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Original Research Article

Efficacy of nebulized hypertonic saline versus normal saline and salbutamol in treating acute bronchiolitis in a tertiary hospital: a randomized control trial

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ABSTRACT

Background: Bronchiolitis is an acute seditious lesion of the lower respiratory tract. Further, than 70 cases are caused by a respiratory syncytial virus (RSV); other less common pathogens include parainfluenza, influenza, rhinovirus, adenovirus, mortal metapneumovirus, mortal Boca contagion and mycoplasma pneumonae. The aim of the study was to evaluate the efficacy of nebulized hypertonic saline in children with acute bronchiolitis in the improvement of clinical features and decreasing length of hospital stay.
Methods: The study was a randomized control trial carried out in the department of paediatrics, Dhaka medical college hospital (DMCH), Dhaka between January to December 2013. A total of 100 children from 1 month to 24 months of age irrespective of sex with clinical presentation of bronchiolitis admitted in the paediatric wards of DMCH were included in the study and were randomly assigned to either 4 ml 3% hypertonic saline nebulization (group I=50) or to 4 ml normal saline and 0.4 ml salbutamol respiratory solution nebulization (group II=50). The therapy was repeated 8 hours every day for 120 hours.
Results: The clinical severity scores (CS) based on respiratory rate, wheezing, chest retraction and general conditions at baseline on the first day of treatment were 9.0±1.0 in group I and 9.3±1.8 in group II (not significant). The study demonstrated that clinical severity score improved by three days but the improvement was more significant in children who received nebulized hypertonic saline (1.7±1.2) compared to those who received nebulized normal saline and salbutamol (3.5±1.8). The cases of group I required a shorter duration of oxygen therapy compared to those of group II (15±6.0 hours versus 26.4±5.4 hours; $p<0.05$). Forty-seven patients (94%) were discharged within 72 hours of treatment in group I and 29 patients (58%) in group II. The length of hospital stay was shorter in group I 58.1±22.0 hours compared to group II 74.7±27.2 hours. None of the cases of any group encountered any side effects due to study drugs.
Conclusions: 3% hypertonic saline nebulization significantly reduces clinical severity and length of hospital stay of children suffering from acute bronchiolitis in comparison to those treated by normal saline and salbutamol nebulization.

Keywords: Bronchiolitis, Respiratory syncytial virus, Wheezing, Hypertonic saline, Salbutamol

INTRODUCTION

Bronchiolitis is an acute inflammatory lesion of the lower respiratory tract. More than 70% of cases are caused by a RSV; other less common pathogens include parainfluenza, influenza, rhinovirus, adenovirus, human metapneumovirus, human Boca virus and mycoplasma pneumonae.[1,2] Children become infected with RSV by age of 2 years with the peak incidence being in 2-6 months.[3-5] Only 1% of these children require hospitalization.[6] In a recent study in different hospitals in Dhaka city, 348 cases were diagnosed with bronchiolitis and were found positive for RSV antibody in 50% of these cases.[7] Despite 4 decades of efforts to deal with the problem, there was no evidence-based clinically effective treatment of bronchiolitis.[6] The standard treatment for acute bronchiolitis remains supportive care like ensuring sufficient oxygenation and maintaining adequate hydration and nutrition.[8] Bronchodilators like salbutamol, adrenaline, anticholinergic drugs like ipratropium bromide and saline nebulization have been used with varying results. There is a lack of sufficient evidence for almost all the interventions that are usually tried, including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactants and chest physiotherapy. None of the treatment modalities is specific. Antiviral agents are available, but their use in most patients is controversial and is therefore not routinely indicated. Most of the studies using glucocorticoids in the treatment of bronchiolitis denied a positive therapeutic effect.[8-10] The use of ß2-agonists occasionally resulted in a short-term improvement in patients with bronchiolitis, especially when using epinephrine, while others failed to show a significant effect.[8,11-16] Several studies suggested the use of nebulized 3% NaCl solution for infants with bronchiolitis, due to its ability to lower the viscosity of secretions, reduce airway edema and improve mucociliary function.[17-19] The common practice was to treat hospitalized babies with acute bronchiolitis with inhalation of salbutamol diluted in normal saline solution. The present study hypothesized that simply inhalation of hypertonic saline solution without salbutamol in the form of inhalation by the babies with bronchiolitis may improve their clinical severity scores thereby shortening the length of hospitalization.

