Efficacy of Nebulisation with 3 % (Hypertonic Saline) vs 0.9 % (Normal Saline) in the Treatment of First Episode of Wheeze in Children <18 Months- A Randomized Controlled Study

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ABSTRACT

BACKGROUND

Nebulised hypertonic saline for bronchiolitis is becoming a popular modality in the treatment of bronchiolitis. Definite guidelines in the management of bronchiolitis are still lacking. We wanted to compare the efficacy of nebulized 3% saline versus nebulized normal saline (0.9%) when used with levosalbutamol in infants <18 months, hospitalized with first episode of wheeze.

METHODS

This is a randomized controlled study conducted in a tertiary care setting, over a period of one year, among infants <18 months of age, who presented with 1st episode of wheezing, meeting the clinical diagnostic criteria for bronchiolitis. The Respiratory Distress Assessment Instrument (RDAI) score was calculated at admission and regular intervals. The duration from enrollment to readiness for discharge was recorded. Infants were considered as fit to discharge when the RDAI becomes zero.

RESULTS

In this group of 72 infants, the pre inhalation mean RDAI score was 3.8 as compared to post inhalation score of 3.1 in the normal saline group and 4.2 and 3.1 respectively in the hypertonic saline group. Though both the groups showed a statistically significant clinical improvement (p=0.000) in terms of RDAI scoring at the end of one hour, the improvement was substantially more in case of hypertonic saline nebulisation (mean difference 1.1) compared to normal saline (mean difference 0.7). Hence patients receiving hypertonic saline nebulization had better improvement in terms of RDAI scoring at the end of I hr.

CONCLUSIONS

Hypertonic saline nebulisation is a better alternative to normal saline for nebulisation in children <18 months of age with first episode of wheeze.

KEY WORDS

Bronchiolitis, Hypertonic Saline, Nebulisation, RDAI Scoring

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BACKGROUND

Acute bronchiolitis is the most commonly encountered respiratory infection in infants. In most cases the etiology is viral, the commonest organism being the respiratory syncytial virus (RSV). the less common pathogens include parainfluenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and Mycoplasma pneumoniae (M. pneumoniae).[1-3] Infants are commonly affected by RSV within the two years of age, involving the lower respiratory tract in 40% to 50% develop. A small percentage, about 1% to 2% develop severe disease requiring hospitalization.[4] Infant first develop a mild upper respiratory tract infection with prodromal symptoms of sneezing and rhinorrhea. This is followed by moderate grade fever. After a few days respiratory distress may set in. The infant is often tachypneic with increased work of breathing, which may interfere with feeding. The physical examination is characterized mostly by wheezing, prolonged expiration, fine rales and rhonchi. The increase in work of breathing is characterized by nasal flaring, intercostal and subcostal retractions, emphysematous chest, restlessness and peripheral cyanosis. Most of the infants may show symptomatic improvement within 3–4 days after the onset of the disease but those who don't will require hospitalisation and care to avoid worsening of the clinical condition

The disease severity is usually categorised by clinical findings or by the need for health care facilities. The management of bronchiolitis in the past decade reflects that of asthma treatment, however, none of the medication used for asthma treatment is really beneficial in bronchiolitis. There is lack of convincing evidence for almost all the interventions that are usually tried including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. The standard treatment for acute bronchiolitis remains supportive care including adequate oxygen exchange, fluid intake and feeding of the infant. 0.9% saline nebulisation therapy has been current standard of care of bronchiolitis. Novel therapies like hypertonic saline and nebulized epinephrine have been found to be promising in studies. Use of hypertonic saline for nebulization in infants with bronchiolitis is a relatively inexpensive treatment but the potential economic and social gain is enormous. Hypertonic saline may be beneficial and is less toxic than many of the over the counter preparations prescribed for children with bronchiolitis. It increases mucociliary clearance in normal people and patients with asthma, bronchiectasis, cystic fibrosis and sino-nasal diseases. Similar benefits would also be expected in infants with acute bronchiolitis.[6] Other postulated mechanisms of benefit include increasing osmotic flow into mucus layer and improving the clearance of mucus, breaking ionic bonds thus lowering viscosity of mucus and stimulating ciliary beat.

