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Original Research Article

Comparison of the efficacy of hypertonic saline (3%) with salbutamol nebulization for treatment of acute bronchiolitis: a randomized clinical trail

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ABSTRACT

Background: Acute bronchiolitis is a common respiratory condition in infants and nebulized solutions are often used as part of its management. This study compares the efficacy and safety of nebulized 3% hypertonic saline (HS) versus salbutamol with normal saline (NS) in treating bronchiolitis.
Methods: This was a Randomized controlled trial conducted in the Department of Pediatrics of Chattogram Medical College Hospital and Chattogram Maa- O- Shishu Hospital, Chattogram, Bangladesh, during the period from February 2018 to February 2019. We included 204 children and divided them into two groups – Group A (Children who were given nebulized 3% HS (4 ml) with an oxygen flow rate of 6-8 l/min) and group B (Children who were given nebulized salbutamol in a dose of 0.15 mg/kg body weight in normal saline).
Results: The mean age of patients was comparable between groups (8.54±4.41 vs. 8.25±4.46 months, p=0.644). Both groups had a male predominance (63.7% vs. 62.7%, p=0.885). Baseline clinical characteristics, including respiratory rate, heart rate, temperature and oxygen saturation, were similar across groups. At 72 hours, CSS showed significant improvement in both groups (p<0.001), with a greater reduction in the HS group (Group A) compared to the salbutamol group (Group B) (p=0.034). LOS was significantly shorter in the HS group, with 82.35% discharged within 72 hours compared to 55.9% in the salbutamol group (p=0.013). No adverse events were reported in either group.
Conclusions: Nebulized 3% hypertonic saline demonstrated greater efficacy in reducing clinical severity scores and shortening hospital stays compared to salbutamol with normal saline, with no adverse events reported. This suggests that 3% HS is a safe and effective option for the management of acute bronchiolitis in infants.

Keywords: Acute bronchiolitis, Hypertonic saline, Nebulization, Salbutamol

INTRODUCTION

Bronchiolitis is an inflammatory disease of the smallest airways (bronchioles) and is the leading cause of respiratory distress in small children.[1] It is a clinical diagnosis, characterized by cough and respiratory distress associated with wheezing, preceded by runny nose with or without fever in young children below 2 years of age particularly between 2 and 6 months of age.[1] It is predominantly a viral disease.

Respiratory Syncytial Virus (RSV) is responsible for more than 50% of cases. Other less common pathogens include parainfluenza, influenza, rhinovirus, adenovirus, human metapneumovirus, human bocavirus and mycoplasma pneumonia.[2] Bronchiolitis is regarded as the

most common acute lower respiratory tract illness (ALRI) among infants in both developed and developing countries. The reported attack rates in Western literature are as high as 11.6 per 100 children in the 1st year and 6 per 100 children in the 2nd year of life. The 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.[3,4]

In our country too, it is a significant problem as about 21% of children under 5 attending different hospitals in Bangladesh have bronchiolitis.[5] Worldwide, 150 million new cases occur annually, 11–20 million (7–13%) are severe enough to require hospital admission. 95% of all cases occur in developing countries by Shi et al.[6]

Though acute bronchiolitis is usually a self-limiting illness, this condition may be associated with several severe complications, such as apnea, respiratory failure or secondary bacterial infection.[7,8]

Typical symptoms are elongated expiration with the presence of wheezes and crepitations in chest auscultation preceded by several days of upper respiratory tract infection. In the course of the disease, the small bronchi are inflamed, with edema and congestion of mucous and submucous membranes as well as necrosis and exfoliation of respiratory syncytial cells which leads to accumulation of thick mucus in large volume.[9]

It has been proven that the disturbance of mucociliary transport plays a significant role in the pathogenesis of bronchiolitis, similar to cystic fibrosis and other chronic respiratory tract disorders.[10]

As proposed by Mandelberg and Amirav (2006), in RSV bronchiolitis aside above-mentioned pathological changes, there is a disturbed function of the channels that regulate ASL's composition which in consequence disrupts the arrangement of ML/PCL layers and leads to inappropriate mucociliary transport.[11]

