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ORIGINAL ARTICLE

A COMPARATIVE STUDY TO ASSESS THE EFFECTS OF NEBULISED 3% HYPERTONIC SALINE, 0.9% NORMAL SALINE AND SALBUTALMOL IN MANAGEMENT OF ACUTE BRONCHIOLITIS AMONG INDIAN CHILDREN

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ABSTRACT: AIMS AND OBJECTIVES: To compare the effects of nebulised 3% hypertonic saline, 0.9% saline and salbutamol in patients of acute bronchiolitis. **DESIGN:** Randomised controlled trial. **SETTING:** tertiary care teaching hospital. **MATERIAL AND METHODS:** 100 Children with age 1 to 24 months admitted in hospital with clinical diagnosis of acute bronchiolitis for 2 consecutive years were included in the study. Participants were divided into 3 groups –3% hypertonic saline (HS), 0.9% normal saline and salbutalmol. 4 doses of nebulisation at an interval of 6 hours were given daily in each group till discharge. **RESULTS:** The mean age of the patients in the study population was 5.7 ± 3.4 months. Maximum number of the patients i.e. 65.7% belonged to the age group of 0-6 months. There was male preponderance in all 3 groups. Baseline Clinical Severity (CS) scores in 3%HS, 0.9% Normal Saline and Salbutamol groups were 5.9±1.5, 5.5±1.0 and 5.1±2.3 respectively (p=0.146). After treatment, the CS scores dropped to 1.0±1.1, 3.3±0.5 and 1.9±1.1 in 3%HS, 0.9% Normal Saline and Salbutamol groups respectively on the 3rd day of treatment (p<0.01). Length of hospital stay in 3% HS, 0.9% Normal Saline and Salbutamol groups was 3.4±1.7, 4.9±1.4 and 3.7±1.9 days respectively, which was found to be statistically significant (p= 0.001). **CONCLUSION:** 3% Hypertonic Saline nebulization (without additional bronchodilators) is an effective and safe treatment in patients of acute bronchiolitis. It significantly reduces the CS scores and length of hospital stay as compared to 0.9% Normal Saline and Salbutamol nebulizations.

KEYWORDS: 3 % hypertonic saline nebulisation, clinical score, bronchiolitis, management.

INTRODUCTION: Bronchiolitis is regarded as the most common lower respiratory tract infection among infants in both developed and developing countries.[1] The reported attack rates in western literature are as high as 11.6 per 100 children in the first year and 6 per 100 children in the second year of life.[2] Mortality rate is as high as 0.5-1.5% in hospitalized patients, increasing to 3-4% for patients with underlying cardiac or pulmonary disease.[3] In our country too, it is a significant problem judging by the frequency of wheezing episodes among young infants, though it is difficult to routinely identify the causative virus (es).[4]

Acute bronchiolitis usually occurs following exposure to a patient with minor respiratory symptoms within the previous week. Infant first develops a mild upper respiratory tract infection with sneezing and rhinorrhea. This is followed by decreased appetite and moderate grade fever. After a few days respiratory distress ensues. The infant is often tachypneic, which may interfere with feeding. The physical examination is characterized most prominently by wheezing, prolonged expiration, fine rales and rhonchi. The work of breathing increases characterized by nasal flaring,

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intercostal and subcostal retractions, hyperexpansion of chest, restlessness and peripheral cyanosis[5]. Most of the infants show improvement within 3 – 4 days after the onset of the disease.[3]

The diagnosis is usually a clinical one and investigations are not generally needed to confirm it. However, confirmation of RSV infection can be made by Enzyme linked Immunofluorescence Assay (ELISA) and fluorescent antibody techniques for detection of the viral antigen, amplification of the virus using the shell vial method and amplification of viral genome by Polymerase Chain Reaction (PCR) or viral culture[6]. A Rapid Test using monoclonal antibodies against RSV on nasopharyngeal aspirates can identify RSV by the bedside.[3]

Management of bronchiolitis is often frustrating for physicians and care-givers because 'nothing seems to work' in most cases.[4] There is lack of robust evidence for almost all the interventions that are usually tried including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. Some experts have questioned whether bronchiolitis can be treated at all and current research data is far from adequate to draw definite conclusions. It has been suggested that hypertonic saline nebulization may be useful in making secretions less viscous and promoting their excretion, thereby resulting in clinical improvement.