METHODS

A randomized controlled study was conducted in the PICU & PSCU of KIMS (Kerala Institute of Medical Sciences), a tertiary care hospital in South Kerala. Over the study period of one year, all children below the ages of 18 months, who presented to the Emergency Department or out-patient department with a first episode of wheezing, and fitting into the clinical diagnostic criteria for bronchiolitis (as defined by our inclusion/exclusion criteria–vide infra) were enrolled in the study. The diagnosis of bronchiolitis is a clinical one based on history and physical examination. Bronchiolitis is defined as 'a seasonal viral illness characterized by fever, nasal discharge and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high pitched expiratory wheeze.[6]

After taking well informed consent, focused history was obtained from the parents with regards to the Demographic Characteristics, Symptomatology of disease, risk factors for severity, risk factors for asthma and few pertinent exclusion criteria. The Clinical condition, Temperature, Respiratory Rate, Work of Breathing, Heart Rate, spo2 and Presence/absence of Clinical Dehydration and Assessment using the RDAI Scoring was done. Then the child was randomized to either of the groups. Randomization method: Patients were categorized into 2 intervention groups, each of 10 patients using a block Randomization method. The randomization process was done by the Statistician and he was be the only person to have access to the codes. The Study solutions were 'masked' by the pharmacy.

All infants who meet the inclusion criteria of bronchiolitis received three sessions of nebulization, each episode with 2.5 ml of Levosalbutamol (bronchodilator) diluted in 2.5ml of either 0.9% Normal Saline or 3% hypertonic Saline (study solution) and delivered 20 minutes apart. Infants were observed at presentation and 30 minutes after the three nebulisations. The nebulisations were continued 4 hourly for 48 hours and the children were assessed using a respiratory scoring system by the attending physician every 8 hours before nebulisation Trial medications were be delivered through a nebulizer with a firm face mask by pressurized oxygen with a flow rate set at 8 L/min Clinical response to the treatment was assessed based on the RDAI (respiratory distress assessment index) Scoring system.[7,8,9] A child was considered fit for discharge, when the clinical severity scoring? RDAI becomes <0. This applied even in cases where actual discharge from hospital is delayed for logistical or social reasons. (clinical improvement was estimated based on a decrease in RDAI scoring). Patients were withdrawn from the study if oxygen saturation fell below 85% on room air or if found clinically deteriorating (scoring >9), and adequate respiratory support including invasive ventilation was given.

Statistical Analysis

40-60 % infants with bronchiolitis have symptoms of lower resp tract warranting nebulisation. With an expected difference in symptom relief between the two arms and alpha error of 0.05 and beta error of 0.2, the number of babies allotted to each arm was calculated as 35. The decrease in RDAI score was compared using Z scores and duration of "fitness for discharge" tested using paired t test using SPSS software version 17. The results are presented as Mean+/ (standard deviation) and 95% confidence intervals.

Ethics

Informed consent was taken from the parents and Institutional consent was obtained for use of patient data

The study was given approval by the Scientific and Ethical Committee of the institute.

