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LETTER TO THE EDITOR

EFFECTIVENESS OF NEBULIZED HYPERTONIC SALINE AND EPINEPHRINE IN HOSPITALIZED INFANTS WITH BRONCHIOLITIS

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The objective of the study is to verify effects of nebulized 3% saline hypertonic solution (HS) in comparison to normal saline (NS) in addition to epinephrine in hospitalized children with bronchiolitis. Infants were randomly assigned either to receive every 6 hours nebulized NS (group I) or 3% HS (group II) in addition to epinephrine (1.5 mg) and to conventional treatment. The main endpoints of this study were the length of stay (LOS) in hospital and the clinical response score (CSS). Patients presented a significant decrease in CSS from the first through the third day of treatment, present in the first group but even more evident in the second group (p=0.0001). Comparison between group I and II data shows significant decrease in CSS in the 3% HS-treated patients both at the second (p<0.005) and at the third day of treatment (p<0.005). Infants in the NS control group had a mean LOS of 5.6±1.6 days, whereas children treated with 3% HS were discharged with a LOS of 4.9±1.3 days, reaching a significant decrease in stay (p<0.05). In hospitalized patients bronchiolitis nebulized 3% HS and epinephrine significantly decreased symptoms and LOS as compared to 0.9% NS and epinephrine.

Acute bronchiolitis is the main cause of respiratory illness requiring hospitalization in children under 2 years of age and the trend in hospitalization rate has been increasing in recent years (1). Mainly due to Respiratory Syncytial Virus (RSV) infection, the disease leads to hospitalization in only 1% of the children. However, considering that virtually all children before the age of 2 years could be infected, the cost of the disease determined by hospital admissions is elevated. In the United States it has been shown that the burden of the disease is considerable, having an annual cost of more than $500 million (2) and being responsible for 17% of all infant hospitalizations (2). Even though immune prophylaxis with monoclonal antibodies (Palivizumab®) has shown promising results in terms of reduction of the prevalence of the disease, this strategy cannot be applied to the whole population because of the high costs. Indeed, only high-risk categories of children, such as premature babies, have been indicated to receive such immuno-prophylaxis (3).

Considering therapeutic options, the mainstays for treatment are supplemental oxygen and hydration

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(3). Other types of treatment remain controversial: corticosteroid denied positive effect in wheezing and hospitalisation rate (3, 4), adrenergic agents used did not assure univocal results (3, 5-7). The use of nebulized hypertonic saline solution (HS) was demonstrated to be effective to decrease symptoms (8, 9) and length of hospitalization in association to β-adrenergic drugs (9, 10). In a pre-hospital setting, Al-Ansari et al. compared the effects of 5% vs 3% HS in addition to epinephrine, showing a better response to the more concentrated solution in term of clinical severity scores (11). More recently, it has been shown that in the treatment of acute bronchiolitis in an emergency department setting, the use of nebulized 3% HS added to epinephrine did not improve clinical outcomes more than normal saline (NS) and epinephrine (12). However, therapies that may contribute to the reduction in hospital stay could potentially greatly reduce health costs related to bronchiolitis (2). Therefore, it would be of great importance to have a sure definition of the effects of therapeutic options, such as HS, on clinical indices and length of hospitalization.

The present study aims to verify the effects of nebulized 3% saline solution in comparison to NS, in addition to epinephrine, in hospitalized children with bronchiolitis.

MATERIALS AND METHODS

Patients

All parents of children aged under 2 years with a clinical diagnosis of bronchiolitis admitted to the Division of Pediatrics at the Saint Mary Hospital in Pozzuoli, Naples (Italy) between November and April of two consecutive years (2008-2009 and 2009-2010) were invited to participate to the study. The diagnosis of bronchiolitis was defined as the first episode of wheezing and clinical symptoms of a viral respiratory infection, an oxygen saturation <94% in room air and significant respiratory distress measured by using a clinical severity score (CSS) described by Wang et al. (13). Briefly, the scoring system assigns a number from 0 to 3 to each respiratory variable (respiratory rate, wheezing, retraction) or general condition with increased severity receiving a higher score with a maximum of 12 (13).