In vitro and clinical research have shown the beneficial influence of concentrated saline nebulization on mucociliary transport, with the greatest influence in patients with cystic fibrosis.[12]

This solution, due to its osmotic properties, draws water out from the submucous membrane, reduces edema and restores the appropriate composition of an ASL. Additionally saline in hypertonic concentrations improves the rheological properties of the mucus, stimulates the excretion of PGE2 which promotes the movement of cilia and induces cough to further clear the airways mechanically.[13]

As hypertonic saline solution has been shown to increase mucociliary clearance in normal patients, in asthma, bronchiectasis, cystic fibrosis and sinonasal diseases such benefits would also be expected in infants with acute bronchiolitis.[11] The postulated mechanisms of benefit are 1) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance 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 3) hypertonic saline stimulates cilial beat via the release of prostaglandin E2.[11,12] Moreover, by absorbing water from the mucosa and submucosa, hypertonic saline solution can theoretically reduce edema of the airway wall in infants with acute bronchiolitis.[11,13,14]

Hypertonic saline inhalation can also cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction.[13] The above-mentioned theoretical benefits provide the rationale for the treatment of acute bronchiolitis with nebulized hypertonic saline solution.

The common practice is to treat hospitalized babies with acute bronchiolitis with inhalation of salbutamol diluted in a normal saline solution. Given the high prevalence of bronchiolitis in infants and the huge burden on healthcare systems in our context, any benefits of nebulized HS may be considered clinically relevant.

The present study aimed to compare the efficacy of hypertonic saline (3%) with salbutamol nebulization for the treatment of acute bronchiolitis among the children admitted at our institution.

METHODS

This was a randomized controlled trial conducted in the Department of Pediatrics of Chattogram Medical College Hospital and Chattogram Maa- O- Shishu Hospital, Chattogram, Bangladesh, during the period from February 2018 to February 2019.

We included 204 children admitted to the Pediatrics Department of CMCH and CMOSH with a diagnosis of acute bronchiolitis during the study period. Children were then divided into two groups-Group A (Children who were given nebulized 3% HS (4 ml) with an oxygen flow rate of 6-8 L/min) and Group B (Children who were given nebulized salbutamol in a dose of 0.15 mg/kg body weight in normal saline).

Inclusion criteria

These are the following criteria to be eligible for enrollment as our study participants: a) Children aged between 2 months to 24 months; b) Children having a history of preceding viral upper respiratory infection that is, fever>380C, cough or coryza; c) Children with the first episode of respiratory distress associated with wheezing; d) Children with a clinical severity score of>3;

e) Parents who were willing to let their children participate were included in the study.

Exclusion criteria

a) Children having a history of two or more episodes of respiratory distress in the past; b) Children with a history of mechanical ventilation in the neonatal period; c) Children with a clinical severity score>9 and oxygen saturation<85 %; d) Children with a diagnosed case of asthma; e) Children with progressive respiratory distress requiring mechanical ventilation; f) Children receiving any steroid therapy within 48 h or history of preadmission antibiotic; g) Children with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD, etc.) were excluded from our study.

Data collection

Informed written consent was obtained from a primary caregiver or guardian after a full explanation of the outcome, complications and purpose of the study. They were informed of their right to withdraw from the study at any stage. Data were collected using standardized forms to document pertinent history and physical exams. Each child's weight, temperature, respiratory rate, SpO2 in room air (determined by pulse oximeter), heart rate, CSS (Clinical Severity Score) and hydration status were recorded.

To reduce the likelihood of including children with atopic wheeze, all children received a single inhalation of 2.5 mg salbutamol before entering the study. Children were excluded if the Wang score improved at least 2 points after inhalation.

Interventions

Children in group A were given nebulized 3% HS (4 ml) with an oxygen flow rate of 6-8 L/min and children in Group B were given nebulized salbutamol in a dose of 0.15 mg/kg body weight (minimum dose 1 mg) in normal saline to make a total volume of 4 ml using an oxygen flow rate of 6-8 l/min. We used a conventional jet nebulizer with a face mask. Oxygen is also given through the nasal cannula at a rate of 1-2 l/min.

