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Outcome of treatment with nebulized 3% hypertonic saline solution in infants hospitalized with moderate bronchiolitis

Background

Bronchiolitis is the most common lower respiratory infectious disease in infants presenting with cough and/or wheeze and occurs most frequently in the winter months. Treatment of bronchiolitis by means of nebulization with inhaled corticosteroids and bronchodilator such as salbutamol or ipratropium bromide considered an effective method. Usually, 0.9% normal saline used together with the medications mentioned above. However, there are studies showing that 3% hypertonic saline might be a better choice compared with the normal saline.

Objective: Our main aim of this study is to determine the improvement of patient's condition by comparing the length of hospital stay and improvement in clinical severity score (CS score) in infants with moderate bronchiolitis nebulized with 3% hypertonic saline or 0.9% saline.

Methods: 124 patients were arranged randomly to nebulize either 3% hypertonic saline with salbutamol plus budesonide (Group 1) or 0.9% saline with salbutamol plus budesonide (Group 2) three times per day until conditions were stable enough for discharge (with a CS score below 3). We recorded the SC scores of each patient before and after the first nebulization every day.

Outcomes, considered mainly as ①differences in the length of hospital stay from admission to time taken to reach CS score < 3; ②the change in CS score after the first nebulization every day. A P value <0.05 was considered statistically significant.

Results: 124 patients of them completed the study. Their mean age was 6.92±0.24 months (range, 3 to 12 months). The cases were diagnosed as moderate bronchiolitis with CS scores varying from 6 to 9. The mean length of hospital stay from admission to time taken to reach CS score <3 was 4.83 ±0.077 days for the whole subjects investigated, and it differed significantly between the two groups: 4.27±0.90 days in Group 1 and 5.39±0.610 days in Group 2. On the first day of treatment, the mean CS scores at baseline were 7.34±0.1 and 7.39±0.99 for Group 1 and Group 2, respectively. After the first nebulization, the CS scores decreased to 5.94±0.89 (SD-0.698) and 6.50±0.094 (SD 0.741) of Group 1 and Group 2, respectively. The P value in both groups were less than 0.001, indicating statistically differences between CS scores before and after nebulization by both groups of solutions in the treatment of moderate bronchiolitis. However, the differences of the mean values and standard deviation (SD) results after nebulization in the two groups suggested a better treatment outcome of 3% hypertonic saline with salbutamol plus budesonide than 0.9% normal saline. There were no significant differences between the respiratory rate, heart rate, saturation and add-on therapy in the two groups. No adverse events noted in both groups.

Conclusion: The curative effect of 3% hypertonic saline group was significant better in comparison with the 0.9% normal saline group in terms of the improvement of CS score and length of hospital stay. In conclusion, 3% hypertonic saline is safe and effective in infants with moderate bronchiolitis.

Keywords: bronchiolitis, clinical severity score, 3% hypertonic saline, nebulization

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BS Majagaiya,[1] Huan-Ji Cheng,[1] Jia-Ning Yin,[1] MP Joshi,[2] M Chaudhary[3]

[1]Resident, Department. of Pediatric Pulmonology, The First Hospital of Jilin University, China
[2]Resident, Department of Pediatric Surgery, BSMMU, Bangladesh
[3]Consultant Radiologist, Chaudhary Polyclinic, India

Correspondence: MP Joshi, Resident, Department of Pediatric Surgery, BSMMU, Bangladesh, Tel +977 9841402781, Email mriduljoshee@gmail.com

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Introduction

According to American academy of pediatrics, bronchiolitis is an acute inflammation, edema and necrosis of epithelial cells lining small airways with increased mucus production, and bronchospasm.[1] Another useful definition, which used in many clinical studies, is the first episode of wheezing in a child younger than 12 to 24 months who has physical findings of a viral respiratory infection and has no other explanation for the wheezing, such as pneumonia or atopy.[2] Bronchiolitis is usually more common in children younger than 2 years, with a peak in infants aged 2 - 5 months. Its incidence peaks between December and March.[3] Respiratory syncytial viruses are the main cause of bronchiolitis worldwide and can cause up to 70 or 80% of lower respiratory tract infections during high season.[4] Bronchiolitis is the most common viral disease which usually gets diagnosed on the basis of etiology and findings on physical examination and clinically. Clinical diagnosis of disease and its severity depends on the clinician's interpretation on the characteristic findings and which is independent from any specific clinical features and diagnostic tests. Usually in bronchiolitis children may present with wide range of clinical symptoms from mild respiratory distress to incipient respiratory failure[5] so careful physical examination (rhinorrhoea, cough, crackles, wheezing, dyspnea, polypnea, feeding difficulties, apnea, lethargy) combined with the collection of clinical history (to assess the course and high risk condition for the disease) are warranted as the

cornerstone of the diagnosis of bronchiolitis. Clinicians in different countries use different criteria to diagnose acute bronchiolitis.[6]