METHODS

The study was a randomized controlled trial conducted in the department of paediatrics, DMCH from January 2013 to December 2013. Informed consent was obtained from a parent or legal guardian of each patient enrolled in the study. Children aged between one month to two years presenting with preceding or existing runny nose, cough, breathing difficulty, chest in-drawing and whose chest x-ray showed hyperinflation, hyper-translucency without any cardiac problem and admitted during the study period were enrolled consecutively as the study population. Exclusion criteria were previous history of wheezing, chronic cardiac or respiratory disease or respiratory failure or requiring mechanical ventilation, inhaling the nebulized any hypertonic saline within 12 hours of intervention. After inclusion and exclusion, this study included 100 patients with acute bronchiolitis. The two groups were randomly assigned to 7% hypertonic saline nebulization (n=50) and 0.9% normal saline with salbutamol nebulization (n=50) by lottery method. Relevant history and physical findings were recorded in a pre-tested, semi-structured questionnaire. Variables like clinical severity score are assessed by using the respiratory distress assessment instrument described by Wang et al.[20]

Oxygen saturation was measured by using a non-invasive pulse oximeter and recorded on admission as baseline characteristics. A child with an oxygen saturation value <90% was designated as having significant hypoxia.6 After taking written informed consent drug was given according to the dosing schedule. Group-I received nebulization with 3 ml of 7% hypertonic saline and group II received nebulization with 3 ml of 0.9% normal saline with 0.3 ml salbutamol three times every day at intervals of 8 hours until they were improved enough for discharge. Each of the two groups received the same supportive measures like propped up positioning, O-P, nasal suction when needed, iv fluid, feeding, oxygen therapy (when oxygen saturation <90%), paracetamol for fever, antibiotic and counselling. Cases were monitored by respiratory distress assessment instrument (RDAI) score at 12 hourlies initially then 24 hourly till the patient was ready for discharge. The time required from the initiation to the withdrawal of oxygen therapy was recorded. Oxygen therapy was stopped when the patients maintained SpO_2 >95%. Length of hospital stay from admission to the time taken to discharge was measured. The decision to discharge the patients was made in the morning rounds by the attending physician, based on clinical grounds alone. The outcome variables were clinical severity score; length of hospital stay; oxygen saturation in room air; duration of oxygen supplementation; side effects of drugs. Collected data were processed and analyzed using computer software SPSS (statistical package for social sciences), version 19. The test statistics used to analyse the data presented on a categorical scale were Chi square and unpaired t test (for comparison of data between groups). Level of significance was set 5% and $p<0.05$ (at 95% CI) was considered significant.

RESULTS

This was a randomised control study, a total of 100 patients were included and analysed in this study. The result was described in two groups, group-I (HS) with 50 patients and group-II (NS+salbutamol) with 50 patients. Table 1 shows the demographic characteristics of the cases, 32 (64%) patients (group-I) were from the age group <6 months and 29 (58%) patients (group-II) were from the same age group. The mean±SD of group-I was

5.2±3.8 and the mean±SD of group-II was 5.5±3.2 and the p=0.82. From the gender distribution of the study, the male was 26 (52%) and the female was 24 (48%) in group-I and the male was 25 (50%) and the female was 25 (50%) in group-II. The p value of the gender distribution is 0.5 (Table 2). Table 2 shows the clinical presentation of cases on admission. The mean clinical severity score is shown in Table 3. Table 4 shows the comparison of oxygen therapy between the two groups, the mean±SD of group-I is 15.0±6.0 and the mean±SD of group-II is 26.4±5.4 and the p value is 0.02 (Table 4). The comparison of recovery and discharge from hospital between two groups in Table 5. A total of 47 (94%) patients were recovered and discharged rapidly and 3 (6%) patients were recovered and discharged gradually in group-I, 29 (58%) patients were recovered and discharged rapidly and 21 (42%) patients were recovered and discharged gradually of group-II and the p value is <0.001 which shows significantly changed (Table 5). The p value of the length of hospital stay is 0.002 which change is significant (Table 6).

Table 1: RDAI.

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

Disease severity rank: 0-4.9=mild, 5-8.9=moderate, 9-12=severe disease.

