Pulmonary Pharmacology & Therapeutics 24 (2011) 633–637

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis☆,☆☆

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ARTICLE INFO

Article history:
Received 5 June 2011
Received in revised form
12 September 2011
Accepted 17 September 2011

Keywords:
Aerosol therapy
Bronchiolitis
Hypertonic saline
Salbutamol

ABSTRACT

Background: The mainstay of treatment in bronchiolitis includes oxygenation, aspiration of secretions from the respiratory tract and maintenance of hydration. The first choice medical agent in clinical practice is nebulized bronchodilators, although their place in treatment is controversial.
Objectives: We investigated the therapeutic benefit of nebulized hypertonic (3%) saline (HS), by comparing four different nebulized regimens in the treatment of bronchiolitis in the emergency department.
Methods: A total of 120 infants were included in this randomized, double-blind, prospective study. Infants were grouped according to the nebulized treatment they received: group 1 - salbutamol + normal saline (NS), group 2 - salbutamol + HS, group 3 - HS, group 4 - NS. Heart beat, Clinical Bronchiolitis Severity Score (CBSS) and oxygen saturation of the patients were determined before and after the nebulizations and at 48–72 h after admission by the designated study physician.
Results: Post-treatment mean CBSS were significantly lower than pre-treatment scores in all groups ($p = 0.0001$) with no significant difference within groups. Improvement percentages for CBSSs were significantly higher in infants without a history of atopy treated with HS and NS ($p = 0.023$, $p = 0.0001$, respectively).
Conclusions: The CBSSs of all the infants improved after three doses of nebulized therapy regardless of the treatment regimens. The combination of salbutamol with hypertonic saline did not lead to an additive effect in the improvement of CBSSs compared to the standard salbutamol + NS combination. Atopic children benefited from salbutamol/NS combination whereas non-atopic children improved with HS and NS nebulizations based on improvement percentages of CBSS.

1. Introduction

Acute bronchiolitis is the most common cause of lower respiratory tract disease in infancy. The importance of the disease is associated with its high frequency, asthma-like clinical signs, and potential recurrence. The mainstay of treatment in bronchiolitis includes supportive care such as oxygenation, aspiration of secretions from the respiratory tract and maintenance of hydration. Despite current clinical practice guidelines, which do not recommend the routine use of any medication for bronchiolitis, the use of various medical therapies is still frequent [1]. Besides supportive care, nebulized bronchodilators (salbutamol, epinephrine, ipratropium bromide) and corticosteroids are commonly used in clinical practice. Antiviral treatment (ribavirin), heliox, surfactant, cysteinyl leukotriene receptor antagonists and extracorporeal membrane oxygenation are also used in the treatment of bronchiolitis [2–4]. Since the efficacy and cost-effectiveness of the treatment have recently become of great importance, any treatment that could decrease the severity of the disease with minimum cost is always preferred.

Hypertonic (3%) saline (HS) solution, by absorbing water from the submucosa and thereby decreasing edema, improves mucociliary function. It has been shown that HS in vitro and in vivo accelerates mucus transport rates [5,6]. Since HS is inexpensive, easy to acquire, and applicable for use for ambulatory patients, we investigated the therapeutic benefit and safety of nebulized HS in

☆ The research was primarily done in Istanbul Zeynep Kamil Maternity and Children's Diseases Training and Research State Hospital where Dr Ipek was also previously worked.
☆☆ This study was presented in poster format in Excellence in Paediatrics 2010, London.

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doi:10.1016/j.pupt.2011.09.004

Table 1
Evaluation of clinical bronchiolitis severity score.[a]

Score	0	1	2	3
Respiratory rate (breaths per minute)	<30	30–45	46–60	>60
Wheezing	None	Terminal expiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Severe with nasal flaring
General condition	Normal	–	–	Irritability, lethargy, poor feeding

[a] From Wang et al. [7].

the emergency department. In this study, The Clinical Bronchiolitis Severity Scores (CBSSs) were compared based on the four different treatment regimens and the atopy history of the infants.

We aimed to test the hypothesis that inhaled salbutamol and/or HS would improve CBSS in infants with acute bronchiolitis. A secondary aim was to determine if the presence of atopy could predict the response.