Because no definitive treatment exists for the specific viruses, therapy directed towards supportive one. Manage the symptoms and make the patient comfortable and not letting to progress in severe stage. Medical therapies used to treat bronchiolitis in infants and young children are controversial. Although numerous medications and interventions used to treat bronchiolitis, at present, only oxygen appreciably improves the condition of young children with bronchiolitis. Supportive Treatment includes Oxygen, Bronchodilator therapy (short acting beta 2 agonist, epinephrine), Nebulized hypertonic (3%) saline, Anti-inflammatory therapy (corticosteroids – oral and nebulized), In-hospital use of antiviral treatments, Anticholinergic agents, Antibiotics, Andrographolide, Physiotherapy, and other therapies such as Montelukast, DNase, inhaled furosemide, methylxanthine.

Hypothesis

According to the literature, HS solution, by absorbing water from the submucosa, can theoretically reverse some of the sub mucosal and adventitial edema and decrease the thickness and dryness of the mucous plaques inside the bronchiolar lumen. The aim of this study is to evaluate the outcome of nebulizing 3% HS with SABA plus ICS in patients with moderate bronchiolitis aging from 3 to 12 months old.

Objective of study

Our main aim of this study is to determine the improvement of patient's condition by comparing the length of hospital stay and improvement in clinical severity score (CS score) in infants with moderate bronchiolitis through nebulizing 3% HS.

Study design

We designed a randomized control trial on children aged 3-12 months hospitalized with moderate bronchiolitis to compare the treatment outcome between 3% HS and 0.9% normal saline. All the cases were from inpatients of Pediatric Pulmonary Department 1 of the first Norman Bethune hospital of Jilin university, Changchun, china.

Methods

We analysed 125 patients undergoing moderate bronchiolitis (with a CS score between 6 and 9) who admitted in pediatric pulmonary department of the first hospital of Jilin University from 1st December 2014 to December 2015. Patients, arranged randomly to nebulize either 3% HS with salbutamol plus budesonide (Group 1) or 0.9% saline with salbutamol plus budesonide (Group 2) three times per day until conditions were stable enough for discharge (with a CS score below 3). We recorded the SC scores of each patient before and after the first nebulization every day. There were no differences on color, smell, and other physical properties of the solutions between the two groups. We used a nebulizer (PARI Vios compressor with PARI LC PLUS nebulizer) with tightly fitting facemask providing an efficient delivery of aerosol with a mass median aerodynamic diameter of 0.5 to 5μm range. Monitoring parameters for improvement or worsening, recorded according to CS scores described by Wang et al.

Basic therapy

1. Antipyretics if necessary (temperature >38.3°C)
2. Nasal suction if the nose blocked
3. Supplementary O2 by face mask if necessary (tachypnoea or mild cyanosis)
4. Hydration if necessary
5. Andrographolide 0.2ml/kg/day once a day.

Discharged criteria: feeding well orally, no need of intravenous fluids and supplement oxygen, clinical severity score<or=3, absence of accessory muscle use or tachypnoea (RR<31 breaths/min), and oxygen saturation>92% on air.

Outcomes were considered mainly as: ① the length of hospital stay from admission to time taken to reach CS score < 3; ② the improvement in CS score after the first nebulization every day. Other minor outcomes include respiratory rate, heart rate, saturation and none add-on treatments.

Inclusion criteria

a. Age 3-12 months
b. First episode of wheezing
c. Meets clinical definition of bronchiolitis
d. Moderate bronchiolitis, CS score between 6-9.

Exclusion criteria

a. Any underlying disease (e.g. Cystic fibrosis, bronchopulmonary dysplasia and cardiac or renal disease)
b. Prior history of wheezing
c. Family history of asthma, pneumonia, TB, allergic history
d. Discharged before CS score below 3
e. Progressive respiratory distress requiring mechanical ventilation.

Division of patients

Patients, divided into two groups: Group 1 nebulized with ICS+SABA+ 3%hypertonic saline; Group 2 nebulized with ICS+SABA+0.9% saline.

Statistical analysis

Each variable visually scanned of their histograms, normal Q-Q plots for normalcy of distribution. Categorical data compared using the chi-square test and all continuous variables compared using the pair or unpaired t-test as appropriate. A P value <0.05 was considered statistically significant.