Table 2: Demographic characteristics of the cases (n=100).

Characteristics	Group		P value
	Group-I (HS) (n=50)	Group-II (NS+salbutamol) (n=50)	
Age in months			
<6	32 (64)	29 (58)	0.82
6-12	15 (30)	17 (34)	
>12	3 (6)	4 (8)	
Mean±SD	5.2±3.8	5.5±3.2	
Gender			
Male	26 (52)	25 (50)	0.5
Female	24 (48)	25 (50)	

Figures in the parentheses indicate the corresponding percentage.

Table 3: Clinical presentation of cases on admission (n=100).

Clinical presentation	Group		P value
	Group-I (HS) (n=50)	Group-II (NS+salbutamol) (n=50)	
	N (%)	N (%)	
Runny nose	50 (100)	50 (100)	>0.05
Cough	50 (100)	50 (100)	>0.05
Breathing difficulty	50 (100)	50 (100)	>0.05
Feeding difficulty	28 (56)	29 (58)	0.08
Wheeze	47 (94)	48 (96)	>0.05
Chest in-drawing	50 (100)	50 (100)	>0.05
Nasal flaring	04 (8)	08 (16)	0.07
Tachypnoea	45 (90)	44 (88)	>0.05
Tachycardia	48 (96)	43 (86)	>0.05
Rhonchi	50 (100)	50 (100)	>0.05
Fever	14 (28)	13 (26)	>0.05
Oxygen saturation (mean±SD)	94.9±1.7	94.6±2.6	>0.05

Table 4: Mean clinical severity score at a different time (n=100).

Mean clinical severity score	Group		P value
	Group- I (HS) (n=50)	Group- II (NS+salbutamol) (n=50)	
At baseline	9.0±1.0	9.3±1.8	0.943
At 12 hours	8.2±1.5	9.0±1.3	0.008
At 24 hours	5.3±0.9	7.8±2.0	< 0.001
At 48 hours	2.6±1.7	4.3±2.6	0.001
At 72 hours	1.7±1.2	3.5±1.8	0.001

Table 5: Comparison of duration of oxygen therapy between two groups (n=100).

Duration of oxygen therapy (hours)	Group		P value
	Group- I (HS) (n=50)	Group- II (NS+salbutamol) (n=50)	
Mean±SD	15.0±6.0	26.4±5.4	0.02

Table 6: Comparison of recovery and discharge from hospital between two groups (n=100).

Recovery and discharge	Group		P value
	Group- I (HS) (n=50)	Group- II (NS+salbutamol) (n=50)	
	N (%)	N (%)	
Rapid (within 72 hours)	47 (94)	29 (58)	< 0.001
Gradual (after 72 hours)	3 (6)	21 (42)	

Table 7: Comparison of length of hospital stays between two groups (n=100).

Length of hospital stay (hours)	Group		P value
	Group- I (HS) (n=50)	Group- II (NS+salbutamol) (n=50)	
Mean±SD	58.1±22.0	74.7±27.2	0.002