The nebulization was continued till the nebulization chamber was empty. Four doses at intervals of 6 h were given daily until discharge. The study drugs were prepared by a pharmacist and administered by a nurse and compliance with medication administration was assured by the investigator's direct observation of each nebulization.

All children were evaluated twice a day, which was based on the Wang score, heart rate, saturation, respiratory rate, need for supplemental oxygen and tube feeding. The evaluations were done by the investigator till the patients were discharged.

Statistical analysis

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation qualitative data was expressed as frequency distribution and percentage. The differences were analyzed by the independent sample t-test or Mann-Whitney-U, Chi-square test or Fisher's exact test.

Between groups across time analysis of changes in clinical severity scores was analyzed by repeated measures analysis of variance (ANOVA) test using the chi-square (X2) test, Fisher's exact test. A p-value<0.05 was considered as significant. Statistical analysis was performed by using SPSS 23 (Statistical Package for Social Sciences) for Windows version 10.

RESULTS

Table 2 shows that the mean age of the patients was 8.54 and 8.25 months respectively in the hypertonic saline (HS) group and salbutamol group with no statistically significant difference (p=0.644). The maximum number of cases in each treatment group was reported in the age group 7-12 months.

Table 3 shows the gender distribution of the study patients. It depicts that, there was male predominance (63.7% vs 62.7%) in the study in both groups. However, with respect to the gender distribution both the groups were similar (p=0.885).

Table 4 shows that both the groups were comparable with respect to their mean duration of illness before admission and mean interval of admission to enrollment (p-value was 0.452 and 0.876 respectively).

Table 5 shows that all the cases in both groups presented with cough, wheezing and retraction. Moreover, both groups were comparable in their baseline temperature, respiratory rate, heart rate and oxygen saturation. Regarding temperature, respiratory rate, heart rate and oxygen saturation, the differences were not significant between both groups.

Table 6 presents a comparison of clinical parameters between two groups of patients treated with nebulized solutions: 3% hypertonic saline (n = 102) and salbutamol with normal saline (n = 102). The table evaluates various components of the clinical severity score (CSS), including respiratory rate, wheezing, retraction, general condition and the overall CSS.

There were no statistically significant differences in any of the evaluated clinical parameters between the two groups, suggesting comparable outcomes for both

treatments (p-value>0.005). (CSS: Clinical Severity score; Group A: HS group; Group B: Salbutamol group).

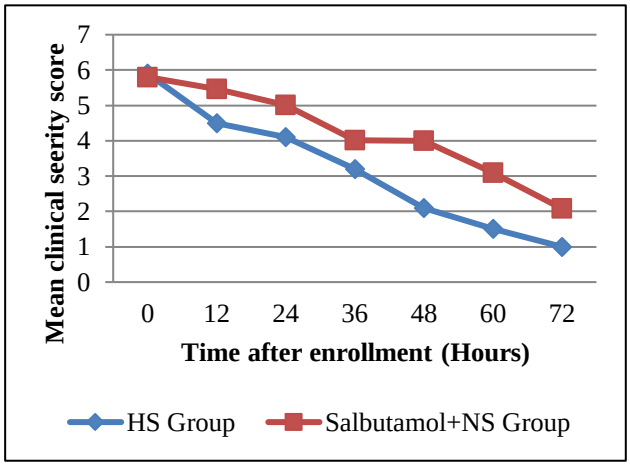

Figure 1: Comparison of the mean CSS at 12 hourly intervals up to 72 hours.

Figure 1 shows the mean clinical severity scores at baseline, at 12 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours and 72 hours in Group-A (HS) were 5.90, 4.50, 4.10, 3.20, 2.10, 1.50, 1.0 while in Group-B (Salbutamol+NS) score were 5.86, 5.46, 5.01, 4.01, 4.00, 3.09, 3.08, 2.09 respectively.CSS of both the treatment groups were reduced by three days but reduction was more significant in children who received 3% nebulized HS.

A between-group, across-time analysis of change in CSS, was conducted through repeated measures analysis of variance (ANOVA). Pair-wise comparisons were also performed between the two groups at 12-hours intervals till 72 hours from enrolment in the study using the least square estimate. There was a significant effect of time on the improvement of mean grades in both groups (p=<0.001). Moreover, the improvement was significantly more in group A than in group B (p=0.034).