2. Materials and methods

This double-blinded, randomized, controlled, clinical trial was conducted between October 2009 and March 2010 in the short-stay unit of the Pediatric Emergency Department of a training and research hospital. Inclusion criteria were: age < 2 years, a history of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation, and a CBSS of 4–8 on admission [7] (Table 1). Viral respiratory infection was diagnosed on clinical grounds. Exclusion criteria were: infants with CBSS <4 or >8, oxygen saturation < 85% on room air, chronic cardiac illness, premature birth, birth weight < 2500 g, history of recurrent wheezing episodes, proven immune deficiency, severe neurological disease, age < 1 month or >2 years, consolidation or atelectasis on a chest roentgenogram. Signed informed consent was obtained from the parents of each infant and the study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children's Training and Research State Hospital. A standard follow-up form, which included data on age, gender, cause of admission, type of nutrition, number of household persons, exposure to tobacco smoke, family or individual history of atopy, type of heating, response to treatment, necessity of corticosteroid administration and hospitalization was completed for each child.

Family or individual history of atopy were defined as positive when any of the parents, siblings or the patient has been suffering from asthma, allergic rhinitis, atopic dermatitis or any documented allergy. Supportive care including oxygen supplementation, aspiration, and hydration when necessary were provided to all patients. Heart and respiratory rates of the infants were measured using a bedside monitor (SC 6002 XL Multiparameter Monitor; Siemens; Germany). Each of the 120 patients enrolled in the study was given 4 mL of a nebulized solution via a compressor nebulizer through a facemask with continued flow of oxygen at 4–5 L/min (Mini-compressor nebulizer, CN-02WD, Ace-Tec Co., Ltd., Guangdong, China). All eligible patients were randomly assigned to one of four groups according to the consecutive order of their admission to the short-stay unit: group 1 received 0.15 mg/kg salbutamol plus NS, group 2 received 0.15 mg/kg salbutamol plus HS, group 3 received only HS and group 4 received only NS. The nebulized solution was administered in a double-blind setting every 20 min until 3 doses had been administered (0, 20 and 40th min). A second assessment was performed 20 min after the last nebulization (at 60th min). All patients completed the treatment protocol, none of them withdrawn from the study.

The primary outcome for this study was the changes in CBSSs of each group after the treatment. Difference between pre- and post-treatment values were compared to pre-treatment values and defined as improvement percentage. Corticosteroid need, hospitalization ratios, and clinical assessment at 48–72 h were also assessed in the study. The decision of corticosteroid use and hospitalization is made when CBSS deteriorated and/or arterial oxygen saturation (SaO_2) detected <85 on room air after the treatment. Children necessitating hospitalization were continued on nebulized salbutamol/NS treatment and the others were discharged without any treatment. Children were asked to return at 48–72 h after the admission. All the children were reexamined at 48–72 h by the same physician and CBSSs were rescored.

The secondary outcome was the comparison of the improvement percentages of children with and without a history of atopy.

Heart beat, CBSS and SaO_2 of the patients were determined before and after the nebulizations and at 48–72 h after admission by the designated study physician who was blinded to the contents of all solutions.

2.1. Statistical analysis

The NCSS 2007 statistical software was used to analyze the data [8]. Descriptive analyses were completed for the overall study population and for each group separately. Categorical variables were examined by ×2 test; one-way analysis of variance (ANOVA)

Table 2
Baseline clinical characteristics.

Characteristics	Group 1 ($n = 30$)	Group 2 ($n = 30$)	Group 3 ($n = 30$)	Group 4 ($n = 30$)	*P*
Age (months)	8.13 ± 4.75	7.90 ± 3.57	8.40 ± 4.19	7.40 ± 3.08	0.791
Gender [n(%)]					
Female	13(43.3)	12(40.0)	13(43.3)	11(36.7)	0.940
Male	17(56.7)	18(60.0)	17(56.7)	19(63.3)	
Number of household persons	4.67 ± 1.49	4.57 ± 1.52	4.83 ± 1.72	4.33 ± 1.40	0.647
Exposure to tobacco smoke [n(%)]					
No	13(43.3)	11(36.7)	10(33.3)	13(43.3)	0.815
Yes	17(56.7)	19(63.3)	20(66.7)	17(56.7)	
Family/Individual History of atopy [n(%)]					
No	18(60.0)	22(73.3)	22(73.3)	22(73.3)	0.592
Yes	12(40.0)	8(26.7)	8(26.7)	8(26.7)	
Breastfeeding [n(%)]					
No	6(20.0)	5(16.7)	4(13.3)	5(16.7)	0.742
Yes	24(80.0)	25(83.3)	26(86.7)	25(83.3)	

Table 3
The comparison of the groups according to respiratory and heart beat rates, oxygen saturation and clinical bronchiolitis severity scores.