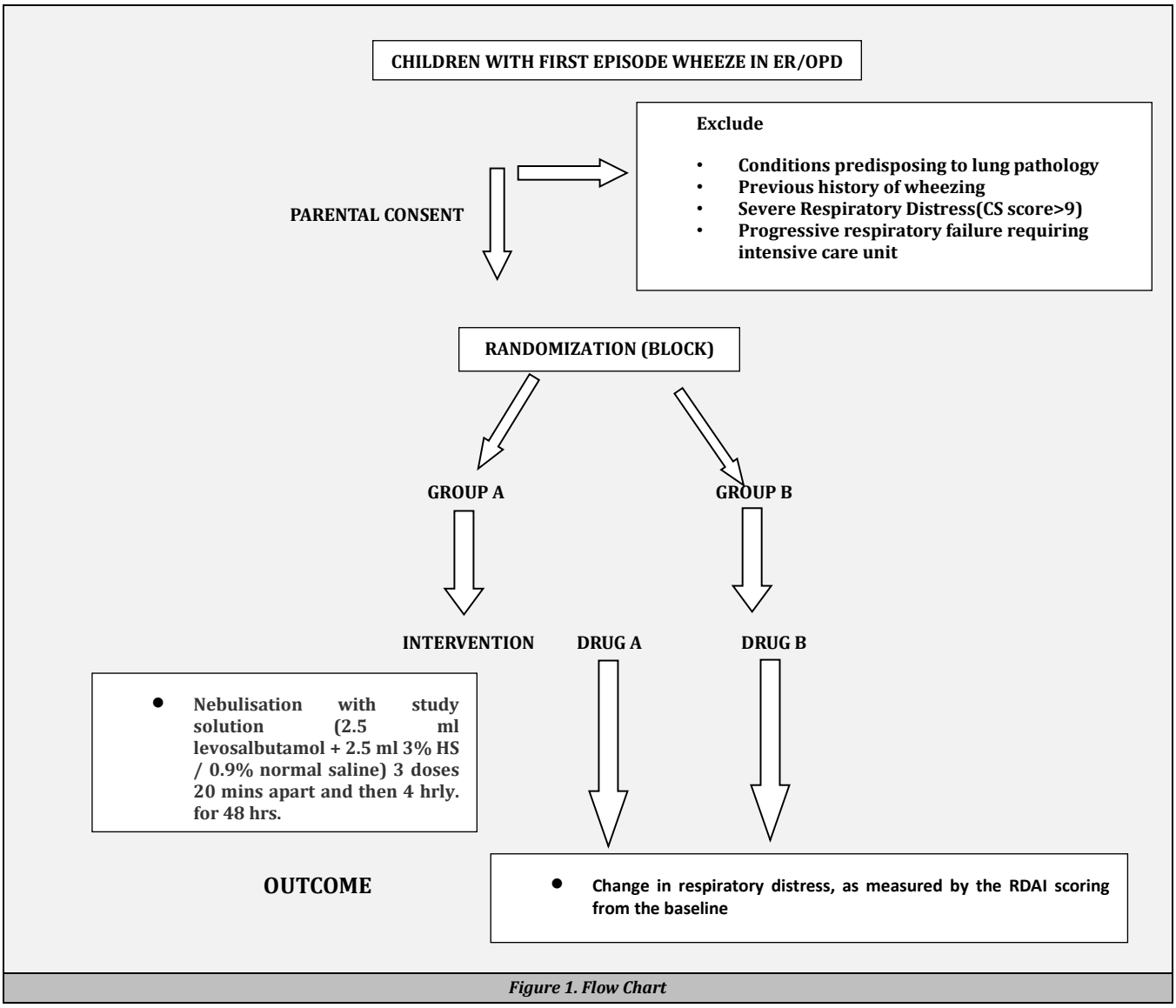

Figure 1. Flow Chart

RESULTS

72 infants < 18 months were enrolled in our study, 46 (63.8% belonging to the age < 5 months and 26 (36.1%) > 5 months. They were randomized to the normal saline group and the hypertonic saline group. The mean age in the normal saline group was 4.8 months and that in the hypertonic saline group was 4.5 months respectively. 5.6% of the infants in the normal saline group and 13.9% in the hypertonic saline group were born preterm. A positive family for wheezing was documented in 39% in the normal saline group and in 31 % of the hypertonic saline group. All the infants considered in the study had a HR and SpO2 in an acceptable range for the age group. In our study, we observed that the pre inhalation mean RDAI score was 3.8 as compared to post inhalation score of 3.1 in the normal saline group and 4.2 pre-inhalation score and 3.1 post inhalation in the hypertonic saline group (table 3). Though both the groups showed a statistically significant clinical improvement (p=0.000) in terms of RDAI scoring at the end of one hour, the improvement was substantially more in case of hypertonic saline nebulisation (Mean Difference 1.1) compared to Normal Saline (mean difference 0.7) We also observed that the mean hours of hospital stay was shorter in the normal saline group 23.4 hours as against 17.8 hrs. in the hypertonic saline which was statistically significant (p= 0.045) (table 4)