DISCUSSION

Bronchiolitis is one of the most prevalent respiratory problems in children less than two years of age and is the most common cause of hospitalization in early childhood.[3-5] The present study was carried out to see whether 3% nebulized hypertonic saline reduced clinical severity and length of hospital stay in children with bronchiolitis than 0.9% nebulized normal saline and salbutamol. The two study groups in the present study were almost similar concerning their demographic characteristics like age and sex, baseline clinical characteristics, respiratory distress score like respiratory rate score, wheezing score, retraction score, general condition score and oxygen saturation in room air. The study demonstrated that the respiratory rate score, wheezing score, retraction score, general condition score and clinical severity score of both the treatment groups of studied children were reduced and oxygen saturation in room air improved within three days but the reduction was much earlier in children who received 3% nebulized hypertonic saline than those who received 0.9% nebulized normal saline and salbutamol. In a meta-analysis done by Chen et al where they analyzed eleven studies that enrolled 1070 infants. Nebulized HS treatment significantly decreased the duration and rate of hospitalization compared with nebulized normal saline (NS) (duration of hospitalization: WMD Z 0.96, 95% confidence interval (CI) Z 1.38 to 0.54, p<0.001; rate of hospitalization: risk ratio Z 0.59, 95% CI Z 0.37e0.93, p Z 0.02). Furthermore, nebulized HS treatment had a beneficial effect in reducing the clinical severity (CS) score of acute bronchiolitis infants post-treatment (day 1: WMD Z 0.77, 95% CI Z 1.30 to 0.24, p Z 0.005; day 2: WMD Z 0.85, 95% CI Z 1.30 to 0.39, p<0.001; day 3: WMD Z 1.14, 95% CI Z 1.69 to 0.58, p<0.001). There was no decrease in the rate of readmission (risk ratio Z 1.08, 95% CI Z 0.68e1.73, p Z 0.74).[21] In another meta-analysis published in 2020 Hsieh et al analyzed 32 publication that included 4186 children showing compared to the control group, the HS group exhibited significant reduction of severity of respiratory distress, included studies used the CS score (n=8; MD, −0.71; 95% CI, -1.15 to -0.27; I2=73%) and full stop after RDAI (n=5; MD, -0.60; 95% CI, -0.95 to -0.26; I2=0%) for evaluation respectively. Further, the HS group decreased the length of hospital stay 0.54 days (n=20; MD, -0.54; 95% CI, -0.86 to -0.23; I2=81%).[22] Mandelberg et al found significant improvement in the hypertonic saline nebulization group.[23] One outpatient and two patients trials used the same scoring system for comparing the efficacy of HS nebulization with normal saline and salbutamol nebulization.[23-25] Despite the difference in delivery interval across the studies, the effect sizes of the treatment with 3% saline nebulization reported were

similar. This finding was consistent with the present study. That was, there was a significant reduction in clinical severity score in the 3% saline nebulization group.[20-25] The mean duration of oxygen supplementation was 9 hours shorter in the former group than that in the latter group. The majority (93.3%) of the 3% HS group children recovered within 72 hours, whereas 57.8% of the children of the 0.9% saline group recovered from the disease during the same period. None of the patients in the present study encountered any side effects. As the entire pertinent baseline clinical characteristics of the two groups of children were similar, the differences in outcome between the groups (better outcome in 3% nebulized hypertonic saline) can be attributed to the intervention. A double-blinded clinical trial study was conducted in Hajar Hospital, Shahrekord, Iran, Zamani et al studied a total of 70 patients under the age of two years with bronchiolitis and were divided into two groups of 35 each. Their finding revealed that the mean duration of recovery was significantly lower in the hypertonic saline group indicating that a 3% saline nebulizer had more pleasant therapeutic effects on acute bronchiolitis. These findings supported the results of the current study.[27] In the present study 3% HS significantly reduced the length of hospital stay. Most patients in the HS group were discharged within 3 days of treatment. A similar observation was seen in another study done by Khalid et al where the mean length of hospital stay was shorter in the hypertonic saline group.[26] In another study conducted from January 2018 to June 2019 in the pediatric ward of a tertiary care teaching hospital in Jaipur, Rajasthan, Singh et al showed that there was a significant reduction of LOS (p=0.0011) and in the clinical severity score from the 2nd day onward in HS group which supports the findings of our study.[28] Consistent with the findings of the present study several investigators have reported the use of the hypertonic saline solution for infants in bronchiolitis with substantial benefits of therapy reported by many of them.[21,22] The investigators showed that nebulized HS decreases the length of stay in the hospital (LOS) as compared with normal saline (NS) among infants hospitalized with the disease. None of the studies reported any side effects. These findings went in favour of the findings of the present study as in the present study the mean length of hospital stay was much shorter (on an average 17 hours shorter) in the HS group than that in the isotonic saline group.

Limitations

The study had a too-small sample size. The study was conducted in a single centre which doesn't reflect the original scenario of Bangladesh. So there needed a large multi-scale, multi-centre countrywide study for the authentic outcome. Moreover, after 72 hours of treatment, only 17 patients were left in the HS group as opposed to 36 patients in the normal saline group and, as such, valid statistical analysis between the groups was not feasible.

CONCLUSION

In this study, both treatment groups demonstrated clear evidence of clinical improvement and oxygen saturation but the 3% HS group in comparison with the 0.9% NS group showed more efficacy in relieving symptoms, improving oxygenation and reducing the length of hospital stay in an infant with acute bronchiolitis.

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Conflict of interest: None declared
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