		Group 1 (salbutamol/NS) ($n = 30$)	Group 2 (salbutamol/HS) ($n = 30$)	Group 3 (HS) ($n = 30$)	Group 4 (NS) ($n = 30$)	p
Respiratory rate	Pretreatment	45.53 ± 6.43	42.33 ± 7.61	42.60± ± 6.71	42.93 ± 6.38	0.242
	Posttreatment	37.20 ± 8.78	38.0 ± 9.23	35.67 ± 9.37	39.20 ± 8.21	0.480
	p	**0.0001**	**0.004**	**0.0001**	**0.005**	
Oxygen saturation	Pretreatment	95.57 ± 2.22	95.10 ± 2.62	93.90 ± 2.86	95.30 ± 2.14	0.052
	Posttreatment	96.10 ± 3.11	96.07 ± 3.66	96.37 ± 3.33	96.33 ± 3.35	0.979
	p	0.330	0.065	**0.0001**	**0.037**	
Heart beat rate	Pretreatment	123.33 ± 10.20	125.60 ± 10.48	125.73 ± 12.24	129.80 ± 8.57	0.120
	Posttreatment	150.67 ± 9.24	150.33 ± 11.86	121.87 ± 10.22	127.47 ± 13.85	**0.0001**
	p	**0.0001**	**0.0001**	**0.044**	0.135	
Clinical bronchiolitis score	Pretreatment	4.87 ± 1.01	5.13 ± 1.20	5.03 ± 1.27	4.73 ± 0.98	0.525
	Posttreatment	2.47 ± 2.16	2.47 ± 1.93	2.27 ± 2.07	3.10 ± 2.43	0.469
	p	**0.0001**	**0.0001**	**0.0001**	**0.0001**	

The statistically significant results are represented with bold.

and Tukey's multiple comparison test were used for continuous variables. Groups with and without a history of atopy were compared using the Mann–Whitney non-parametric U test. A p value < 0.05 for the two-tailed t test was considered statistically significant.

3. Results

3.1. Study population

One hundred twenty infants (mean age 7.96 ± 3.91 months) met the inclusion criteria and were enrolled in the study. All patients were previously healthy – it was their first episode of wheezing. Baseline clinical characteristics of the groups were shown in Table 2. There were no significant difference between groups when baseline age, gender, number of household persons, exposure to tobacco smoke, family or individual history of atopy, type of home heating, type of nutrition and symptoms at the time of admission were compared.

Evaluating the socioeconomic factors, we found that the median value for household populations was 5 persons (min = 3; max = 10), that 60.8% of the patients were exposed to tobacco smoke, and that 45.8% were heating with coal stoves. The vast majority (83.3%) of subjects were breast-fed so it was not possible to determine if there was a relationship between breast-feeding and bronchiolitis.

3.2. Responses to treatment

Heart rates, SaO_2 and CBSS values were evaluated at baseline and 20 min after the last nebulization. Baseline values of the aforementioned parameters were not significantly different between the groups ($p > 0.05$) (Table 3).

Post-treatment mean CBSS were significantly lower than pre-treatment scores in all groups ($p = 0.0001$) with no significant difference within groups.

Pre- and post-treatment oxygen saturation levels were within normal limits in all groups so higher post-treatment values observed in groups 3 and 4 ($p = 0.0001$ and $p = 0.037$, respectively) were not clinically significant.

The mean post-treatment heart rates were significantly lower in group 3 ($p = 0.044$), while it was significantly higher in groups 1 and 2 treated with salbutamol ($p = 0.0001$).

Of the 120 children, 13 were hospitalized and the rest were asked to return for reassessment at 48–72 h with no treatment. Groups were compared for the necessity of corticosteroid administration, hospitalization ratios and clinical assessment at 48–72 h (Table 4).

Respiratory and heart rates, oxygen saturation and CBSS values of the groups were separately analyzed with regard to the presence of a family or individual history of atopy. Atopic children benefited from salbutamol/NS combination whereas non-atopic children improved with HS and NS nebulizations based on improvement percentages of CBSS (Table 5).

4. Discussion

Our study shows that combination of nebulized salbutamol with NS or HS and administering HS or NS alone are all effective in decreasing the CBSS in the first attack of moderate bronchiolitis in the emergency department.

To date, majority of the studies investigating the use of nebulized HS solution in bronchiolitis were conducted in hospitalized infants. There are 3 previously published trials on the use of nebulized HS in bronchiolitis in ambulatory setting. In the first study published in 2002, the authors compared the utility of HS and NS with adjunctive terbutaline and concluded that aerosolized HS plus terbutaline is effective in decreasing symptoms as compared to NS plus terbutaline in nonasthmatic, mild-to-moderate viral bronchiolitis [9]. Differently from our study, the treatments were performed 3 times a day for 5 days. In another study conducted in the emergency department setting, patients were randomized to receive nebulized racemic epineprine in either hypertonic or normal saline [10]. Although the co-administered bronchodilator was different from ours, the authors also reported no differential benefit for HS compared with NS similar to our result [10]. Reasoning from the hypothesis that a HS concentration >3% could be more efficacious, the authors compared the efficacy and safety of nebulized 5%, 3%, and 0.9% saline mixed with epineprine in

Table 4
The data concerning the necessity of corticosteroid administration, hospitalization ratios and clinical assessment at 48–72 h.