Despite the lack of sufficient data, many physicians use this, though sometimes more for psychological than clinical benefit. Against such a background, it is relevant to ask the clinical question, "In infants with bronchiolitis (population), does hypertonic saline nebulization (intervention) result in better clinical response (outcome) compared to no intervention or nebulization with normal saline (comparison)".[4] A few studies have been done to see the effectiveness of 3% hypertonic saline nebulization in acute bronchiolitis. A recent Cochrane review showed that nebulized 3% HS may significantly reduce the length of hospital stay among infants hospitalized with non-severe acute viral bronchiolitis and improve the CS score in both outpatient and inpatient populations and no significant adverse effects related to hypertonic saline inhalation were recorded.[7]

We carried out this study with the primary objective of finding out the effectiveness of 3% HS nebulization and comparing it with Normal Saline and Salbutamol nebulization in acute bronchiolitis among Indian children.

METHODS: This prospective study was conducted on one hundred children admitted in the Pediatrics Department of Govt. Medical College, Amritsar with the diagnosis of acute bronchiolitis from October 2012 to February 2014. All children aged 1-24 months with clinical diagnosis of acute bronchiolitis with a CS score of more than 3 were included in the study. Children with chronic cardiopulmonary disease viz congenital heart disease, cystic lung disease etc., preterm birth or history of mechanical ventilation in the neonatal period, family history of asthma and critical illness at presentation suggesting incipient respiratory failure were excluded. A written and informed consent was taken from the parents on a prescribed format. The study was approved by the ethical committee of Govt. Medical College, Amritsar.

The data of all the cases was recorded on a predetermined proforma. The diagnosis of acute bronchiolitis was clinical, based on the history and physical examination. The severity of the illness was assessed by using CS score described by Wang et al.[8]

The children were assigned randomly in sequential manner to three groups designated as A, B and C.

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1. Children in group A were nebulized with 4ml of 3% Hypertonic Saline (HS) with oxygen flow rate of 8L/min.
2. Children in group B were nebulized with 4ml of 0.9% Normal Saline (NS) with oxygen flow rate of 8L/min.
3. Children in group C were given nebulized Salbutamol (0.15mg/kg) using oxygen flow rate of 8L/min.

Four doses at interval of 6 hours each were given daily till discharge. CS scores were recorded before and 30 min after first nebulization at the time of admission and then once every morning before and 30 min after first nebulization of the day till 3rd day of admission.

CRITERIA FOR DISCHARGE:

1. C.S score of <3.
2. Child feeding well.

STATISTICS: Two major outcomes of interest were considered i.e., change in the CS score after 3%HS, 0.9% NS and Salbutamol inhalation every day and length of hospital stay.

As patients under study were from the same environment and factors affecting an individual to suffer from this disease were the same, the data was homogenous for the study. Therefore, we used the Complete Randomized Design (CRD). One way ANOVA technique under CRD was used to compare the average CS score and length of hospital stay before and after giving the specific treatment among the three groups. Observed level of significance (p-value) was compared with the theoretical level of significance (α-value). Post Hoc analysis was also performed to test the pair wise significance of the average scores under study. To check the significance of the average CS score in individual therapy on the assigned group, paired t test was applied. Significance of difference between males and females was analyzed using Chi- square test and p value was obtained.

RESULTS: The study groups were similar in baseline characteristics (Table 1) including age, sex and CS score.

PATIENT DEMOGRAPHICS AND ILLNESS STATUS AT THE BASELINE:

Clinical Characteristics	Group A (3% Hypertonic Saline)	Group B (0.9% Saline)	Group C (Salbutamol)
Age (months)	6.03±3.71	5.69±3.34	5.48±3.35
% Male	66.7	75.8	66.7
Baseline CS * Score	5.9±1.5	5.5±1.0	5.1±2.3
Duration of illness before study entry (Days)	2.2±1.1	2.9±1.3	3.0±1.3

TABLE 1: Shows baseline clinical characterstics

*Clinical Severity.

One patient in Group A was excluded from the analysis because the parents refused to give consent to participate in the study. The mean age of the patients in the study population was 5.7 ± 3.4 months. Maximum number of the patients i.e. 65/99 (65.7%) belonged to the age group of 0-6 months. In the present study, 69.7% of the patients were males and 30.3% were females The Male: Female ratio was 2.3: 1.