Study limitation

The study did not include outpatients with mild bronchiolitis and cases with complications like pneumonia, pleural effusion, lung collapse etc. It was also lack of a follow-up observation after discharge.

Results

125 previously healthy infants were enrolled in the study from 1st December 2014 to December 2015. Their mean age was 6.92±0.24 months (range, 3 to 12 months). The cases were diagnosed as moderate bronchiolitis with CS scores varying from 6 to 9.

124 patients of them completed the study, except only one patient in Group 2 who was excluded for the reason of discharging before CS score below 3. Among 124 patients who completed the study, 62 patients were in Group 1 who received 3% hypertonic saline + 0.25ml salbutamol + 0.5mg budesonide, and another 62 patients were in Group 2 who received 0.9% normal saline + 0.25 ml salbutamol +

0.5 mg budesonide. The two groups had similar variables and clinical characteristics at base line.

The mean length of hospital stay from admission to time taken to reach CS score < 3 was 4.83±0.077 days for the whole subjects investigated, and it differed significantly between the two groups: 4.27±0.90 days in Group 1 (Figure 1) and 5.39±0.610 days in Group 2 (Figure 2). An independent sample test conducted to examine whether there was significance difference between the effect of hypertonic group and normal saline group in relation to the days of hospital stay or not. A P value less than 0.001, revealed statistically significant difference in the lengths of time taken to reach CS score < 3 between the two groups (Table 1).

Table 1 Baseline clinical characteristics

Characteristics	Group 1 (3%Hypertonic saline + salbutamol + budesonide)	Group 2 (0.9%Normal saline + salbutamol + budesonide)	P value
(variables)	(n=62)	(n=62)	
Age, mo	Mean-6.77,SD 2.5±314	Mean 7.06,SD-2.7±0.34	0.79
Female/male gender (No and %)	Male 33 (53%)	Male 37(59.7%)	0.47
	Female 29 (46%)	Female 25 (40.3%)	
Length of time taken from admission to CS score < 3 (day)	Mean 4.27±o.90,	Mean 5.39±0.610	<0.001
Change in CS score before and after nebulization (mean)	Before -7.34±0.10	Before -7.39±0.99	<0.001
	After -5.94±0.89	After -6.50±0.94	
Baseline CS score on entry (mean)	7.34±0.1	7.39±0.99	NS (Not significant)
Mean heart rate (HR)	128.2±1.251	129.06±1.394	NS
Mean respiratory rate (RR)	44.76±0.431	45.19±0.437	NS
Oxygen saturation (SpO2%)	95.39±0.293	95.44±0.271	NS
Pyrexia (percentage)	6.5%,n=4	9.7%,n=6	NS
Add on therapy (Percentage)	4.8%,n=3	3.2%,n=2	NS

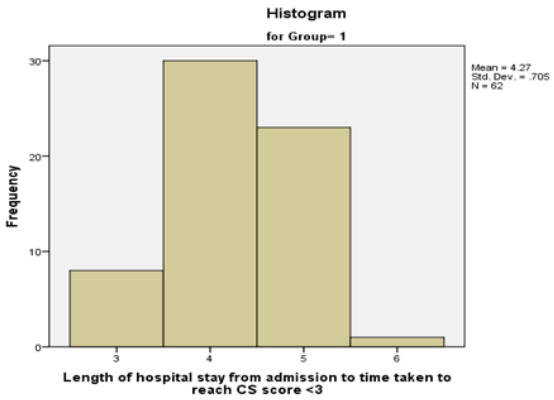

Figure 1 Length of time taken to reach CS score < 3 in Group 1.

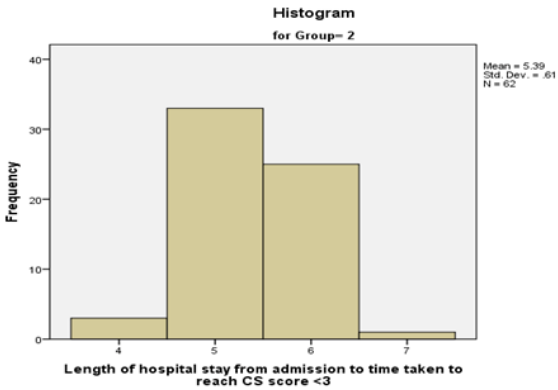

Figure 2 Length of time taken to reach CS score < 3 in Group 2.

