A. All data were checked for consistency and correctness and scrutiny. Finally, all the filled-up questionnaires were collected. In uni-variate analysis, simple means and standard deviations and proportion were used. For comparison of the efficacy among the groups Chi square test, paired t-test and ANOVA test were done. p value <0.05, <0.001 and >.05 were considered as significant highly significant and not significant respectively. The data entry, data clean and data analysis were done in SPSS software.

Results:

Socio demographic profile age, weight, sibs, sex, residence area normal vaginal delivery, breastfeeding, atopy in family and smoking were matched in all three groups. The Clinical severity score included presence of wheezing, presence of retractions and respiratory rate and also oxygen saturation and heart rate were observed and explained with statistical analysis

Table I reveals that mean respiratory rate among all groups of children were almost similar before nebulization. Respiratory rate decreased after 3rd dose of nebulization in group A from 64.8±8.5/min to 45.6±7.9/min in group B from 63.1±7.1/min to 47.7±10.3/min and in group C from 62.3±5.2/min to 45.8±5.2/min and the decrement was higher in group C. The mean difference of respiratory rate was not statistically significant (p>0.05) in ANOVA test (Table I).

Average heart rate of the children at nebulization was 126. Heart rate increased after 3rd dose of nebulization in all three groups and the increment was higher in group C. The mean difference of heart rate was not statistically significant (p>0.05) in ANOVA test (Table II).

Chest indrawing was found in all three groups of children. After 3rd dose of nebulization chest indrawing declined in all three groups of children but higher in group C, however no significant difference was found in all three groups.

Breathing difficulties was present in all three groups of children. After 3rd dose of nebulization breathing difficulty was improved in all three group but improvement was significantly (p<0.05) higher group C compared other two groups.

Oxygen saturation increased after 3rd dose of nebulization in all three groups and the increases was higher in group C. The mean difference of hypoxia (SaO2) were statistically significant (p<0.05) in ANOVA test. The mean hypoxia (SaO_2) increased 3.8±1.7% in group A, 1.6±2.8% in group

B and 4.8±2.5% in group C after 3rd dose of nebulization and the increased was significantly ($p<0.05$) higher in group C (Table III).

CS score decline after 3rd dose of nebulization in all three groups and the declinement was higher in group C. The mean difference of CS score was statistically significant ($p<0.05$) in ANOVA test

The mean CS score was about 8 among all group of children. The mean CS score decrease (Table IV)2.0±1.3 in group A, 1.1±0.9 in group B and 3.1±1.2 in group C after 3rd dose of nebulization and the decreased was significantly ($p<0.05$) higher in group C.

Table-I

ANOVA table for respiratory rate at different times in three groups

	Sources	SS	df	MS	F value	p value
Before nebulization	Between groups	51.50	2	25.750	0.521	0.598
	Within groups	2225.75	45	49.461		
	Total	2277.25	47			
Dose 1	Between groups	14.54	2	7.271	0.111	0.895
	Within groups	2955.94	45	65.688		
	Total	2970.48	47			
Dose 2	Between groups	78.17	2	39.083	0.527	0.594
	Within groups	3334.81	45	74.107		
	Total	3412.98	47			
Dose 3	Between groups	43.17	2	21.583	0.330	0.721
	Within groups	2945.81	45	65.463		
	Total	2988.98	47			

Group A: 1.8% Sodium Chloride solution
Group B: 0.9% Sodium Chloride solution and
Group C: 3.6% Sodium Chloride solution

Table-II

ANOVA table for heart rate at different times in three groups

	Sources	SS	df	MS	F value	p value
Before nebulization	Between groups	153.38	2	76.688	0.363	0.698
	Within groups	9518.94	45	211.532		
	Total	9672.31	47			
Dose 1	Between groups	209.38	2	104.688	0.534	0.590
	Within groups	8815.88	45	195.908		
	Total	9025.25	47			
Dose 2	Between groups	520.29	2	260.146	1.560	0.221
	Within groups	7506.38	45	166.808		
	Total	8026.67	47			
Dose 3	Between groups	173.79	2	86.896	0.461	0.634
	Within groups	8482.69	45	188.504		
	Total	8656.48	47			

Group A: 1.8% Sodium Chloride solution
Group B: 0.9% Sodium Chloride solution and
Group C: 3.6% Sodium Chloride solution

Table-III

Mean Hypoxia (SaO_2) on base line and after 3rd dose in all groups

	Group A (n=16) Mean±SD	Group B(n=16) Mean±SD	Group C(n=16) Mean±SD
Hypoxia (SaO_2)			
Before nebulization	91.6±3.0	91.7±2.4	91.9±2.6
Dose 3	95.3±3.3	94.3±3.7	96.0±3.6
Pair difference	3.8±1.7	1.6±2.8	4.8±2.5
P value 0.001	0.001	0.001	

Table-IV

Mean CS score on baseline and after 3rd dose in all groups

	Group A (n=16) Mean±SD	Group B(n=16) Mean±SD	Group C(n=16) Mean±SD
CS score			
Before nebulization	8.2±0.8	8.3±0.7	8.0±0.8
Dose 3	6.3±1.3	7.1±0.8	4.9±0.7
pair difference	2.0±1.3	1.1±0.9	3.1±1.2
p value	0.001	0.001	0.001

Group A: 1.8% Sodium Chloride solution
Group B: 0.9% Sodium Chloride solution and
Group C: 3.6% Sodium Chloride solution

Discussion:

This randomize control trial provided the opportunity to examine the management of bronchiolitis with adrenaline and saline of different tonicity. This RCT suggest that children with bronchiolitis can get relief by increasing tonicity of normal saline and adrenaline solution by nebulized form. This was a single blind randomized control study done in Paediatric Pulmonology unit of BSMMU from January 2007 to June 2008.