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3% HS nebulization caused a significant reduction in the CS scores, as compared to 0.9% Saline nebulization and salbutamol nebulization. The baseline CS scores in 3%HS, 0.9%Saline and Salbutamol groups were 5.9±1.5, 5.5±1.0 and 5.1±2.3 respectively (p=0.146). After giving treatment the CS scores dropped to 1.0±1.1, 3.3±0.5 and 1.9±1.1 in 3%HS, 0.9%Saline and Salbutamol groups respectively on the 3rd day of treatment (p<0.01). Further Statistical analysis revealed that the fall was maximum in 3% HS group followed by Salbutamol group (TABLE 2).

COMPARISON OF CS SCORES BEFORE AND 3 DAYS AFTER TREATMENT:

		Before treatment				After treatment			
Treatment	**N**	**Mean**	**Std. Dev.***	**F****	**P value**	**Mean**	**Std. Dev.***	**F****	**p value**
Group A (3% Hypertonic Saline)	33	5.9	1.5	1.96	0.146	1.0	1.1	49.46	<0.01***
Group B (0.9% Saline)	33	5.5	1.0			3.3	0.5		
Group C (Salbutamol)	33	5.1	2.3			1.9	1.1		

TABLE 2

*standard deviation; **The F statistic determines if the variation between sample means is significant; *** Highly significant; α= 0.05.

Length of hospital stay in 3% HS, 0.9% Saline and Salbutamol groups was 3.4±1.7, 4.9±1.4 and 3.7±1.9 days respectively, which was found to be statistically significant (p= 0.001). 3% HS reduced the length of stay by as much as 30.6% when compared with Normal Saline group. The reduction in length of stay with Salbutamol nebulization was also as much as 24.5% (TABLE 3).

LENGTH OF HOSPITAL STAY ACCORDING TO TYPE OF TREATMENT IN EACH GROUP:

		Length of hospital stay (days)			
Treatment	**N**	**Mean**	**Std. Deviation**	**F**	**p value**
Group A (3% Hypertonic Saline)	33	3.4	1.7	7.77	0.001*
Group B (0.9% Saline)	33	4.9	1.4		
Group C (Salbutamol)	33	3.7	1.9		

TABLE 3

* Significant

DISCUSSION: Nebulized 3% hypertonic saline (HS) is a new modality of treatment for acute bronchiolitis. It helps in reversing the pathophysiology of acute bronchiolitis by hydrating the Airway Surface Liquid (ASL) and improving mucus clearance by ciliary and cough actions. It also improves mucus rheology by breaking the ionic bonds within the mucus gel. This in return reduces the degree of cross-linking and entanglement. It increases ciliary beat frequency via the release of Prostaglandin E_2 and it absorbs water from the mucosa and sub mucosa because of its higher ionic concentration.

The edema of the airway wall is thus reduced. With bronchodilators having no proven effect on course of acute viral bronchiolitis, it is currently recommended that they should not be routinely used in management of this condition.[9] Search for an alternative like 3% HS or 0.9% normal saline alone has led to various studies as described above. Hence, this study was planned.

The mean age of the patients in our study population was 5.7± 3.4 months, the youngest being 2 months and the oldest being 14 months. Most of the children (65.7%) presented in the first six months of age. This is in accordance with the peak age of presentation of acute bronchiolitis[10].The mean age observed in similar studies by Sarrell et al is 12.5±6 months (Range, 3 to 24 months),[11] Mandelberg et al is 2.9±2.1 months (range, 0.5 to 12 months),[12] Guy Tal et al is 2.6±1 months (range, 1-5 months)[13] and by Kuzik et al is 4.7±4.2 months (Range, 10 days to 18 months).[14]

In our study, 69.7% of the patients were males and 30.3% were females. The male: Female ratio was 2.3:1. The male: female ratio in 3%HS, 0.9% Saline and Salbutamol groups were 2:1, 3.1:1 and 2:1 respectively. Thus, males were more affected than females. Similar findings have been reported by Som et al. in their study of ninety one children, 71% were males and 29% were females.[2] Kuzik et al also observed a slight male preponderance (62.5%).[14] The high incidence of acute bronchiolitis in males as compared to females may be attributed to presence of two X chromosomes which provide greater genetic diversity to the female immunologic defences.[15] It could also be due to greater health care seeking attitude of parents towards the male child in the Indian Subcontinent.