On the first day of treatment, the mean CS scores at baseline were 7.34±0.1 and 7.39±0.99 for Group 1 and Group 2, respectively. After the first nebulization, the CS scores decreased to 5.94±0.89 (SD-0.698) and 6.50±0.094 (SD 0.741) of Group 1 and Group 2, respectively. The P value in each group was less than 0.001, indicating statistically differences between CS scores before and after nebulization by both groups of solutions in the treatment of moderate bronchiolitis. However, the differences of the mean values and standard deviation (SD) results after nebulization in the two groups suggested a better treatment outcome of 3% hypertonic saline with salbutamol plus budesonide than 0.9% normal saline.

No adverse effect observed in any study group. No significance differs in respiratory rate, heart rate, and saturation between the two groups. In addition, no one transferred to PICU. 4.8% and 3.2% of patients from Group 1 and Group 2 went on add on therapy (antibiotics) respectively. The percentage of patients who got pyrexia from Group 1 and Group 2 was 6.5% and 9.7% respectively. Thus, the conditions of pyrexia and add on therapy did not show any significance between the two groups.

Discussion

Bronchiolitis is the most common lower respiratory tract infectious disease in infants. Cough and wheezing are the main clinical symptoms. Treatment of bronchiolitis by means of nebulization with different solutions such as HS, bronchodilators, steroids etc, considered effective. In order to identify the effectiveness of 3% HS in moderate bronchiolitis, we designed a randomized control study of two types of nebulization. One type contains 3% HS with salbutamol plus budesonide, whereas another type contains 0.9% saline with salbutamol plus budesonide.

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Bronchodilator (salbutamol) and ICS (budesonide) commonly used in treating bronchiolitis. Salbutamol shows effect in the dilation of bronchioles and steroids plays role as anti-inflammatory. 3% HS solution, by absorbing water from the submucosa, can decrease the airway edema and improves mucociliary function by accelerating mucus transport rates. The use of inhaled HS to treat bronchiolitis was first reported in 2005[7] and the evidence in favour was strengthened with the publication of a 2 –year extension of the original study.[8] HS is inexpensive and easily available and applicable in all patients without significant side effects. HS solution has shown to increase mucociliary clearance in normal subjects, in asthma, bronchiectasis, cystic fibrosis, and sinonasal diseases.[9]

We conducted a randomized control trial in inpatient department of pediatric pulmonary in tertiary center to evaluate the effectiveness on treatment of moderate bronchiolitis with 3% HS + salbutamol + budesonide compared with 0.9% normal saline + salbutamol + budesonide. We found advantages of 3% HS over normal saline in terms of the length of hospital stay from admission till the patients' CS score <3 and the significant mean difference of -1.113 in length of hospital stay was noticed between two groups. Change in CS score before and after nebulization in each group was significant. The comparison of CS score after nebulization showed significant difference between the two groups. These results indicate that both groups of therapeutic regimens are effective in moderate bronchiolitis, and HS group presents an even better outcome than normal saline group. In this trial, we found that HS is safe for infants with moderate bronchiolitis; there were no apparent adverse effects attributable to frequently inhaled HS. Patients finished the entire treatment without bronchospasm, cough or wheezing aggravation. A normal height of the periciliary liquid is crucial for normal airway mucociliary clearance. Viral (e.g. RSV) infections decrease the mucous layer water contents; damage the airway surface liquid epithelium. In addition, reduces the height of the periciliary liquid and clearance of mucus.[10] The pathology of bronchiolitis is peribronchiolar mononuclear infiltration, epithelial cell necrosis, sub-mucosal edema and an increase in the rate of mucous secretion, and therefore an increase in the mucin/water ratio,[11] which causes relative a reduction in the airway surface liquid.[12] The Pathophysiology of bronchiolitis is quite distinct from that of asthma; these patients are less, if at all, responsive to bronchodilators.[13] Nebulized HS alone is safe for infants with moderate or severe bronchiolitis.[14] Many studies been conducted in this field; however, the results were not unanimous. Some studies showed HS was effective than normal saline and some showed there was no difference between them.

