Original Article

Nebulised Hypertonic Saline with Salbutamol for Wheeze in Children: A Randomised, Double-blind Controlled Study

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Abstract

Background. Wheezing in children is one of the common problems in pediatrics. Recent research has shown that hypertonic saline has shown potential benefit in children with bronchiolitis.

Methods. In this randomised, double-blind controlled trial (n=72), children aged two months to eight years, presenting with wheeze were block randomised to receive salbutamol with 3% hypertonic saline (3%) (Group A) or salbutamol with normal saline (0.9%) (Group B). Wang *et al*[1] clinical severity score was used to assess severity. The primary outcome was length of stay in the hospital. Secondary outcomes were to know the adverse effects in both the groups, to assess the rate of re-admission within seven days.

Results. Between the two groups there was no statistically significant difference with respect to demographic data, risk factors studied and the underlying pathology. Salbutamol with hypertonic saline nebulisation reduces the length of stay. There was statistically significant difference in the mean number of doses of salbutamol required in both the groups (p=0.03).

Conclusions. We recommend that nebulised hypertonic saline (3%) with salbutamol to be considered more effective and safe alternative to nebulisation with normal (0.9%) saline and salbutamol. ***Trial registration***. ClinicalTrials.gov identifier number: Trial REF/2013/03/004799. **[Indian J Chest Dis Allied Sci 2016;58:237-240]**

Key words: Hypertonic saline, Normal saline, Wheeze, Salbutamol.

Introduction

Wheezing in children is a common problem encountered by pediatricians worldwide. One in every three children would have experienced an acute wheezing illness before the age of three years.[2] Though there are various causes of wheeze, bronchiolitis is the most common in children less than two years. In older age groups (>2 years), the commonest cause is transient wheezing.

The underlying pathology in all cases of wheezing is airway inflammation, mucus plugging, and bronchospasm. Till recently, normal saline (0.9%) was used as the diluting agent for salbutamol nebulisation. Recent research has shown that hypertonic saline has potential benefit over normal saline.[3] Hypertonic saline draws water and restores the liquid layer lining the airways and hydrates the secretions, improves mucus rheology and enhances mucociliary clearance.[4] It increases the beating of cilia by releasing prostaglandin E2, which reduces neutrophil chemotaxis, thereby decreasing inflammation. It also breaks the ionic bonds within the mucus gel, and thus, reduces the cross-linking and entanglements, thereby reducing viscosity and elasticity.[5]

There are many studies on use of hypertonic saline vehicle in bronchiolitis but the evidence regarding the utility of hypertonic saline as an agent of mucociliary clearance in wheeze in older children is comparatively less and is lacking in India. This study was undertaken to demonstrate the utility of hypertonic saline in wheezers of all aetiologies across all pediatric age groups.

The objective of the study was to determine the effectiveness of hypertonic saline (3%) with salbutamol nebulisation when compared with normal saline (0.9%) with salbutamol nebulisation in the treatment of wheeze in children aged between two months to eight years.

Material and Methods

This randomised, double-blind, controlled study included children aged between two months and eight years presenting to the emergency services, or out-patient department of Pondicherry Institute of Medical Sciences, Pondicherry, South India from

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October 2012 to April 2014. The study was approved by Institutional Ethics Committee (Ref No: IEC/RC/12/83) and was registered in the clinical trials.gov (Trial REF/2013/03/004799). With a level of significance of 0.05 and power 80%, the sample size was calculated to be 72 which consisted of 36 subjects each in each group (*vide infra*).

All children aged two months to eight years reporting with wheezing, having a Wang *et al*[1] score >2 were included in the study. Exclusion criteria were: children with respiratory failure requiring mechanical ventilation at admission, children with clinically apparent major respiratory tract or thoracic cage abnormalities, children with symptomatic cardiac disease.

After obtaining signed informed consent from parents, the children were block randomised (groups of 10) into Groups I and II. Group I was treated with nebulisation with salbutamol (0.4mg/kg/dose) and 2.5mL of hypertonic saline and group II was given salbutamol (0.4mg/kg/dose) with 2.5mL of normal saline.

There was no detectable difference in colour, smell, or other physical properties between 3% hypertonic saline solution and 0.9% saline solution. All children were admitted to the pediatric ward and given nebulisation as per the department protocol and monitored by the consultant in-charge and the principal investigator. All the patients received three doses of nebulisation at an interval of 20 minutes each, and thereafter, according to the standard protocol of the department.

