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Original Article

A randomized controlled study of nebulized 3% saline versus 0.9% saline with adrenaline in the treatment of acute bronchiolitis

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Abstract

Objective: The objective was to determine whether nebulized hypertonic (3%) saline with adrenaline is more effective than nebulized 0.9% saline with adrenaline in the treatment of acute bronchiolitis. **Materials and Methods:** In this randomized, double-blind, controlled study 100 patients were randomly allocated into two groups (50 patients in each group). In Group A (normal saline group), 4 ml of normal saline (0.9%) and 1 ml of 1:1,000 adrenaline was given as nebulization with oxygen flow of 6-8 L/min. In Group B (hypertonic saline group), 4 ml of hypertonic saline (3%) and 1 ml of 1:1,000 adrenaline was given as nebulization with oxygen flow of 6-8 L/min. The nebulization was given at an interval of 4 h, 6 times daily till the patient was ready for discharge. **Results:** The percentage improvement in clinical severity scores after inhalation therapy was not significant in Group A on 1st-3rd day after admission (3.4%, 2.1%, and 4%, respectively). In Group B, significant improvement was observed on these days (7.4%, 8.7%, and 9.9%, respectively, $p<0.001$). Furthermore, the improvement in clinical severity scores differed significantly on each of these days between the two groups. Using 3% saline decreased the hospitalization stay by 25%, from 3.4±1.7 days in Group A to 2.5±1.4 days in Group B ($p<0.05$). **Conclusion:** In the treatment of acute bronchiolitis, 3% saline nebulization with adrenaline decreases the length of hospitalization and symptoms as compared to 0.9% saline nebulization.

Key words: *Bronchiolitis, Hypertonic saline, Normal saline, Adrenaline*

Acute bronchiolitis is the most frequent lower respiratory infection requiring hospitalization in infants [1-3]. Peribronchial inflammation, airway edema, mucus plugging and necrosis, and desquamation of ciliated epithelial cells are the predominant pathological processes implicated in acute bronchiolitis [4]. Theoretically, any therapeutic modality which can improve clearance of airway secretions and minimize edema should be beneficial. Four such modalities that have been studied targeting the above are inhaled epinephrine, recombinant deoxyribonuclease, chest physiotherapy, and hypertonic saline [5].

Of these, hypertonic saline has recently shown some promising results, the basic premise for its use stemming from extrapolation of its benefits seen in asthma, bronchiectasis, cystic fibrosis, and sinonasal diseases [4]. It has been postulated that saline hydrates airway surface liquid, improves impaired mucociliary clearance and aids water absorption from the mucosa, thereby reducing airway edema [5]. This modality has enormous potential for cost-saving, both in developing and developed countries, more so if it could actually reduce the length of hospitalization as suggested by a recent Cochrane review [6].

We conducted this study to evaluate the efficacy of nebulized hypertonic (3%) saline in children diagnosed with clinical bronchiolitis. Limited number of studies has been published from India and abroad regarding the use of hypertonic saline with adrenaline nebulization in bronchiolitis in children.

MATERIALS AND METHODS

The present study was a randomized double-blind, controlled trial conducted at a tertiary care teaching institution of Karnataka during the period from March 2013 to January 2015. Children 1-24 months of age with a clinical diagnosis of acute bronchiolitis were enrolled. Bronchiolitis was defined by the first episode of wheezing along with prodrome of upper respiratory tract infection including rhinorrhea, cough, and sometimes low-grade fever. Children with obtunded consciousness, cardiac disease, chronic respiratory disease, previous wheezing episode, progressive respiratory distress requiring respiratory support other than supplemental oxygen, and those having received nebulized hypertonic saline or adrenaline within the previous 12 h were excluded from the study. The Institutional

Ethical Committee of our hospital approved the study. Signed informed consent was obtained from the parents of all children.