In this study 50% in group A i.e. 08 out of 16, in group B also 08 out of 16 and in group C 10 out of 16 were exclusively breast-fed up to 5 months. 42 cases among all groups lived in urban area and only 9 cases lived in rural area. In group A 43.7% family members, in group B 31.2% and in group C 37.5% were smokers. Cough was found in all cases but after 3rd dose of nebulization 09 children out of 16 in group A, 14 out of 16 in group B and 07 out of 16 had suffered from cough. Existing running nose or history of running nose was found in about 44%, 44% and 31% of group A, group B and group C respectively and no significant difference was found in between groups. Rhonchi was present in 87.5%, 93.8% and 75% in Group A, Group B and Group C respectively after 3rd dose of nebulization and difference was not found significant among all groups.

Mean respiratory rate decreased significantly after 3rd dose of nebulization which was 45.6±7.9/ min in group A, 47.7±10.3/min in group B and 45.8±5.2/min in group C. The mean difference of respiratory rate was not statistically significant. After 3rd dose of nebulization chest indrawing was present in about 75% in group A, about 81% in group B and 69% in group C. However, no significant difference was found in between groups. Breathing difficulty was present in about 88% case in group A, again 94% case in group B and 69% case in group C. After 3rd dose, improvement was detected in all groups but significantly higher in group C. Oxygen saturation was also significantly improved after 3rd dose of nebulization. Mean oxygen saturation was 95.3±3.3% in group A, 94.3±3.7% in group B and 96.0±3.6% in group C after 3rd dose of nebulization. CS score had also significantly improved after 3rd dose of nebulization. The

mean CS score after 3rd dose of nebulization was 6.3±1.3, 7.1±0.8 and 4.9±0.7 in group A, group B and group C respectively. Mean heart rate increased significantly after 3rd dose of nebulization which were 135.6+12.3/min in group A, 132.8+14.8/min in group B and 137.4+14/min in group C. But after 3rd dose of nebulization, the difference of mean heart rate was not statistically significant in all three groups.

Comparing the study results with the body of research done in the past in this field, certain salient differences both on terms of methodology and results were emerged. Several of the earlier studies used changes in total pulmonary resistance (TPR) to measure clinical outcome[7,8] Yet, experience suggests that TPR may not necessarily reflect the clinical status. With the use of sympathomimetic drugs if there is any reduction in FRC (functional residual capacity), simultaneously with the amelioration in airway narrowing there may be no change in measured total resistance, despite an improvement in the child's initial condition. Therefore, the measured changes in TPR may not necessarily correlate with clinical benefits. The problem of objective PFT (Pulmonary Function Test) measurement in small children further limits the use of this modality [8]. Certain authors used sedation with chloral hydrate before recording PFT in children, but this itself may affect respiratory status. Therefore, in our study we used CS score and oxygen saturation to assess the respiratory functional status and degree of distress. This score is non-invasive, have low inter-observer variation[9].

In this study relatively, low concentration i.e. up to 3.6% saline was used in order to decrease the possible negative effects of higher concentrations. The safety of an even higher concentration of 7% hypertonic saline with beta-2 agonists in cystic fibrosis patients was also documented.[5,10] Hypertonic saline not backed up with beta-2 agonists may cause bronchoconstriction especially in asthmatic patients. No such detrimental effect occurred using adrenaline and hypertonic saline mixture in our study. This is in concordance with the excellent safety profile reported by[11].

The study could not reflect weather hospital stay was reduced after therapy but still revealed data gave some promising result in terms of decreasing respiratory rate, increasing oxygen saturation and also relieving symptoms for a longer period (>8 hours). More research with higher saline concentrations and more frequent inhalation of hypertonic saline is warranted to further clarify this potential treatment modality. This treatment has an excellent safety profile.

Conclusion:

The present study concluded that nebulized normal saline with adrenaline and hypertonic saline with adrenaline were found effective in children with bronchiolitis. Nebulized hypertonic saline with adrenaline was found more effective than normal saline with adrenaline. The study only included 48 patients. Larger number of cases and multicenter trial are needed for such study. This single blind study can't rule out the chance of biasness. We could not detect RSV antigen of any patient due to economical constraint. The patients were observed only for forty eight hours due to lack of resource. So along with relieving symptoms whether the hypertonic and adrenaline solution can cut short hospital stay or not, could not be revealed through this study.

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