ORIGINAL ARTICLE

Efficacy of nebulized hypertonic saline versus normal saline in the treatment of acute bronchiolitis in inpatient infants

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ABSTRACT

Aim Compare the efficacy of nebulized hypertonic saline and normal saline in the treatment of infants hospitalized for bronchiolitis.

Methods This retrospective study was conducted at the Department of Pulmonology, Paediatric Clinic, Clinical Centre University of Sarajevo, covering the period from January 2015 to December 2019 and comprising 380 children aged between 1 and 12 months having bronchiolitis. One group received nebulized hypertonic saline (NHS, 3% NaCl)), and another group received nebulized normal saline (NNS, 0.9% NaCl). The control group did not receive any of these treatment options.

Results There was no statistically significant difference between the treatment groups regarding length of hospital stay (LOS) and Clinical Severity Score (CSS) at admission and discharge as well as in oxygen therapy duration and antibiotic use, the duration of symptoms before hospital admission, frequency of nasal discharge, elevated temperature, dyspnoea, cough and dehydration.

Conclusion The results of this study are consistent with several recent studies or meta-analyses and support the evidence against the use of NHS in hospitalized infants with mild or moderate bronchiolitis.

Key words: bronchioles, infection, therapy, NaCl

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INTRODUCTION

Bronchiolitis is the most common acute infection of the lower respiratory tract in infants and the main reason for hospitalization at this age (1,2). In America, bronchiolitis is usually defined as the first episode of respiratory distress induced by infection at the age of under 24 months (2,3), while in Europe, this condition applies to ages under 12 months with or without wheezing but necessarily without a previous wheezing history (3,4). In most cases, the causative agent is a respiratory syncytial virus (RSV) (5), although other causative agents such as human metapneumovirus (hMPV) and human rhinovirus (hRV) (6) can be isolated.

Infection results in acute inflammation of the small airways (bronchioles), which is followed by mucosal edema, epithelial cell necrosis, and increased mucus secretion (7). All these factors pathophysiologically lead to narrowing or obstruction of the small airways, which is clinically presented by wheezing and signs of respiratory distress (8).

Bronchiolitis, as an infection, has a seasonal character, and the highest incidence is recorded from November to April (9). As with many other respiratory viral infections, the reason for this distribution lies in the so-called "residential crowding" (10). Initially, an upper respiratory tract infection usually occurs as runny nose, sneezing, coughing, and as the disease progresses, wheezing, dyspnoea, tachypnea, and possibly respiratory distress development. There is no consensus regarding the therapeutic approach for infants with bronchiolitis, so the treatment is generally based on supportive therapy in the form of adequate hydration, oxygen therapy, airway toilets, and methods of physical respiratory treatment (11). However, systemic antibiotics, systemic or inhaled corticosteroids, and beta-agonists are not routinely recommended (11).

Nebulised hypertonic saline (NHS) has been actively studied in the last ten or more years through numerous randomized control studies without a clear consensus on its effectiveness (11). The positive aspects of NHS in treating acute bronchiolitis in infants include improving mucociliary clearance, reducing airway mucosal edema, reducing the formation of mucus plugs, and increasing hydration of airway surface liquid (ASL) (1,12). Initial trials of NHS in bronchiolitis in newborns and infants showed that the treatment was beneficial (13- 16), mainly after more than a few days of use. Several recent studies questioned these results (17-20). Thus, the NHS found itself on the list of controversial drugs that are given in bronchiolitis therapy. According to the guidelines for the treatment of bronchiolitis of the American Academy of Pediatrics (AAP) from 2014, the use of this solution makes sense only in hospital conditions and if the length of hospital stay (LOS) is 72 hours or longer (11). Although the AAP and numerous international guidelines have attempted to provide clinicians with the best possible evidence-based recommendations, they have failed to solve practical clinical challenges.

Despite being studied for more than 70 years and the high incidence of the disease, the approach to treating bronchiolitis is controversial and still the subject of discussion (21,22). In addition, there are many doubts and controversial data in everyday clinical practice and available literature, and a small number of evidence-based recommendations for effective therapy for this disease, which occurs very often and can be life-threatening (23).

The results of studies regarding the treatment of bronchiolitis by nebulized normal saline (NNS, 0.9% NaCl) and NHS, in terms of positive impact on disease outcomes (24-26).

We had the impression that during daily clinical work, NHS had a positive effect on the clinical course of hospitalized infants with bronchiolitis and we wanted to prove it and further justify its use in the treatment of bronchiolitis.

The aim of this study was to compare the efficacy of two therapeutic approaches, NHS and NNS, in infants hospitalized for bronchiolitis, to assess whether the hypertonic solution is superior to normal saline.