Table 7 shows that the length of hospital stay was significantly less in children nebulized with 3% HS compared to the children nebulized with salbutamol and NS. 84 (82.35%) of the children in the HS Group were discharged by 72 hours from the hospital whereas 57 (55.9%) of the children in the salbutamol Group were recovered and discharged during the same period (p=0.013).

Table 8 summarizes the adverse events observed in patients treated with nebulized 3% hypertonic saline (n=102) and nebulized salbutamol with normal saline (n=102). Across both groups, no adverse events were reported, indicating that both nebulized 3% hypertonic saline and salbutamol with normal saline were well-tolerated by the patients.

Table 1: Clinical severity score.[15]

Variables	Score			
	0	**1**	**2**	**3**
Respiratory rate	<30	30-45	46-60	>60
Wheezing	None	Terminal expiration /only with a stethoscope	Entire expiration or audible on expiration without stethaudibleoscope	Inspiration and expiration without a stethoscope
Retraction	None	Intercostals	Tracheo-sternal	Severe with nasal flaring
General condition	Normal			Irritable, lethargic, poor feeding

Table 2: Comparison of age between two groups.

Age of the patients (months)	Nebulized with		P value
	3% Hypertonic saline (n=102)	**Salbutamol and NS (n=102)**	
Age groups (in months)			
2-6	37 (36.3%)	44 (43.1%)	
7-12	46 (45.1%)	41 (40.2%)	0.603
13-18	19 (18.6%)	17 (16.7%)	
Mean±SD	8.54±4.41	8.25±4.46	0.644
Range	2-18	2-22	

Table 3: Comparison of gender distribution between two groups.

Gender of the patients	Nebulized with		P value
	3% Hypertonic saline (n=102)	**Salbutamol and NS (n=102)**	
Male	65 (63.7%)	64 (62.7%)	0.885
Female	37 (36.3%)	38 (37.3%)	

Table 4: Comparison of duration of symptoms and interval from admission to enrolment between two groups.

Parameters	Nebulized with		P value
	3% Hypertonic saline (n=102)	Salbutamol and NS (n=102)	
Duration of illness before admission, in days			
Mean±SD	3.61±0.97	3.70±0.89	0.452
Range	1-5	1-5	
The interval from admission to enrollment, in hours			
Mean±SD	15.88±3.11	15.56±3.08	0.876
Range	10-20	10-20	

Table 5: Comparison of baseline clinical characteristics of the patients between two groups.

Parameters	Nebulized with		P value
	3% Hypertonic saline (n=102)	Salbutamol and NS (n=102)	
Cough	102 (100.0%)	102 (100.0%)	NA
Wheeze	102 (100.0%)	102 (100.0%)	NA
Retraction	102 (100.0%)	102 (100.0%)	NA
Temperature, ^{0}F	99.2±0.78	99.1±0.15	0.071
Respiratory rate, min	57.5±4.48	57.9±3.45	0.131
Heart rate, min	127±9	129±11	0.226
Oxygen saturation, %	89.5±1.11	89.2±0.93	0.085

Table 6: Comparison of baseline clinical severity score (CSS) between two groups.

Parameters of CSS	Nebulized with		P value
	3% Hypertonic saline (n=102)	Salbutamol and NS (n=102)	
Respiratory rate score	2.00±0.00	2.02±0.14	0.320
Wheezing score	2.02±0.01	2.11±0.05	0.124
Retraction score	1.50±0.33	1.32±0.25	0.524
General condition score	0.36±0.99	0.54±1.16	0.406
Clinical severity score	6.58±1.47	6.90±1.28	0.094

Table 7: Comparison of length of stays (LOS) in hospital between groups.

LOS in hospital	Nebulized with		P value
	3% Hypertonic saline (n=102)	Salbutamol and NS (n=102)	
≤48 hours	22 (21.6%)	9 (8.8%)	0.013
49-72 hours	62 (60.8%)	48 (47.1%)	
73-96 hours	14 (13.7%)	26 (25.5%)	
>96 hours	4 (3.9%)	19 (18.6%)	

Table 8: Comparison of the adverse events rate between two groups.