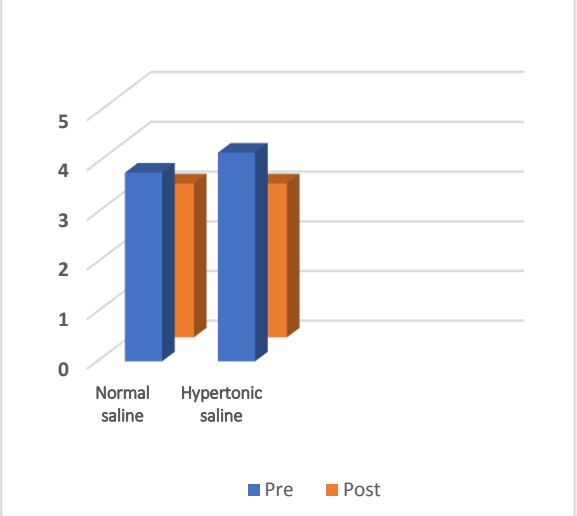

Figure 2. Effectiveness Based on RDAI at the End of 1 Hour in Both Groups

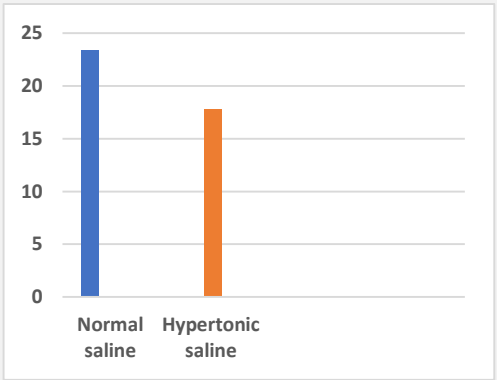

Figure 3. Comparison of Mean Hours of Hospital Stay

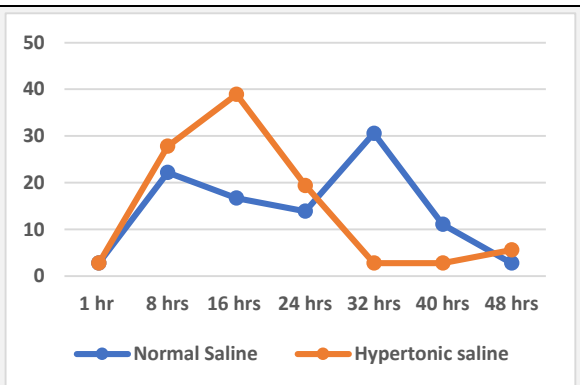

Figure 4. Comparison of Distribution of Time of Discharge

Parameter	Score 0	Score 1	Score 2	Score 3
RR	<40/mt	40-60/mt	60-70/mt	>70/mt
Accessory muscle	None	One	Two	Three or more
Cyanosis	Pink in room air/ No cyanosis	Cyanosed when crying	Pink with O_2 or Cyanosed in room air	Cyanosed with O_2 or Cardiorespiratory arrest
Auscultation	Normal	AE decreased No rhonchi	AE decreased Rhonchi +	Silent Chest

Table 1. Respiratory Distress Assessment Scoring (RDAI Scoring)[7,8,9]

Baseline Data	Normal Saline Nebulisation (n= 36)	Hypertonic Saline Nebulization (n= 36)
Mean age in months (±SD)	4.8 ± 3.6	4.5 ± 2.9
Male Female	23 (63.9 %) 13 (36.1%)	23 (63.9 %) 13 (36.1%)
Pre -Term Term	2(5.6%) 34(94.4%)	5(13.9%) 32(86.1%)
Positive family history Negative family history	14 (38.9%) 22(61.1%)	11 (30.6%) 25(69.4%)
Presenting complaints: Nasal Discharge Cough Fever Breathing difficulty Poor feeding	 23(63.9%) 34(94.4%) 12(33.3%) 24(66.7%) 9(25%)	 23(63.9%) 33(91.7%) 17(47.2%) 26(72.2%) 8(22.2%)
Adverse effects	0(0%)	0 (0%)

Table 2. Characteristics of Study Subjects

Group	Stage	Mean	SD	Mean Difference	Paired t	p
Normal saline n = 36	Pre	3.8	1.3	0.7	5.56**	0.000
	Post	3.1	1.3			
Hypertonic saline n = 36	Pre	4.2	1.2	1.1	8.91**	0.000
	Post	3.1	1.3			

Table 3. Effectiveness Based on RDAI at the End of 1 Hour in Both Groups

Group	Mean	SD	n	T	p
Normal saline n = 36	23.4	12.2	36	2.04*	0.045
Hypertonic saline n = 36	17.8	10.8	36		

Table 4. Comparison of Hour of Discharge (Mean Hours of Hospital Stay)

* Significant at 0.05 level

Hour of Discharge	Normal Saline		Hypertonic Saline	
	Count	Percent	Count	Percent
1 hr.	1	2.8	1	2.8
8 hrs.	8	22.2	10	27.8
16 hrs.	6	16.7	14	38.9
24 hrs.	5	13.9	7	19.4
32 hrs.	11	30.6	1	2.8
40 hrs.	4	11.1	1	2.8
48 hrs.	1	2.8	2	5.6

Table 5. Comparison of Distribution of Time of Discharge

DISCUSSION

Bronchiolitis is one of the most common conditions requiring hospital admission in infants. In spite of being so common, there are no definite guidelines for the treating this condition. standardization of inpatient management would be desirable. The main stay of treatment is supportive care. Infants with respiratory distress should be hospitalized and treated with supplemental oxygen and hydration if needed. Studies have evaluated the effectiveness of Beta-2 agonist bronchodilators in the treatment of bronchiolitis and found no effect on hospital admission rates and duration of hospital stay. So Beta 2 bronchodilators should not be routinely used in the routine management of bronchiolitis [10,11]. A trial of bronchodilators maybe used initially as bronchiolitis may be difficult to be differentiated from Asthma especially in bigger infants[12,13] There is substantial practice variations, both within centers and across geographic regions reflecting the absence of clear consensus on the treatment of bronchiolitis.[14,15]