		Group 1 n %	Group 2 n %	Group 3 n %	Group 4 n %	p
Corticosteroid administration	No	22 73.3	23 76.7	23 76.7	19 63.3	0.61
	Yes	8 26.7	7 23.3	7 23.3	11 37.7	
Hospitalization	No	27 90.0	28 93.3	27 90.0	25 83.3	0.65
	Yes	3 10.0	2 6.7	3 10.0	5 16.7	
Clinical Assessment at 48–72 h[a]	1	27 90.0	27 90.0	27 90.0	28 93.3	0.98
	2	2 6.7	2 6.7	2 6.7	2 6.7	
	3	1 3.3	1 3.3	1 3.3	0 0.0	

1 - Clinical Bronchiolitis Severity Scores (CBSS) lower than post-treatment values.
2 - CBSS same as the post-treatment values.
3 - CBSS higher than post-treatment values.
[a] Clinical assessment at 48–72 h.

Table 5
The comparison of the improvement percentages of respiratory and heart beat rates, oxygen saturation and clinical bronchiolitis scores of groups according to the presence of atopy.

		Improvement percentage in infants without atopy	Improvement percentage in infants with atopy	*p*
Group 1	RR	13.11 ± 17.09	23.80 ± 20.55	**0.019**
	$SatO_2$	0.33 ± 2.66	−1.94 ± 3.46	0.054
	HR	−22.75 ± 12.52	−27.84 ± 13.01	0.189
	CBS	41.92 ± 31.42	68.27 ± 39.94	**0.021**
Group 2	RR	6.60 ± 16.40	18.20 ± 13.24	0.067
	$SatO_2$	−0.39 ± 2.82	−2.77 ± 2.66	**0.024**
	HR	−19.47 ± 14.68	−23.21 ± 9.25	0.557
	CBS	48.02 ± 26.93	70.85 ± 31.49	0.073
Group 3	RR	17.27 ± 17.54	12.44 ± 15.34	0.373
	$SatO_2$	−2.83 ± 2.91	−2.19 ± 3.76	0.690
	HR	1.70 ± 8.22	5.25 ± 6.09	0.250
	CBS	65.53 ± 32.29	42.81 ± 21.86	**0.023**
Group 4	RR	8.97 ± 14.67	6.32 ± 18.70	0.869
	$SatO_2$	−1.29 ± 2.57	−0.52 ± 3.30	0.833
	HR	2.88 ± 8.13	1.24 ± 11.23	0.557
	CBS	53.29 ± 28.92	4.05 ± 26.74	**0.0001**

RR: Respiratory rate, $SatO_2$: Oxygen saturation, HR: Heart beat rate, CBS: Clinical bronchiolitis score.
The statistically significant results are represented with bold.

a recently published study (2010) and found 5% HS superior to 3% HS and NS for improving the bronchiolitis severity score [11].

The effect of nebulized HS in improving clinical score was found to be greater among outpatients than inpatients [12]. Although no adverse event related to HS nebulization was reported, the authors suggested the use of the salbutamol/HS combination as a possible way to avoid the potential bronchospasm effect of HS in patients for whom asthma was not ruled out [12]. On the other hand, higher concentrations (5%, 7%) of nebulized HS solutions were also considered safe [11,13]. All HS recipients in our study group completed the treatment protocol without bronchospasm, aggravated wheezing or cough, so we suggested that HS is a safe treatment for infants with moderate bronchiolitis.

The place of nebulized bronchodilators in treatment of bronchiolitis is controversial. Some authors reported that bronchodilators were as effective as an oral placebo in the management of bronchiolitis, while others found it safe and effective in relieving the respiratory distress of young infants [14,15]. A Cochrane review of bronchodilators for bronchiolitis stated that they provide small, short-term improvements in clinical scores. Thus, the decision to use bronchodilators should be made by weighing this small benefit against the costs and adverse effects of these agents [16]. Furthermore, Hofhuis et al. [17] determined that inhaled beta-2 agonists cause a significant reduction in mean forced expiratory flow rates in infants with recurrent wheezing. In our study group, which did not include any recurrent wheezers, no significant difference was detected between salbutamol/NS, salbutamol/HS, HS and NS groups for post-treatment values of respiratory rate, oxygen saturation and CBSS. Additionally, we compared the response to four treatment protocols of patients with and without individual or family histories of atopy. Contrary to the previous reports, we observed that with nebulized salbutamol/NS, improvement percentages of respiratory rate and CBSS were higher in infants with a history of atopy [18,19]. This difference might be associated with the characteristics of the study groups as the mentioned studies were conducted on persistent and/or recurrent wheezers [18,19].

