The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 3762-3766

Treatment of Bronchiolitis Using Nebulized Hypertonic Saline in Asthma-Prone and Non-Asthma-Prone Patients

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ABSTRACT

Background: In bronchiolitis, children under the age of two experience cough, dyspnea and wheezing, following a viral upper respiratory infection. Frequently recurrent bronchiolitis in infants with atopic background is the best example of asthma-prone viral-induced wheeze. In bronchiolitis management, inhaled hypertonic saline is the subject of debate among pediatricians and researchers. Nebulized hypertonic saline acts by increasing fluidity of airway surface liquid. Bronchospasm is a theoretical risk for inhaled hypertonic saline when used without adjunctive bronchodilators.

Objective: To compare the response to nebulized hypertonic saline plus B 2 agonists, with nebulized isotonic saline plus B 2 agonists, in asthma-prone and non-asthma-prone bronchiolitis patients.

Patients and methods: This study was a randomized double blind controlled trial, which was carried out at Pulmonology Unit, Pediatric Department, Zagazig University Children Hospital. The study was conducted on 104 infants with acute viral bronchiolitis of mild to moderate severity. They were divided into two groups 52 in each group. Group 1: Asthma-prone patients and group 2, which included non-asthma-prone patients. Patients were randomly assigned to receive inhalation of 0.3 mg/kg salbutamol added to 5 ml of either normal saline 0.9% or hypertonic saline 3%. Within each group the number of patients receiving hypertonic or isotonic saline inhalation was equal to 26.

Results: Nebulized hypertonic saline salbutamol mixture resulted in better improvement of the studied asthma-prone and non-asthma prone bronchiolitis patients. Hypertonic saline decreased case severity and days of hospital stay. **Conclusion**: Nebulized hypertonic saline shortened the days of hospital admission and improved the respiratory distress in mild to moderate bronchiolitis. Nebulized hypertonic saline is equally effective in asthma-prone and non-asthma-prone patients and its beneficial effect outweighs its theoretical broncho-constrictive effect.

Keywords: Treatment of bronchiolitis, Nebulized hypertonic saline, Asthma.

INTRODUCTION

The American Academy of Pediatrics (AAP) guidelines 2014 defined bronchiolitis as wheeze cough following viral upper respiratory infection in children less than two years old [(1)]. Recurrent early bronchiolitis may predispose to childhood asthma [(2)]. The Global Initiative for Asthma (GINA) developed diagnostic criteria for diagnosing asthma in children under 5 years old with recurrent virus caused wheezing [(3)].

The updated AAP (American Academy of Pediatrics) guidelines 2014 recommended nebulized hypertonic saline as a treatment option for bronchiolitis [(4)]. In bronchiolitis management, inhaled hypertonic saline is the subject of debate among pediatricians and researchers. Hypertonic saline creates high osmotic pressure in the lumen of bronchioles withdrawing water from submucosa to hydrate airway surface liquid. This results in substantial reduction of edema in the submucosa and increased fluidity of the mucus layer [(4)].

Since Hypertonic saline is used as a challenge test for diagnosis of bronchial asthma by inducing bronchospasm [(5)], bronchoconstriction is a possible theoretical side effect of inhaled hypertonic saline when used without bronchodilators [(6)]. During treatment of bronchiolitis, nebulized hypertonic saline is usually mixed with either terbutaline [(7)] or epinephrine [(8)] to guard against bronchoconstriction. Considering the aforementioned facts about the action of nebulized hypertonic saline, we expected different response in asthma-prone and non-asthma prone patients with bronchiolitis. The aim of our study was to compare the therapeutic response to nebulized hypertonic saline plus B 2 agonists, with nebulized isotonic saline plus B 2 agonists, in asthma-prone and non-asthma-prone bronchiolitis patients.

SUBJECTS AND METHODS

This study was a randomized double blind-controlled trial, which was carried out at Pulmonology Unit, Pediatric Department, Zagazig University Children Hospital. The study was conducted on 104 infants with acute viral bronchiolitis of mild to moderate severity dividing them into two groups 52 in each group. Group 1: Asthma-prone patients and group 2 that included non-asthma-prone patients. Patients were randomly assigned to receive inhalation of 0.3 mg/kg salbutamol added to 5 ml of either normal saline 0.9% or hypertonic saline 3%. Within each group the number of patients receiving hypertonic or isotonic saline inhalation was equal to 26.

Ethical approval: All Parents of participants signed informed consent forms and submitted them to Zagazig University's Research Ethics Committee, which approved the study (ZU-IRB#6192/20-9-2020). The study followed the World Medical Association's

Received: 7/8/2021
Accepted: 30/9/2021

ethical code for human experimentation, the Helsinki Declaration.