As airway edema and mucus plugging are the predominant pathological features in acute bronchiolitis, any therapeutic modality which can reduce these pathological changes and improve the clearance of airway secretions may be beneficial. Hypertonic saline solution has been shown to increase mucociliary clearance in normal patients and sinopulmonary diseases. Such benefits would also be expected in infants with acute bronchiolitis.[3]

The postulated mechanisms of benefit are as follows

1. Hypertonic saline induces an osmotic flow of water into the mucus layer, improving mucus clearance by rehydrating the airway surface liquid.[6]
2. Hypertonic saline breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion.[6]
3. Hypertonic saline stimulates cilial beat by activating the release of prostaglandin E2.[6]

Moreover, by absorbing water from the mucosa and submucosa, hypertonic saline solution helps reduce edema of the airway wall in infants with acute bronchiolitis.[5,6] Substitution of higher concentrations of saline for nebulization has shown benefit., The objective of this study was to compare not only the Length of hospital stay but also the daily patient clinical parameters, thereby allowing comparisons with and also assessment of the recommendations for saline nebulisation. We enrolled 72 infants in our study, belonging to an average age group of 5 months. Of the 72 children 36 were randomized to the normal saline group and 36 to the hypertonic saline group.

In our study, we included children < 18 months. The mean age in the normal saline group was 4.8 months and that in the

hypertonic saline group was 4.5 months respectively there were 64 % and 36 % males in the two groups respectively. Most of the infants were born term but 5.6 % of the infants in the normal saline group and 13.9 % in the hypertonic saline group were born preterm. A positive family history for wheezing was documented in 39 % in the normal saline group and in 31% of the hypertonic group. All the infants considered in the study had a HR and SpO_2 in an acceptable range for the age group. The addition of a specific bronchodilator did not have any specific bearing on the treatment of bronchiolitis but since a first episode of wheeze could not be distinguished from the first episode of an asthma, we added levosalbutamol to both the groups irrespectively. We used the RDAI scoring, which is one of the most validated scoring for respiratory distress.

In our study, we observed that the pre inhalation mean RDAI score was 3.8 as compared to post inhalation score of 3.1 in the normal saline group and 4.2 pre-inhalation score and 3.1 post inhalation in the hypertonic saline group both the groups showed a statistically significant clinical improvement in terms of RDAI scoring at the end of 1 hr., but the improvement was substantially more in case of hypertonic Saline nebulisation compared to Normal saline. Hence patients receiving hypertonic saline nebulisation had better improvement in terms of RDAI scoring at the end of 1 hr. In our study, we observed that the mean hours of hospital stay in the normal saline group was 23.4 hours as against 17.8 hrs. In the hypertonic saline group, which was statistically significant (p=0.000), (table 4). Hence patients treated with nebulised 3% saline had significantly shorter mean length of hospital stay.

We also compared the pattern of time of discharge in either group. Among infants in the hypertonic group, maximum number got discharged on Day 1 itself while majority of the normal saline group got discharged only by Day 2. None of the previous studies have highlighted the trend of discharge. Our observations strengthen the efficacy of hypertonic saline in reducing the length of hospital stay and hence reducing the economic burden and inconvenience to the family.

Cochrane review published in The Cochrane Database of Systematic Reviews 2011 Issue 7 [4] which included seven trials (581 infants) with mild to moderate acute viral bronchiolitis (282 inpatients, 65 outpatients and 234 emergency department patients). Patients treated with nebulized 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline. The 3% saline group also had a significantly lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment. The effects of improving clinical score were observed in both outpatients and inpatients. Two emergency department-based trials[16] failed to show significant short-term effects (30 to 120 minutes) of up to two doses of nebulized hypertonic saline in improving clinical score and oxygen saturation. No significant adverse events related to 3% saline inhalation were reported.

Joseph L Mathew in his critical review of literature on 'Hypertonic Saline Nebulisation for bronchiolitis' [17] analyzed 96 citations including the Cochrane review. He remarked on the need of further trials in the setting of a developing country. The establishment of a therapeutic role for hypertonic saline solution in acute bronchiolitis has relevant clinical implications. This modality will provide a cheap and effective therapy for children hospitalized with acute bronchiolitis.

CONCLUSIONS

Hypertonic saline nebulisation is a better alternative to normal saline for nebulisation in children <18 months of age with first episode of wheeze.

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