Sample size was calculated using Epi-info 06 software and sample of 100 was selected to provide 80% power and a confidence interval of 95%. Recruited children were randomly allocated into two groups (50 patients in each group) using a computer-generated random number table. In Group A (normal saline group), 4 ml of normal saline (0.9%) and 1 ml of 1:1,000 adrenaline was given as nebulization with oxygen flow of 6-8 L/min. In Group B (hypertonic saline group), 4 ml of 3% saline and 1 ml of 1:1,000 adrenaline was given as nebulization with oxygen flow of 6-8 L/min [4]. The nebulization was given at intervals of 4 h, 6 times daily till the patient was ready for discharge. Antibiotics were used in the presence of fever, high white blood cell count, infiltration on chest X-ray.

The following parameters (Table 1) were measured and recorded at admission using a clinical severity score described by Wang et al. along with pulse rate and oxygen saturation [7]. Patients were monitored for improvement or worsening of the condition using above-mentioned parameters at 12 h intervals until they were ready for discharge. Discharge criteria included feeding well orally, no need for intravenous fluids and supplemental oxygen, clinical severity score <3, absence of accessory muscle use or tachypnea (respiratory rate <31 breaths/min), and oxygen saturation >92% on room air.

Outcome Measures

Primary outcome: Length of hospital stay; secondary outcome: Improvement in clinical severity score, oxygen saturation, pulse rate, number of add-on treatment.

Statistical Analysis

All continuous variables were examined using the paired or unpaired *t*-test as appropriate. Non-continuous variables were examined using χ^2 test. The mean ± standard deviation (with 95% confidence interval) expresses the central tendency of the data. To examine the change in clinical severity score after nebulizer, paired *t*-test was carried out in each treatment groups separately. For the analysis, $p<0.05$ was considered significant.

RESULTS

Total 100 patients were included in the study with 50 cases in each group (Fig. 1). Two study groups were similar in baseline characteristics (Table 2) including age, sex, and clinical severity score.

Primary Outcome

The mean hospitalization stay was 2.9±1.6 days for the entire study group. This parameter differed significantly between two groups, being 3.4±1.7 days for Group A and 2.5±1.4 for Group B ($p<0.05$).

Secondary Outcome

The percentage fall of clinical severity score after inhalation therapy was not significant in Group A on first, second, and 3rd day after hospitalization (3.4%, 2.1%, and 4%, respectively). In Group B, significant differences were observed on each of the first 3 days (7.4%, 8.7%, and 9.9%, respectively, $p<0.001$). Furthermore, fall in clinical scores differed significantly between the two groups on each of these days. In first 3 days, there was a trend for more add-on inhalation therapy needed per day for Group A (1.1±0.9) as compared to Group B (0.9±0.7). However, it was statistically not significant ($p=0.1$). No adverse effects were observed in patients in either of the groups and no significant difference was seen in pulse rate and oxygen saturation at any time between two groups.

In Group A (0.9% saline group), 22 children received antibiotics, 5 received steroid (injectable or oral). Similarly in Group B (hypertonic saline group), 23 received antibiotics, 6 received steroid (injectable or oral). These extra additions did not have any impact on the intervention outcome, as they were all statistically not significant.

DISCUSSION

Our study shows that by substituting normal saline solution with hypertonic saline in the inhalation mixture for delivering adrenaline to hospitalized infants with viral bronchiolitis, the hospital stay was reduced by 25%, from 3.4 days in the 0.9% saline solution group (Group A) to 2.5 days in the 3% saline

Table 1: Clinical severity score

Variables	0	1	2	3
Respiratory rate/min				
<1-year	<50	50-60	60-70	>70
>1-year	<30	31-45	46-60	>60
Wheezing	None	Terminal expiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Severe with nasal flaring
General condition	Normal			Irritable, lethargic, poor feeding