Inclusion criteria: Patients with bronchiolitis under the age of 2 years, excluding the newborn period, are eligible for the trial. Bronchiolitis was clinically diagnosed by history of upper respiratory symptoms followed by tachypnea, cough and chest wheeze [(1)].

Exclusion criteria: Parents refusing to share in the study, age > 2 years or < one month, patients who had any underlying chronic condition (e.g., cardiac, renal disease, cystic fibrosis, bronchopulmonary dysplasia or any other chronic disease), oxygen saturation < 85 % on room air, Wang clinical severity score > 8, increasing respiratory distress requiring PICU admission and patients with previous treatment with bronchodilators within last 4 hours or systemic steroid therapy within 48 hours before admission.

Patients were classified into two groups:

Group 1: Asthma-prone patients (N 52), and group 2: Non-asthma-prone patients (N 52).

In our study we adopted and adapted GINA model for diagnosing asthma in pre-school children. Asthma model has the advantage of being purely clinical model taking into consideration, the frequency of recurrence of chest wheeze, the length of each attack, symptoms between attacks and atopic background of the patient. One disadvantage of GINA model is that the boundaries between the three columns of the model are not clear.

To transform GINA model into a practical one, we adapted GINA model into a scoring system. We considered the patient to be asthma-prone if he fulfilled three of the following 4 criteria: (1) Symptoms of cough, wheezing, and heavy breathing >10 days during upper respiratory tract infections. (2) More than 3 episodes per year or sever episodes and/or night worsening. (3) Between episodes child have symptoms of cough, wheeze or heavy breathing during play. (4) Child is suffering from other allergic diseases as eczema food allergy or family history of asthma [(9)].

All of the participants in this research were subjected to the following:

1. Detailed history taking and thorough clinical examination.
2. Patients were randomly distributed to receive inhalation of 0.3 mg/kg salbutamol added to 5 ml of either normal saline 0.9% or hypertonic saline 3%. Within each group the number of patients receiving hypertonic saline or isotonic saline inhalation was equal (26 patients each). We used the only salbutamol drops available in the Egyptian market (farcolin drops of Pharco pharmaceutical company, Alexandria, Egypt) as a wet nebulized aerosol, repeated every 6 hours till improvement and hospital discharge.
3. Patients were examined at the start of the study, and every morning by senior staff. Patients were re-examined before each nebulizer session and 30 minutes after by another pediatrician unaware of the patient grouping. Clinical severity was assessed using Wang score [(9)].
4.
5. **Devices:** A single-patient disposable latex-free nebulizer set with pediatric size face mask (Medical industries Nebulizer Set, first industrial Zone, Bader city Egypt) regularly available in our ward connected to wall oxygen supply and adjusted at 5 liters per minute. This produced acceptable particle size and reasonable nebulization time of 5-10 minute for a 4 ml nebulizer solution.

Statistical analysis

In order to analyze the data acquired, it was loaded into a computer and run via the Statistical Package of Social Sciences, version 25. (SPSS). Tables and graphs were used to present the findings. The Shapiro–Wilk test was used to examine the distribution properties of variables as well as the homogeneity of variance. The quantitative data were expressed as mean, median, standard deviation, and confidence interval. The frequency and proportions of qualitative data were used to present the information. For quantitative independent data, the student's t test (T) and the Mann-Whitney test (MW) were employed to examine the data as needed. To examine qualitatively independent data, researchers employed the Pearson Chi-Square Test and the Chi-Square for Linear Trend (χ^2). P value equals or less than 0.05 was considered significant.

RESULTS

Table (1) showed that there was statistically non-significant difference between the studied groups regarding age, gender or exposure to passive smoking.

Table (2) showed that there was statistically non-significant difference between the studied groups regarding Wang score at admission.

Table (3) showed that there was statistically significant difference between use of hypertonic saline and normal saline in non-asthma-prone and asthma-prone bronchiolitis patients. Hypertonic saline decreased duration of hospital stay in both ($P < 0.001$).

Figure (1), multiple line graph showed comparison between the studied groups regarding Wang score over time. Hypertonic saline group showed more rapid improvement over days of hospital admission.

Table (4) showed that although there was non-statistical difference between both age groups regarding Wang score, infants below one year have statistically significant shorter length of stay (LOS).