Exclusion criteria were pre-existing cardiac or pulmonary diseases, premature birth < 36 weeks of gestational age, previous diagnosis of asthma, an initial oxygen saturation of 85% or less, or a respiratory distress which was severe enough to require resuscitation.

Study design

Of 136 patients assessed for enrolment in the study, 109 (69 males) agreed to participate, gave informed consent and were randomly assigned either to receive every 6 hours the nebulized 0.9% saline (NS) (group I) or the 3% HS (group II) in addition to aerosolized epinephrine (1.5 mg) and to the conventional treatment (oxygen, fluids). Patients were randomized to receive different saline treatments using a computer-based randomization program. Study solutions, prepared by the local hospital pharmacy, were blinded to participants and investigators. Each treatment was delivered by a nebulizer with continuous flow of oxygen at 6 L/min through a tight-fitting facemask.

The main end-points of this study were the length of stay (LOS) in hospital and the clinical response. LOS in hospital was defined as the time between the study entry (within 12 hours of admission to the hospital) and the time at which the infant was discharged on the basis of the clinical grounds by the attending physician. Clinical response was determined using daily CSS evaluation which was made before and 30 minutes after nebulisation.

The study protocol was approved by the local hospital committee and informed consent was obtained from the children's parents or caregivers. The study was registered at www.clinicaltrial.gov and received the identifier N°: NCT01300325.

Statistical analysis and data definitions

Three major outcomes of interest were considered: a) the difference of LOS in hospital between the two groups; b) the difference in the decline in CSS from baseline between the two groups every day; c) the changes in CSS after epinephrine in addition either to 0.9% NS or to HS every day.

Descriptive statistics were firstly performed and quantitative parameters were reported as means and standard deviations (SD). Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among the two groups of patients was made by the chi-square test (or by the Fisher's Exact test in case of expected frequencies less than five).

Quantitative normally distributed data were compared between the two groups of patients using the paired or unpaired t test as appropriate; when the homoscedasticity assumption was not fulfilled (age, days of illness at hospital admission, hospitalization days and the subtraction of post-treatment observation from pretreatment observation each day), the Mann-Whitney test was used as a non-parametric counterpart.

Quantitative variables (CSS score) for paired data (pre-inhalation and post-inhalation values) were compared using the Wilcoxon test. The Anova Friedman test was

used to compare CSS data, for the two groups of patients at each day.

Linear correlation between pairs of quantitative variables was evaluated by Spearman's correlation coefficient (r). For the analysis, a p value < 0.005 for two-tailed t test was considered significant due to multiple comparison. Otherwise, $p < 0.05$ was considered statistically significant. A statistical software program (StatSoft Italia s.r.l. 2005. Statistica, Vigonza, Italy) was used for all the analyses.

RESULTS

Data are presented as means ± SD. After randomization the parents of 3 children denied consent to participate in the study (2 in group I and 1 in group II). The demographics of the 106 evaluated patients are shown in Table I. No significant difference was observed between the two groups in terms of gender, age, disease course and severity, oxygen saturation at baseline and RSV positivity.

Table II depicts the CSS for the two groups of patients at each day for the first three days of treatment. Patients presented a significant decrease in CSS from the first through the third day of treatment that was present in the first group but even more evident in the second group ($p=0.0001$). However, comparison between group I and group II data shows significant decrease in CSS in the 3% HS-treated patients both at the second ($p<0.005$) and at the third day of treatment ($p<0.005$).

CSS evaluated in the morning, before and 30 minutes after the first inhalation, for each of the first three days of treatment are shown in Table III. As a result, the treatment with epinephrine and 3% saline solution (group II) produced significant decreases in CSS after each inhalation from the first day of treatment and remained significant from the first to the third days of treatment ($p<0.0001$). This effect was not evident and, therefore, not significant in the NS-treated group (group I).