The final diagnosis was made based on clinical presentation, complete blood count, C-reactive protein and chest radiograph that was done in selective cases. Based on this, children were categorised into wheeze associated lower respiratory tract infection or bacterial pneumonia or transient wheezers.

Parameters studied were clinical severity Wang *et al*[1] score (respiratory rate, retractions, wheeze and level of consciousness), adverse effects (tachycardia, nausea, vomiting, tremor and urinary retention), oxygen saturation (SpO_2) and oxygen requirement.

The primary outcome of interest was to estimate the length of stay (time taken for the modified Wang *et al* clinical severity score to become zero) and the secondary outcomes were adverse effects and rate of re-admission with wheeze within seven days in both the groups.

The end-point of the study was resolution of signs and symptoms; tolerating oral feeds and not requiring any further nebulisation.

Statistical Analysis

The continuous variables were expressed as mean and standard deviation. Categorical and dichotomous variables were expressed as percentages. Independent sample t-test was used to compare the means of two independent, normally distributed, sample groups. Chi-square test was used to compare two categorical variables or a categorical and a dichotomous variable. Kruskal Wallis test was used to compare more than two sample means of small and skewed groups. Mann-Whitney U test was used to compare the medians of two independent, small, and/or skewed samples. A p value <0.05 was considered to be statistically significant.

Results

Fifty-one (70.8%) children belonged to less than two years of age. The male to female ratio was 1.57:1. There was no statistically significant difference in fever, cough, intercostal retractions, fast breathing, baseline clinical severity, Wang, *et al*[1] score and baseline saturation between the two groups (Table 1).

Table 1. Comparison of baseline characteristics.

Characteristics	Group I Hypertonic Saline No. (%)	Group II Normal Saline No. (%)	p-value
Age			
<2 years	23 (63.9)	28 (77.8)	
2–5years	11 (30.6)	8 (22.2)	0.227
>5 years	2 (5.6)	0	
Sex			
Male	20 (55.6)	24 (66.7)	0.334
Female	16 (44.4)	12 (33.3)	
Cough			
<3 days	27 (75.0)	25 (69.4)	0.599
>3 days	9 (25.0)	11 (30.6)	
Fever			
<3 days	22 (61.1)	20 (58.3)	0.516
>3 days	5 (13.9)	3 (11.1)	
Baseline CSS (Wang *et al* score) (mean±SD)	3.50±1.159	3.64 ± 1.291	0.6
Baseline heart rate			
Normal	19 (52.8)	16 (44.4)	0.479
Abnormal	17 (47.2)	20 (55.6)	
Baseline SpO_2			
Normal	31 (86.1)	22 (61.1)	0.056
Abnormal	5 (13.9)	14 (38.9)	

Definitions of abbreviations: CSS=Clinical Severity Score; SpO_2=Oxygen saturation by pulse oximetry

Past history, family history, exposure to pets and firewood, smokers at home, history of atopy and food allergy and history of transient tachypnoea in newborn period showed no statistically significance difference between the two groups.

Distribution of transient wheezers, and wheeze associated lower respiratory tract infection were similar in the two groups (Table 2). The mean length of hospital stay was shorter in the 3% saline group compared to the normal saline group (p=0.05) (Figure 1). The mean oxygen requirement was similar in both the groups (p=0.84). The normal saline group required more number of doses of nebulisation when compared to the 3% hypertonic saline group (p=0.03) (Figure 2).

Table 2. Distribution of transient wheezers and wheezer based on clinical diagnosis.

Clinical Diagnosis	Hypertonic Saline (Group I)	Normal Saline (Group II)	P-value
Transient wheezers	19 (52.8%)	14 (41.7%)	
Wheeze associated lower respiratory infection	11 (30.6%)	15 (38.9%)	0.666
Bacterial pneumonia	6 (16.7%)	7 (19.4%)	
Total	**36**	**36**	

More number of children in the normal saline group had tachycardia compared to 3% hypertonic saline group; however, this difference was not statistically significant (p=0.31). No other adverse effects were noted in both the groups. None of the children were re-admitted with same complaints within seven days in both the groups. The sub-group analysis of length of stay with respect to clinical diagnosis did not show any statistically significant difference between the two groups.