A past study showed that infrequently inhaled HS is an effective treatment for infants with moderate to severe bronchiolitis. It took less time to relieve symptoms and pulmonary signs: 1.2 days on average for wheezing and cough alleviation, and 1.8 days for pulmonary moist crackles to disappear. The CS scores decreased more significantly in the HS group than in the NS group on each day within 96 h after hospitalization. The hospital length of stay reduced by 1.6 days, from 6.4 ± 1.4 to 4.8 ± 1.2 days.[15] And the same author previously demonstrated that nebulized hypertonic saline and salbutamol decreased the clinical symptoms more quickly and shortened the length of hospital stay for infants with mild to moderate bronchiolitis.[16]

In other studies, shorter length of hospital stay and lower admission rates have been reported to be objective and clinically meaningful measure of cost effectiveness.[17,18] In the Cochrane Meta analysis (four studies) 24.1% shorter (mean 1.16 days, 95% CI -1.55 to - 0.77 days) length of hospital stay reported with HS.[19] Another studies reported the maximum reduction (-1.4) days with hypertonic saline had longer stay with (double as compared to other three studies) in both groups leading to heterogeneity of data.[20] Studies with saline plus salbutamol treatment in bronchiolitis show that combination of nebulized salbutamol with NS or HS alone are all effective in decreasing the severity score in the first attack of moderate bronchiolitis in the emergency department.[21] Up to now, the majority of studies investigating the use of nebulized HS solution in bronchiolitis conducted in hospitalized children.

In a study done with 3% HS with epinephrine v/s normal saline with epinephrine on children aged from 2 months to 12 months, the optimal treatment of bronchiolitis remains unclear. Their study showed no clinically significant improvement in CS score with HS in the emergency setting compared with normal saline when a maximum of 2 doses were used.[22] There are four previously published studies on the use of HS in bronchiolitis. The earliest publication in 2002 included 65 infants with bronchiolitis in the ambulatory setting, who randomized to receive either terbutaline and normal saline or terbutaline and 3% HS 3 times a day for 5 days. The authors noted a significant improvement in the clinical score after treatment with HS on each of the 5 days in this modestly sized study.[23]

In another published study (2007) of treatment of bronchiolitis with HS, hospitalized patients randomized to receive repeated doses of either HS or normal saline in addition to routine therapy ordered by the attending physicians. Bronchodilators prescribed approximately 5 times a day in addition to the study solution, making it difficult to state how much of an added effect the bronchodilators had. Overall, the authors found a clinically relevant reduction in length of hospital stay in the HS group. Next study on pre hospital setting, 57 patients was randomized to receive 5% hypertonic saline, 58 to receive 3% hypertonic saline, and 56 to receive 0.9% saline. The mean CS for the 3or 5% saline group was 3.75 ± 1.27, and that for the 0.9% saline group was 3.97 ± 1.40 (P = .38). Nebulization with 3 or 5% HS was safe was the conclusion of that study.[24] In the third study, 52 hospitalized patients with bronchiolitis enrolled in an initial trial. Patients were randomized to either epinephrine in normal saline or epinephrine in 3% HS. Treatment given three times a day until discharge. A further 41 infants were enrolled for a second year ,and the pooled data published 3years later showed significant improvement in the CS scores in the group treated with HS as well as a shortened hospital stay in the same group.

Adverse effects encountered with the use of HS are rare and infrequent. Warkand McDonald[25] described an excellent safety profile for HS after studying 143 patients with severe cystic fibrosis who treated with HS solution inhalations. There is a reported risk of bronchospasm and of decreased ciliary beat frequency; however, these are usually only seen with higher concentrations of HS (>7%).[26] In our study, we used a 3% HS solution to decrease the risk of the above adverse effects.

Other Randomized controlled trials (RCTs) comparing short-term systemic or inhaled glucocorticoids versus placebo in children < 24 months with acute bronchiolitis. Glucocorticoids did not significantly reduce outpatient admissions by days 1 and 7 when compared to placebo (pooled risk ratios (RRs) 0.92; 95% CI 0.78 to 1.08; and 0.86; 95% CI 0.7 to 1.06, respectively). There was no benefit in LOS for inpatients (mean difference -0.18 days; 95% CI -0.39 to 0.04).

By far, there are no studies involving the three compositions (HS, SABA and ICS) altogether. Based on our randomized control trial study, we demonstrated that the combination of 3% HS, salbutamol, and budesonide for nebulization can be used in treating moderate bronchiolitis because we did not find any significant drawbacks. There are some limitations in our study, such as the small number

of enrolled patients, lack of follow-up reports of relapse, etc. Further studies should be conducted on a larger number of patients preferably in multi-centered to evaluate the effectiveness of 3% HS nebulized together with SABA and ICS in infants with moderate bronchiolitis.

Conclusion

We concluded that inhaled 3% hypertonic saline with salbutamol plus budesonide was safe and effective, and might be superior to current treatment of hospitalized moderate bronchiolitis cases. A multiple center trial to explore the clinical benefit of this therapy with a larger sample size is required.

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None.

Conflicts of interest

There are no conflicting interests declared by the authors.

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