PATIENTS AND METHODS

Patients and study design

This retrospective study was conducted at the Department of Pulmonology, Paediatric Clinic, Clinical Centre of the University of Sarajevo, covering the period from January 2015 to December 2019, involving 380 children aged between 1 month and 12 months with bronchiolitis. Bronchiolitis was defined as the first cough episode with incre-

Table 1. Baseline characteristics of 380 children with bronchiolitis

Parameter	Group 0.9% NaCl	Group 3% NaCl	Control group	p
Gender (Male / Female) (%)	56 (37.1) / 95 (62.9)	46 (46.9) / 52 (53.1)	47 (35.9) / 84 (64.1)	0.187
Mean age±SD (months)	3.16±0.16	4.23±0.44	3.78±0.20	0.005
Median birth weight (IQR) (g)	3200.0 (2900.0-3660.0)	3300.0 (2800.0 (3652.0)	3300.0 (2850.0-3650.0)	0.008
Body weight on admission (IQR) (g)	5500.0 (4550.0-6750.0)	6000.0 (5017.0-7500.0)	6100.0 (5000.0-7500.0)	0.977

standard deviation (SD); IQR, interquartile range (25-75 percentiles)

ased respiratory effort and wheezing or crackles following an upper respiratory tract infection. Exclusion criteria were: children with severe bronchiolitis who required relocation to the Paediatric Intensive Care Unit (PICU), second and more episodes of wheezing, comorbidities such as underlying chronic cardiopulmonary, neurological or immunological diseases, premature birth below 37 weeks of gestational age. Official hospital medical records were used. The Ethical Committee of the Clinical Centre of the University of Sarajevo, approved the study protocol.

Methods

The patients were divided into three groups. One group received nebulized 3% NaCl, while another received nebulized 0.9% NaCl. The control group did not receive any of these treatment options. Primary outcomes were the length of hospital stay (LOS) and Wang Clinical Severity Score (CSS) on admission and discharge. Secondary outcomes were the duration of symptoms before admission and clinical symptoms during hospitalization, such as runny nose, fever, dyspnoea, cough, and dehydration. Other outcomes included using other medications such as antibiotics, parenteral corticosteroids, aminophylline and oxygen supplementation.

Statistical analysis

The Kolmogorov–Smirnov test tested the distribution of variables. Values with normal distribution were expressed as mean±standard deviation, while those without normal distribution were shown as median and interquartile range. Depending on the distribution of variables, a comparison between the groups was performed by the ANOVA test, Bonferroni post hoc test, and Kruskal–Wallis test, followed by Mann-Whitney U-test. The $\chi 2$ test was performed to analyse the dependence between categorical variables. Statistical significance was set at $p<0.05$.

RESULTS

The age of patients who received nebulized 0.9% NaCl was 3.16±0.16 months and was significantly lower than that of patients who received 3% NaCl, 4.23±0.44 (p=0.004), as well as from the age of the control group, 3.78±0.20 (p=0.011). The birth weight of patients receiving 0.9% treatment was significantly lower than the birth weight of patients receiving 3% NaCl, 3200.0 g (2900.0-3660.0) and 3300.0 g (2800.0-3652.0), respectively (p=0.008), as well as from the birth weight of the control group, 3300.0 g (2850.0-3650.0) (p=0.009). Other parameters did not differ significantly between the test groups (Table 1).

The duration of symptoms before hospital admission and differences in the frequency of nasal discharge, elevated temperature, dyspnoea, cough and dehydration were not significantly different between the studied groups (Table 2).

Table 2. Frequency and duration of symptoms of 380 children with bronchiolitis during hospitalization

Parameter	Group 0.9% NaCl	Group 3.0% NaCl	Control group	p
	No (%) of patients			
Nasal discharge	115 (76.2)	63 (64.3)	96 (73.3)	0.116
Elevated temperature	54 (35.8)	36 (36.7)	56 (42.7)	0.448
Dyspnoea	124 (82.1)	81 (82.7)	106 (80.9)	0.939
Cough	138 (91.4)	94 (95.6)	121 (92.4)	0.381
Dehydration	24 (15.9)	15 (15.3)	26 (19.8)	0.584
	Median (25-75 percentile)			
Symptom duration prior admission (days)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (1.0-5.0)	0.499

In the group of patients treated with 0.9% NaCl, 93 (61.6%) were treated with corticosteroids; in the group treated with 3% NaCl, 82 (83.7%), while in the control group, 105 (80.2%) ($p<0.001$). In the group of patients treated with 0.9% NaCl, five (3.3%) were treated with aminophylline, in the group treated with 3% NaCl 10 (10.2%), while in the control group, two (1.5%) ($p<0.001$). However, the frequency of antibiotic use and the duration of oxygen treatment did not differ significantly between the groups (Table 3).

Table 3. Frequency of use of antibiotics, corticosteroids, aminophylline, and duration of oxygen treatment

Parameter	Group 0.9% NaCl	Group 3.0% NaCl	Control group	p
	No (%) of patients			
Treatment with antibiotics	112 (74.2)	83 (84.7)	110 (84.0)	0.053
Treatment with corticosteroids	93 (61.6)	82 (83.7)	105 (80.2)	<0.001
Aminophylline treatment	5 (3.3)	10 (10.2)	2 (1.5)	<0.001
	Mean ±SD			
Oxygen treatment (number of days)	0.54±0.12	0.70±0.15	0.36±0.10	0.231

SD, standard deviation;

The duration of hospitalization and CSS on admission and discharge did not differ significantly between the groups (Table 4).