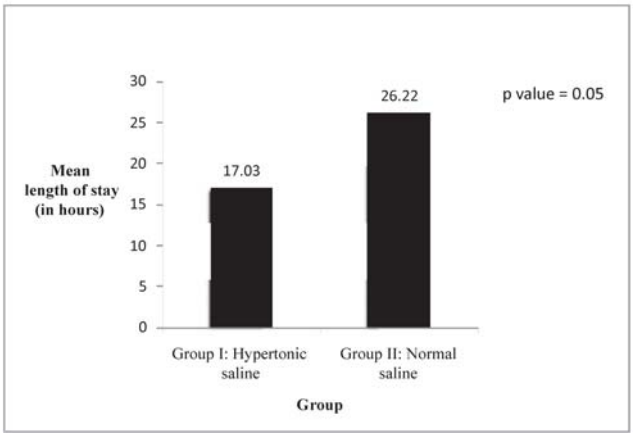

Figure 1. Comparison of mean length of hospital stay among both the groups.

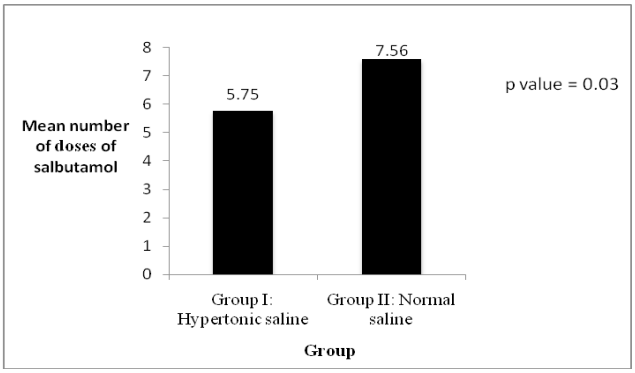

Figure 2. Comparison of salbutamol requirement among both the groups.

Discussion

Our study has shown that adding 3% hypertonic saline to salbutamol instead of normal saline (0.9%) significantly reduces the length of hospital stay by a mean of 9.18 hours. Similar benefit was found in other studies done on children with bronchiolitis.[6-10]

The mean number of doses of salbutamol required for clinical improvement was significantly lower in the 3% hypertonic saline group than the normal saline (0.9%) group, without causing adverse effects like tachycardia and worsening of bronchospasm (p=0.03). Sparse data are available in the literature that has studied the number of doses of salbutamol required for the cessation of wheeze in children.

We observed that 45.8% of the children had past history of wheezing as a risk factor. Our study shows that even in children with risk factors of previous wheeze and recurrent transient wheezers, hypertonic saline (3%) is better compared to normal saline (0.9%). Sparse published data are available in the literature comparing the efficacy of hypertonic saline (3%) in transient wheezers. But a study[11] comparing nebulised salbutamol with either hypertonic saline (5%) or normal saline for pre-school wheezing revealed that hypertonic saline group had lesser admission rate and length of stay.

Most studies in the literature have studied the effect of nebulised hypertonic saline (3%) on children with viral bronchiolitis. But there has been a paucity of studies assessing the role of hypertonic saline nebulisation in the management of wheeze due to various causes like wheeze induced by pneumonia and transient wheezer.

The recent meta-analysis[3] done on infants with a diagnosis of acute bronchiolitis, which included 11 trials (1090 infants) has also shown that the patients had a significantly shorter mean length of hospital stay compared with 0.9% saline with a pooled mean difference of -1.15 days (p<0.00001). This result could have an essential clinical impact that is to change the protocol to use hypertonic saline as the vehicle for salbutamol in the management of wheeze instead of normal saline. This reduction in the mean length of stay is beneficial for the child's family both in terms of convenience and economic benefit.

In our study, all the children recovered well in both the groups with no treatment failure or

significant adverse effects following nebulisation like worsening of bronchospasm or tachycardia.

One of the main limitations of the study is that all these children had mild to moderate disease severity, so these findings cannot be generalised to children with severe wheeze. It would have been ideal to have a placebo group while comparing treatments (hypertonic saline *versus* normal saline). But due to ethical considerations, it was not done. Due to lack of facilities to arrive at a virological diagnosis, the categorisation of children was based on clinical criteria. The exact duration of the effect of hypertonic saline (half-life) and its impact on clinical parameters has not been studied was another limitation of the study.

Conclusions

Our observations suggest that nebulised hypertonic saline (3%) along with salbutamol reduced the mean length of stay by nine hours and had significantly reduced the total number of doses of nebulisation when compared with normal saline (0.9%) with salbutamol among children hospitalised with wheeze. With the above two clinically relevant and significant benefits and excellent safety profile, we recommend that nebulised hypertonic saline (3%) with salbutamol as bronchodilator, be considered as an effective and safe treatment for children with wheeze.

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