Adverse events	Nebulized with	
	3% Hypertonic saline (n=102)	Salbutamol and NS (n=102)
Bronchial obstruction	0	0
Agitation	0	0
Rhinorrhoea	0	0
Vomiting	0	0
Saturation dips	0	0

DISCUSSION

In the present study, the two study groups were almost similar in their demographic characteristics like age and sex, baseline clinical characteristics and clinical severity score. The mean age of the patients in our study population was 8.54±4.41 months and 8.25±4.46 months in group A and group B respectively, the youngest being

2 months and the eldest being 18 months. In our study, most of the children (51%) presented in the age range of 7-12 months of age. About 75% of cases of bronchiolitis occur in children younger than 1 year and 95% in children younger than 2 years. Incidence peaks in those aged 2-8 months.[3] In our study, 63.7% of the patients were males and 36.3% were females. Severe bronchiolitis occurs more frequently in males than in females, a pattern similar to other respiratory viral infections.[16]

Clinical severity score is generally considered a relatively objective measure to assess the severity of illness. In the present study, we used the Wang CSS to assess the clinical improvement with the interventions.[15] The study demonstrated that CSS (respiratory rate score, wheezing score, retraction score, general condition score) of both the treatment groups was reduced within three days of treatment but the reduction was much earlier in children who received 3% nebulized HS than those who received nebulized salbutamol and 0.9% NS. Our study findings are in agreement with the findings of other studies.[17,18]

In the present study, 3% hypertonic saline significantly reduced LOS in hospitals. Most patients in the hypertonic saline group were discharged within 3 days of treatment. Likewise, mean LOS in the hospital was also shorter in the hypertonic saline group than their counterpart. Consistent with the findings of the present study several investigators have reported the use of HS solution for infants with bronchiolitis with substantial benefits of therapy reported by many of them.[13,19]

Many of them used bronchiolitis severity score to evaluate patients over time and they found that inhaled 3% HS (with or without other solutions like salbutamol, albeutarol and epinephrine) administered by nebulization every 6-8 hours improved the bronchiolitis severity score and reduced the LOS in hospitalized patients when compared with 0.9% saline with epinephrine or salbutamol.[14] A systematic review of 24 trials (involving 3209 patients, 1706 of whom received HS) with acute viral bronchiolitis (189 inpatients and 65 outpatients) concluded that nebulized 3% saline may significantly reduce the LOS and improve the clinical severity score.[20]

However, an orthodox finding was reported by another small RCT which investigated the use of hypertonic saline in the ED setting and the authors suggested that immediate clinical benefits may not be seen with nebulized hypertonic saline.[21] Wu et al, (2014) also did not find a difference in LOS.[22] Another study conducted by Al-Ansari et al, (2010) randomized infants to receive 5 ml of 0.9% saline or 3% or 5% HS mixed with epinephrine and found no significant difference in length of stay.[23] Another study found a statistically significant difference in severity score, with 5% performing best and 3% in between. This finding suggests a dose-response relationship.[24] In contrast, hypertonic saline has been demonstrated to improve clinical severity ratings in hospitalized patients with bronchiolitis; however, the extent of improvement varied by treatment day, with the hypertonic saline group showing improvements ranging from 15.7% on day 1 to 29.4% on day 3.[19,20,25] The CS scores of the two groups at enrollment and again at 12-hours intervals until discharge did not differ significantly. The potential side effects of nebulized hypertonic saline, such as severe bronchospasm, remain a concern. A review by Zhang et al, 2013 included 276 infants receiving 3% saline in repeated doses and no significant adverse events were reported.[20]

In this study, we took a small sample size due to the short study period. We did not have a placebo group due to ethical considerations as the only placebo for nebulization therapy could be NS which itself is a treatment modality. We did not attempt a virological diagnosis as we did not have the facility. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION

The present study concludes that 3% HS nebulization (without additional bronchodilators) is an effective and safe treatment for moderately ill patients of acute bronchiolitis. It significantly reduces the clinical severity and length of hospital stay in comparison to salbutamol in 0.9% saline nebulization.

Recommendations

So further study with a prospective and longitudinal study design including a larger sample size needs to be done to validate the findings of our study.

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