The percentage of children from each group remaining in the hospital on different days is shown in Fig. 1. The LOS of the infants of the HS-treated group was significantly decreased ($p<0.05$). In fact, infants in the NS control group had a mean LOS of 5.6±1.6 days, whereas children treated with 3% HS were discharged with a LOS of 4.9±1.3 days, one day less than the NS controls. A modest linear positive correlation was found between LOS and the age of infants ($r=0.38$) and between LOS and the days of disease before hospitalization ($r=0.31$).

DISCUSSION

The results of the present study demonstrate that administration of 3% HS is more effective than NS

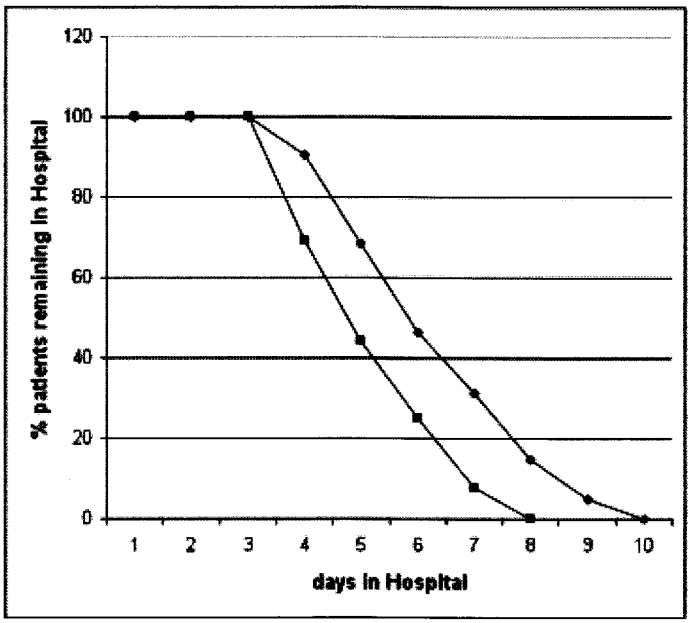

Fig.1. *Percentage of children from each group remaining in the hospital at different days.*

Table I. *Baseline demographic and clinical characteristic of the 106 evaluated patients.*

	0.9% Saline solution Group I N= 54	3% Saline solution Group II N= 52	*P*-value
Gender- males, N (%)	35 (64)	34 (65)	N.S.ǂ
Age (mo.) mean ± SD	4.2±1.6	4.8±2.3	N.S.*
Baseline clinical severity mean ± SD	8.8±1.5	8.5±1.4	N.S.*
Days of illness at hospital admission, mean ± SD	3±1.8	3.6±2.2	N.S.*
Baseline saturation %, mean ± SD	92.7±3.9	93.5±4.2	N.S.**
RSV serum positivity, N (%)	45 (83.3%)	42 (80.7%)	N.S.*

The percentages in round brackets are calculated over the total number of subjects reported at the top of column.
ǂ: *Chi-squared test.*
*: *Mann-Whitney U test*
**: *t-test*

Table II. *Clinical severity score for the two groups of patients at each day.*

	I day	II day	III day	*P*-value
Clinical severity scores, mean ± SD				
0.9% Saline solution Group I	8.8±1.5	8.3±1.7	7.7±1.6	0.0001*
3% Saline solution Group II	8.5±1.4	7.4±1.6	6.5±1.6	0.0001*
P-value	NS**	<0.005**	<0.005**	

*: *Anova Friedman test*
**: *Mann-Whitney U test*

in combination with epinephrine in hospitalized children with bronchiolitis. In our study, infants treated with hypertonic saline nebulization presented a more rapid decrease of respiratory symptoms and ameliorated the general condition as evaluated by the CSS. The effect was already significant after the first 24 hours of therapy and was sustained through the third day of treatment, allowing to discharge the infants treated with 3% HS one day earlier than the NS treated group.