Ho et al. [20] observed desaturation after salbutamol and saline nebulization. The decrease in SaO_2 was greater and more prolonged with salbutamol than with saline. They concluded that salbutamol nebulization during acute bronchiolitis cannot be recommended [20]. The mean post-treatment SaO_2 values were significantly higher than baseline values in our NS and HS groups while the pre/post differences in the salbutamol groups were not significant. An explanation might be that the large decreases in SaO_2 were observed in only a few patients and so the post-treatment mean SaO_2 value was not deeply affected. And as patients with moderate bronchiolitis had normal SaO_2 levels at baseline, this was a limitation about evaluating the improvement in saturation.

A majority of the studies and meta-analyses comparing the efficacy of β2-agonist nebulization with other bronchodilators and placebo did not recommend the routine use of β2-agonist nebulization in bronchiolitis [1,14,20–23]. In a systematic review of the effectiveness of commonly used treatment regimens for bronchiolitis, King et al. [24] reported that there were no significant differences in outcome measures such as the decision to hospitalize and the duration of hospitalization between β2-agonist recipients and controls. Tachycardia and temporarily decreased SaO_2 were reported as adverse effects of treatment with β2-agonist agents in the same review. Tachycardia was also observed in group 1 and 2, but was not detected in NS and HS groups.

Post-treatment CBSSs were significantly lower than baseline values for all treatment groups, but no significant difference was detected between the groups. This means that salbutamol and HS are no more effective than NS in improving CBSS, and combining them does not produce any additive benefit.

Despite lack of evidence for their efficacy, corticosteroids are used in the management of bronchiolitis on the basis of the suggestion that the anti-inflammatory action of corticosteroids might alleviate the symptoms of bronchiolitis. In line with the findings of a meta-analysis describing a statistically significant improvement in clinical symptoms, length of hospital stay, and duration of symptoms on the course of bronchiolitis with corticosteroids, we also used steroids in case of clinical deterioration [25]. In our study, corticosteroid need, hospitalization ratios and clinical assessment at 48–72 h were not statistically significant when the treatment groups were compared.

Bronchodilator responsiveness is a feature of asthma so the beneficial effect of salbutamol only in infants with a history of atopy may be attributed to the presence of bronchoconstriction. The relationship between atopy and bronchodilator responsiveness has been discussed in many studies [19,26,27]. Chavasse et al. [19] reported no beneficial effect of salbutamol in atopic infants but their study group consisted of infants with well documented persistent or recurrent wheeze. Our study included infants with acute moderate bronchiolitis which may be reason for the different results.

Young non-atopic wheezers were proposed to have poor lung function with structural changes that predispose to wheezing with viral infection [27]. Non-atopic infants with smaller airways would be expected to demonstrate high airways resistance. Reticular basement membrane thickening and eosinophilic inflammation, which are characteristics of asthma, were not present in the airway pathology of atopic infants with reversible airflow obstruction [28]. Atopic children responding to bronchodilator treatment better than nonatopics may also be related to the smaller airways of non-atopic children [27].

Our study has some limitations. Since the study was conducted in a single-center setting in infants with moderate bronchiolitis, the results could not be generalized to all infants with bronchiolitis. The same results might not have been seen if the infants with severe bronchiolitis had enrolled the study group.

4.1. Conclusions

A combination of salbutamol with HS instead of NS (the control) does not provide any additive benefit in the improvement of CBSS compared to the control group. In infants with a history of family

atopy, improvement percentages for respiratory rate and clinical scores are higher with nebulized salbutamol + NS treatment than NS only and HS only treatments. Nebulized NS and nebulized HS are better for improving the respiratory rate and clinical score values in infants without a history of atopy.

Observations either consistent with or contradicting our results are both available in the published literature, but we believe that the optimal dose, concentration and treatment intervals of hypertonic saline nebulization have not been established yet. Placebo (except 0.9% saline) controlled multicenter trials conducted with standardized clinical scores, outcome measures, and long follow-up periods are now required to determine the efficacy of HS and salbutamol in the treatment of bronchiolitis.

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