Table 4. Duration of hospitalization and Clinical Severity Score (CSS) at admission and discharge

Parameter	Mean ±SD			p
	Group 0.9% NaCl	Group 3.0% NaCl	Control group	
Days of hospitalization	5.0 (3.0-6.0)	5.0 (3.0-6.0)	5.0 (3.0-6.0)	0.678
CSS at admission	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.236
CSS at discharge	0.01±0.009	0.01±0.01	0.03±0.01	0.439

SD, standard deviation;

DISCUSSION

In our study, in terms of baseline characteristics, infants who received NNS had a statistically significantly lower birth weight and were younger than the other two groups. NHS improves mucociliary clearance, but NNS can also have a positive effect in terms of airway hydration in the treatment of bronchiolitis (17).

In younger infants, we probably opted more often for NNS due to minor respiratory tract irritation and a potentially less pronounced cough reflex. There was no statistically significant difference in relation to gender and body weight at admission between the groups, as well as regarding the duration of symptoms before admission. Up to three days before admission, infants had symptoms from the upper respiratory tract on average, so that by affecting the lower respiratory tract, they developed a picture of respiratory distress and were admitted for hospital treatment. Clinical symptoms such as runny nose and dehydration were less pronounced in the group of infants that received NHS. In contrast, symptoms from the lower respiratory tract, dyspnoea, and cough, were more pronounced compared to the group that received NNS and the control group, but these differences were not statistically significant. Therefore, it is very likely that the clinical picture influenced our patients' choice of inhalation therapy. In the group of infants who received NHS, statistically, significantly more parenteral corticosteroids and aminophylline were used. There was no statistically significant difference in terms of the time required for oxygen supplementation and prescribing antibiotics between the groups. It is possible that the clinical picture in the infants of this group was more severe, so in addition to the NHS, we decided to prescribe long-acting bronchodilators and parenteral corticosteroids.

There was no statistically significant difference between the groups regarding primary outcomes, i.e. LOS and CSS at admission and discharge. These findings are consistent with the results of many recent studies. Jaquet-Pilloud et al., examining the impact of NHS in the therapy of moderate and severe bronchiolitis, following the LOS as the main outcome, concluded that they do not support its use in the therapy of bronchiolitis (28). Pandit et al. comparing the effectiveness of NHS and NNS in terms of LOS, oxygen supplementation, CSS, and oxygen saturation, concluded that NHS is as effective as NNS (17). In some other entities, such as acute viral wheezing, NHS in combination with salbutamol has been proven to have a positive effect in terms of a faster reduction in LOS, the need for oxygen supplementation, and the asthma severity clinical score in children aged five months to five years (28).

The eternal dilemma of whether NHS affects the LOS in infants, as one of the most relevant outcomes in bronchiolitis, has been considered in several meta-analyses. Zhang et al. concluded that NHS is an effective and safe intervention statistically significantly reduces LOS (30). In contrast, Heikkilä et al. suggested that NHS offers only limited clinical benefits (31), while Badgett et al. study suggests that NHS is probably ineffective in reducing LOS (32). According to other authors, NHS is not useful in treating infants hospitalized for bronchiolitis; the minor influence that favours the use of NHS is clinically insignificant, and positive effects derive only from old studies, respectively (33). On the other hand, recent studies proved again that 3% NHS was better than

0.9% NNS in reducing LOS, improving CSS, and in enhancing the severity of respiratory distress (33,34).

In our study, although we wanted to prove that HS has a significant effect on the faster resolution of the disease, that it affects CSS and shortens LOS, this was not the case. In this way, our results align with recent studies' results (17,20,27,32). Although NHS may lead to, at first glance, short-term symptomatic relief, it has not been shown to alter the course of the disease or its main outcomes.

Our study has limitations. A critical point of our study is the absence of blinding. We determined CSS at admission, then at discharge. It would be ideal to determine it after 24 or 48 hours. Our one-centre research probably limits the possibility of generalizing our findings. Furthermore, the use of NNS as a comparator represents a difficulty in clearly crystallizing the actual effectiveness of NHS because it also has its positive sides, such as the hydration of the ASL. For this reason, designing a study that would include some non-irritating inhalation solution that would serve as a placebo would be an excellent option, and in this way, it would be possible to express the real role of hypertonic and isotonic saline. Another limitation includes low statistical power for the primary and some secondary outcomes. Infants with severe acute bronchitis requiring Paediatric Intensive Care Unit admission were excluded from the study. We cannot certainly rule out that NHS could benefit these populations.

In conclusion, the results of this study confirm what has been reported by a number of recent studies or meta-analyses and support evidence against the use of NHS in hospitalized infants with mild or moderate bronchiolitis. However, other studies with larger standardized samples and multi-centre designs would be necessary to conclude whether NHS has clinically significant effects or not.

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TRANSPARENCY DECLARATION

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