Our data confirm previous evidence (8-10, 14) revised in recent reviews on the effectiveness of nebulized HS as treatment for bronchiolitis in infants (15, 16). Four trials involving 254 infants were considered (8-10, 14), showing that nebulized 3% HS effectively determined a shorter mean length of

Table III. *Clinical severity scores at baseline and after inhalation at different days.*

	I day		*P*-value	II day		*P*-value	III day		*P*-value
	Before	After inhalation		Before	After inhalation		Before	After inhalation	
0.9% Saline solution Group I	8.8±1.5	8.8±1.6	N.S	8.3±1.7	8.2±1.7	N.S	7.7±1.6	7.6±1.6	N.S.
3% Saline solution Group II	8.5±1.4	8.0±1.3	0.00002	7.4±1.6	6.8±1.4	0.00001	6.5±1.6	5.8±1.4	<0.00001

P value of Wilcoxon test

hospital stay and a significantly lower post-inhalation clinical score (15, 16). The findings on the clinical scores were more relevant among outpatients than inpatients, probably due to the reduced severity of the disease. For this reason, considering hospitalized infants with more severe forms of the disease, as demonstrated by the baseline CSS and oxygen saturation values, we believe that our study results may add further evidence in favour of the utility of this therapeutic option in treating bronchiolitis. The efficacy of the treatment was particularly evident considering the CSS obtained 30 minutes after the nebulisation of 3% HS, significantly decreased already at the first day of treatment in comparison to NS.

Since acute viral bronchiolitis is characterized, as predominant pathological features, by airway edema and mucus plugging rather than bronchospam, the suggested therapeutic options are limited (2, 6). The role of bronchodilators is debated and the effect of epinephrine is controversial (3, 7). Therefore, the international guidelines suggest that the primary treatment remains largely supportive with administration of fluids and supplemental oxygen if needed, and a trial of bronchodilator therapy (albuterol/salbutamol or epinephrine) as an option (3, 7). Furthermore, to start a time-effective treatment such as the use of HS could timely contribute to ameliorate mucus plugging and edema of the airways and to improve the respiratory symptoms of the infant.

There is no doubt that results of several drug studies on bronchiolitis are confounded by the variety of therapeutic associations (presence or not of β-adrenergic agents, of epinephrine, of systemic or inhaled steroid, administration with or without HS or NS). Other confounding factors are the study outcome measures, which range from short-term clinical scores to long-term outcomes, such as hospitalization or duration of illness, and often represent non-comparable parameters (7). This could be an explanation for recent controversial results showing that nebulized 3% HS with epinephrine in the treatment of acute bronchiolitis in an Emergency Department did not improve clinical outcome any more than NS (12). In fact, in this study the enrolled infants were evaluated only for 120 minutes after the nebulisation, without any difference in respiratory distress scores, change in oxygen saturation, rate of hospital admissions and return to the ED (12). As the authors admit, patients received only a maximum of 2 drug doses and respiratory parameters were measured for no longer than 120 minutes (12). In severe bronchiolitis, as mentioned before, the viral infection causes peribronchial mononuclear infiltration and epithelial cell necrosis, submucosal

edema, increased secretion of mucus and a relative dehydration of the airway surface liquid (17). Mandelberg et al. proposed that HS may substantially contribute to airway rehydratation, reducing edema, enhancing ciliary activity (17). Therefore, a series of studies lead to consider that HS-induced mechanisms on pathological findings and on symptoms of bronchiolitis require probably more doses and a longer follow-up to verify its efficacy.

The optimal concentration of HS to be used for treating acute bronchiolitis has been recently debated: Al-Ansari et al. showed that, in addition to epinephrine, nebulized 5% HS was safe and probably superior in efficacy not only to NS but also to 3% HS (11). However, this study was carried out in a pre-hospital setting and on children with mild bronchiolitis as demonstrated by the lower CSS and the higher O_2 saturation values at baseline in comparison to the parameters of infants enrolled in our study. Nevertheless, Ralston et al. demonstrated that 3% HS was safe even without adjunctive bronchodilators in hospitalized patients with bronchiolitis (18). Additional clinical trials should evaluate the effectiveness of nebulized 3% HS in bronchiolitis also in the absence of any bronchodilator.

We conclude that in infants hospitalized with bronchiolitis, nebulized 3% hypertonic saline solution and epinephrine decreases symptoms and length of hospitalization as compared to 0.9% saline solution and epinephrine. Both treatments have an excellent safety profile.

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