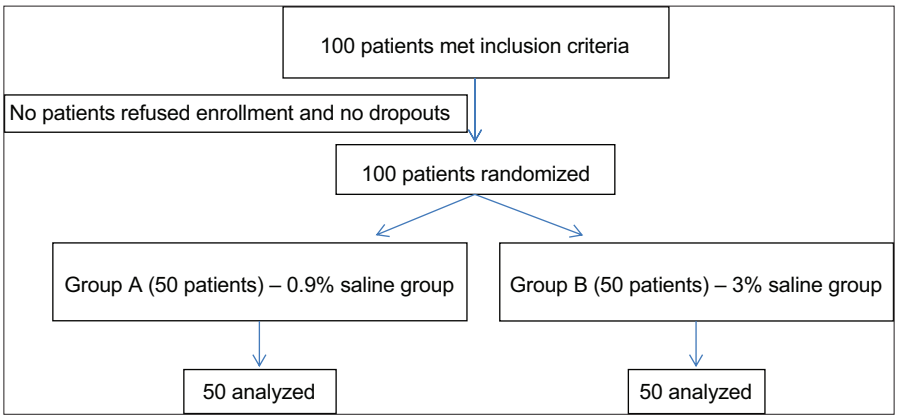

Figure 1: Participants flow diagram

Table 2: Baseline characteristics of study subjects

Characteristics	0.9% saline Group, n=50	3% saline Group, n=50	p value
Age in months	5.5±3.9	4.4±3.4	NS
Male/female	28/22	26/24	NS
Baseline severity score	8.0±1.3	8.18±1.4	NS
Baseline oxygen saturation %	92.8±2.8	91.9±2.6	NS

NS: Not significant

solution group (Group B). This possible effect could bear an important economic and clinical impact worldwide especially in developing countries. This study demonstrated a significantly better improvement in clinical severity score after adrenaline inhalation in hypertonic (3%) saline solution as compared to adrenaline in 0.9% saline solution.

Studies conducted by Grewal et al. [8], Anil et al. [9] and Sarrell et al. [10] did not show any significant advantage of hypertonic saline over normal saline in terms of improvement in clinical severity scores or hospitalization rates. This can be due to their small sample size and enrollment of cases admitted in emergency care settings. Our study was in line with the studies by Kuzik et al. [11], Mandelberg et al. [12], Luo et al. [13] and Tal et al. [14] which showed significant difference in terms of hospital stay and clinical severity scores between normal saline and hypertonic saline groups. This may be due to the enrollment of mild to moderately severe cases of bronchiolitis conducted in hospitalized patients.

Bronchiolitis is an infectious inflammation of respiratory mucosal epithelium, pronounced in small bronchioles. This leads to tissue edema and mucus production, resulting in thick mucus plaques within the airway lumen, and increase in intraluminal deoxyribonucleic acid (DNA) concentration [15]. DNA is released due to lysis of inflammatory and sloughed respiratory epithelial cells which further increases the viscosity and adhesiveness of lung secretions. In our study, possible mechanism can be an improvement in mucociliary transport and better elimination of intracellular debris leading to reduced viral load and milder ongoing inflammation within the airways. This might decrease an opportunity for secondary bacterial overgrowth and thereby may contribute to the favorable effect of decreasing the post-inhalation therapy clinical severity score.

The strength of this study was its randomized control design using standard protocol with a good match of baseline characteristics such as clinical presentation, signs on examination, and laboratory findings between 2 groups. Our study evaluated efficacy in non-critically sick admitted patients with acute bronchiolitis. Furthermore, there were no dropouts or withdrawal of patients during the study period in either group which strengthen confidence in the outcome. We used a lower concentration of hypertonic saline (i.e., 3%) in order to decrease the possible negative effect of higher concentrations (>7% saline) on ciliary beat frequency and to decrease the risk of bronchospasm. In addition, by giving hypertonic saline with adrenaline, a bronchodilator, any additional bronchoconstriction effect secondary to hypertonic saline was avoided.

Limitations of this study were patients enrolled based on clinical diagnosis and not confirmed by virological studies, the exact duration of hypertonic saline effect (half-life) and, therefore, its continuing impact on clinical parameter is not known and should be investigated further. 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

In the treatment of acute bronchiolitis, 3% saline nebulization with adrenaline significantly decreases the length of hospital stay and percentage fall of the clinical severity score as compared to 0.9% saline nebulization.

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