Table (1): Demographic characteristics, and exposure to passive smoking between the studied groups

	Groups				χ^2/KW	P
	Normal saline in non-asthma prone	Normal saline in asthma prone	Hypertonic saline in non-asthma prone	Hypertonic saline in asthma prone		
	N=26(%)	N=26(%)	N=26(%)	N=26(%)		
Gender:						
Male	14 (53.8)	16 (61.5)	16 (61.5)	17 (65.4)	0.765	0.858
Female	12 (46.2)	10 (38.5)	10 (38.5)	9 (34.6)		
Age (months):						
Median	8	8.5	9	9	1.42	0.701
Range	3 – 24	3 – 24	3 – 24	4 – 24		
Passive smoking:						
No	10 (38.5)	10 (38.5)	15 (57.7)	16 (61.5)	4.733	0.192
Yes	16 (61.5)	16 (61.5)	11 (42.3)	10 (38.5)		

χ2: Chi square test KW: Kruskal Wallis test

Table (2): Comparison between the studied groups regarding Wang score at admission

Parameter	Groups				KW	P
	Normal saline in non-asthma prone	Normal saline in asthma prone	Hypertonic saline in non-asthma prone	Hypertonic saline in asthma prone		
	N=26(%)	N=26(%)	N=26(%)	N=26(%)		
Wang score						
Median	5.5	4	5	5		
Range	3 – 9	3 – 8	3 – 8	3 – 8	4.4	0.217

χ^2Chi square test KW Kruskal Wallis test

Table (3): Comparison between the therapeutic effects of normal and hypertonic saline on non-asthma-prone and asthma-prone patients regarding days of hospital stay

Parameter	Non asthma prone		Test	
	Normal saline	Hypertonic saline	Z/χ^2	P
	Median (range)	Median (range)		
Days of admission	6 (4 – 8)	2 (1 – 7)	-5.063	<0.001**
	Asthma prone			Test
	Normal saline	Hypertonic saline	Z/χ^2	P
	Median (range)	Median (range)		
Days of admission	5.5 (4 – 9)	3 (2 – 8)	-4.542	<0.001**

Z Mann Whitney test chi square test **p≤0.001 is statistically highly significant

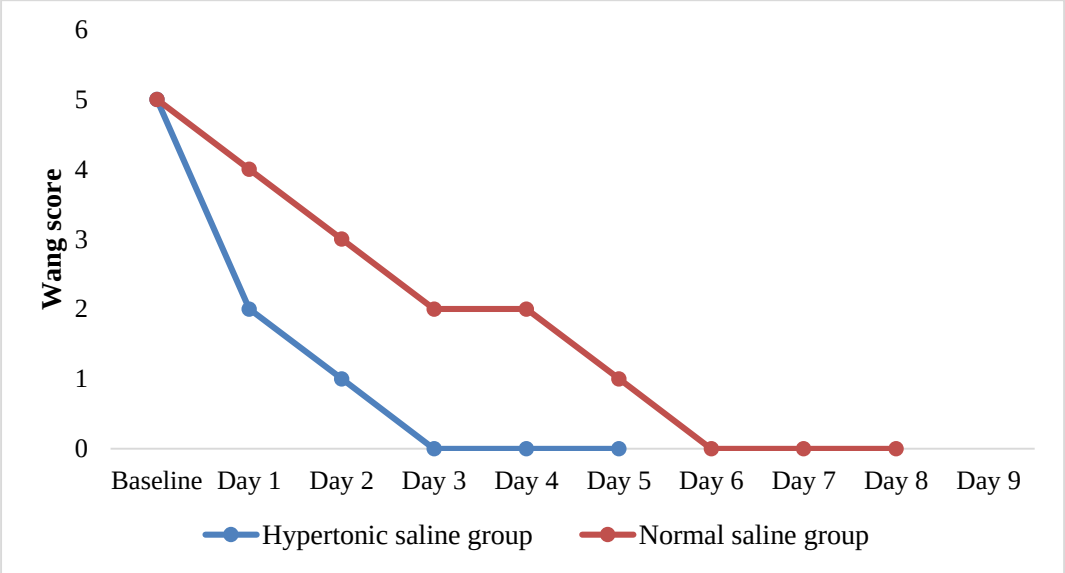

Figure (1): Multiple line graph showing comparison between the studied groups regarding Wang score over time.

Table (5): Comparison between effects of hypertonic saline on LOS above and below one year

Parameter	Groups		Test	
	<1 year	≥1 years	t	P
	Mean ± SD	Mean ± SD		
Wang score	5.16 ± 1.45	4.71 ± 1.58	1.349	0.18
LOS	4.11 ± 1.92	5.36 ± 1.62	-3.325	0.002*

Chi square test **p ≤ 0.001 is statistically highly significant

DISCUSSION

Bronchiolitis is an acute viral-induced inflammation of the bronchioles. It is one of the most common causes of hospital admission to our Pediatric Pulmonology Unit of Zagazig University Hospital. Respiratory syncytial virus (RSV) is the most common causative virus. Other less common viruses include influenza A and B, parainfluenza viruses, adenovirus, and rhinovirus [10]. In Egypt RSV has been detected as a major cause of sever bronchiolitis requiring PICU admission [11].