In our study the mean duration of illness before enrolment in 3% HS, 0.9% Saline and Salbutamol group was 2.2±1.1, 2.9±1.3 and 3.0±1.3 days respectively. The mean duration of illness before study entry observed by Mandelberg et al was 3.0±1.6 days in 0.9% Saline Group and 3.9±2.9 days in 3% HS Group,[12] by Guy Tal et al it was 4.5±2.2 days in 0.9% Saline Group and 4.0±2.2 days in 3% HS Group[13] and as reported by Kuzik et al it was 4.0±2.4 days in 0.9% Saline Group and 4.5±2.3 days in 3% HS Group.[14]

Our study demonstrated that 3% HS nebulization caused a significant reduction in the CS score, as compared to 0.9% Saline nebulization and Salbutamol nebulization. There was 82.57%, 40% and 61.89% reduction in the CS scores in 3% HS, 0.9% Saline and Salbutamol groups respectively. Thus, the effect of treatment was evident as a significant fall in CS scores in all the three groups. However, comparison in the CS scores by Post Hoc analysis showed that the difference was much greater in 3% HS group as compared to 0.9% Saline and Salbutamol groups.

Sarell et al in a study of 70 patients with mild to moderate bronchiolitis on an outdoor basis concluded that in non-severely ill ambulatory children with bronchiolitis, nebulized 3% HS plus terbutaline is more effective in decreasing symptoms as compared to 0.9% normal saline plus terbutaline.[11] Mandelberg et al in a study of 53 patients hospitalized with viral bronchiolitis concluded that in non – asthmatic non-severely ill patients with acute bronchiolitis, nebulized 3%HS (with epinephrine) decreases the symptoms significantly.[12] In 2013, a Cochrane review was done with objectives to assess the effects of nebulised HS solution in infants with acute viral bronchiolitis. They included 11 trials involving 1090 infants with mild to moderate acute viral bronchiolitis (500 inpatients, five trials; 65 outpatients, one trial; and 525 emergency department patients, four trials). They concluded that nebulised 3% HS may significantly reduce the length of hospital stay among infants hospitalized with non-severe acute viral bronchiolitis and improve the CS score in both outpatient and inpatient populations and no significant adverse effects related to HS inhalation were recorded.[7]

It is possible that 3% HS through an improvement in mucociliary transport and a better elimination of intracellular debris may have reduced viral load and decreased ongoing inflammation within the airways. This might have also reduced an opportunity for secondary bacterial overgrowth and thereby contributed to the more favorable effect of decreasing post inhalation therapy CS scores. In our study, the mean duration of hospital stay was 3.4±1.7, 4.9± 1.4 and 3.7±1.9 days in 3% HS, 0.9% Saline and Salbutamol groups respectively.

The difference in Length of hospital stay between three groups was found to be statistically significant (p= 0.001). Post Hoc analysis showed that length of stay was significantly reduced in 3%HS and Salbutamol Groups. In fact the length of stay was reduced by as much as 30.6% in 3%HS Group and 24.9% in Salbutamol Group as compared to 0.9% Saline Group. A similar significant reduction in the length of hospital stay in HS groups in combination or alone, has been observed by various other authors.

Mandelberg et al observed a mean duration of hospital stay of 3±1.2 and 4±1.9 days in 3%HS (with epinephrine) and 0.9% Saline (with epinephrine) groups respectively which was significant ($p<0.05$) and there was 25% reduction in length of hospital stay.[12] Guy Tal et al observed a mean duration of hospital stay of 2.6±1.4 and 3.5±1.7 days in 3%HS (with epinephrine) and 0.9% Saline (with epinephrine) groups respectively which was significant ($p<0.05$).[13] Kuzik et al observed a mean duration of hospital stay of 2.6±1.9 and 3.5±2.9 days in 3%HS and 0.9% Saline groups respectively. Infants in HS group had a clinically relevant 26% reduction in length of hospital stay ($p<0.05$).[14] Luoz et al observed a mean duration of hospital stay of 6±1.2 and 7.4±1.5 days in 3%HS (with Salbutamol) and 0.9% Saline (with Salbutamol) groups respectively which was also statistically significant ($p<0.05$).[16] Our study has similar observations on hospital stay.

Thus, we conclude that 3% HS nebulization (without additional bronchodilators) is an effective treatment in patients of acute bronchiolitis. It significantly reduces the CS scores and length of hospital stay as compared to 0.9% Saline and Salbutamol nebulizations. The economic benefit of this comparably priced modality of treatment can be enormous in terms of hospital costs with parents returning to work sooner.

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