In our study, clinical severity of bronchiolitis was assessed using Wang clinical severity score [9]. Wang score was employed by many clinical studies assessing different therapeutic options for management of bronchiolitis [12, 13]. There was statistically non-significant difference between the studied groups regarding Wang score at admission.

In the present study, nebulized hypertonic saline (HS) salbutamol mixture resulted in better improvement of the studied asthma-prone and non-asthma prone bronchiolitis patients. There was statistically highly significant difference between the hypertonic saline and isotonic saline in both groups regarding length of hospital stay (LOS). The improvement after hypertonic inhalation therapy was more notable in infants below one year. Comparing patients below and above one year with same disease severity showed better improvement in infants below one year. This is probably because infants below one year have smaller radius of their bronchioles. According to Hagen-Poiseuille equation airway resistance is inversely proportional to the radius to the power of 4. Therefore a small improvement of diameter as a result of inhaled hypertonic saline resulted in 16 fold improvement in resistance of the small airways. In our study, no adverse events were reported with the use of either hypertonic or isotonic saline.

Although many studies evaluated the therapeutic effect of nebulized hypertonic saline in bronchiolitis, up to our knowledge, there is no previous study that compared the effect of hypertonic saline in asthma-prone and non-asthma prone bronchiolitis patients. Our study highlighted this issue and proved that the favorable action of nebulized hypertonic saline plus the bronchodilator effect of added B2 agonists outweighted its occasional bronco-provocative effect in both asthma-prone and non-asthma prone bronchiolitis patients [14].

Nebulized hypertonic saline (3%) is a promising safe and effective treatment for acute viral bronchiolitis. The beneficial effect of inhaled hypertonic saline was great in infants under one year of age. Hypertonic saline enhances mucociliary clearance in healthy and sick lungs, according to physiological evidence. As bronchiolitis is characterized by inflammation of the airways and subsequent mucus plugging, it stands to reason that increased fluidity of mucus layer will facilitate mucus clearance. The concept of rehydrating the airway surface fluids has been suggested as a specific mechanism of action [14].

Many studies go on agreement with our results supporting the use of nebulized hypertonic saline for treatment of bronchiolitis. Nebulized hypertonic saline, compared to nebulized isotonic saline, reduced hospitalization risk in infants who were treated in the emergency room by 14 percent, according to the Cochrane database, published in 2017. Although 3% HS was found to be superior, it is possible that nebulized higher concentration could cause paroxysmal cough in some patients [15].

In a systematic review, **Zhang *et al.*** [16] concluded that nebulized hypertonic saline is an effective and safe treatment for infants with acute bronchiolitis. The use of nebulized hypertonic saline in infants with acute bronchiolitis shortens their hospital stay and improves their clinical severity score. Clinical studies done by **Sarrell *et al.*** [7] have suggested that nebulized 3% hypertonic solution is beneficial, cost-effective and increases the quality-adjusted-life-years (QALYs) for infants with bronchiolitis.

On the other hand, less number of studies failed to detect the beneficial action of nebulized hypertonic saline in bronchiolitis management. Nebulized HS treatment did not reduce the rate of hospital admissions among infants with their first episode of acute moderate to severe bronchiolitis who were admitted to the pediatric emergency department according to the study conducted by **Angulvant and colleagues** [17]. **Morikawa *et al.*** [18] studied infants with RSV-induced bronchiolitis and assumed that nebulized HS treatment had no effect on LOS.

The rationale hypertonic saline creates high osmotic pressure in the lumen of bronchioles leading to transfer of water from submucosa to the mucus lining the respiratory mucosa. This results in substantial reduction of edema in the submucosa and

increased fluidity of the mucus layer. The only possible side effect of nebulized hypertonic saline when used without adjunctive bronchodilators solution is the risk of bronchospasm. Considering the aforementioned facts about the action of nebulized hypertonic saline, we expected different response in asthma-prone and non-asthma prone patients with bronchiolitis.

CONCLUSION

Nebulized hypertonic saline shortens the days of hospital stay and improves the respiratory distress in mild to moderate bronchiolitis. Nebulized hypertonic saline is equally effective in asthma-prone and non-asthma-prone patients and its beneficial effect outweighs its theoretical broncho constrictive effect.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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