

## Research Article

# Comparison of the efficacies of normal saline versus hypertonic saline in the management of acute bronchiolitis'

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### ABSTRACT

**Background:** The aim of this study was to compare the efficacies of saline solutions of different concentrations used for the management of infants with mild to moderate bronchiolitis.

**Methods:** A retrospective chart review of 46 children, aged 1-24 months, diagnosed with acute bronchiolitis was performed. The patients were separated into 2 groups: normal saline and 3% hypertonic saline. Length of hospital stay, modified respiratory assessment score (MRAS) at admission, at 48 hours of admission and at discharge were compared.

**Results:** MRAS evaluated at admission, at 48 hours after admission and at discharge and length of hospital stay did not reveal significant difference between the two groups ( $p>0.05$ ).

**Conclusions:** Comparison of two different treatments, salbutamol applied in combination with either normal saline or 3% hypertonic saline, did not reveal any statistically significant differences with respect to symptomatic improvement or length of hospital stay.

**Keywords:** Bronchiolitis, Hypertonic saline solution, Respiratory syncytial virus

## INTRODUCTION

Acute bronchiolitis is a contagious disease of the lower airways in infants, characterized by inflammatory narrowing of the bronchioli and often caused by viruses.<sup>1,2</sup> Its relatively high incidence, possible need for hospitalization, and association with acute or chronic complications constitute a significant health problem.

Acute bronchiolitis shows a seasonal distribution, with epidemics during the winter and spring. The epidemiologic characteristics are often associated with the most common etiologic agent, the Respiratory Syncytial Virus (RSV). General risk factors such as low socioeconomic status, lack of breastfeeding or malnutrition, exposure to tobacco smoke, family history of asthma or atopy affect the course of the illness.<sup>3,4</sup>

In 1963, Reynolds and Cook reported on the vital importance of oxygen support in the treatment of bronchiolitis, and also on the lack of reliable evidence regarding the efficacy of any other continuously or intermittently applied treatment.<sup>5</sup> After 52 years, despite the presence of numerous treatment modalities being experimented, there are currently no widely accepted treatments other than oxygen and hydration.

Hypertonic saline solution absorbs water from the submucosa, therefore theoretically decreases some of the submucosal and adventitial edema, and also the thickness and dryness of the mucous plaques within the bronchial lumen. It decreases the edema and mucous accumulation in the small airways that develop after invasion with virus, and prevents cell injury dependent bronchiolar obstruction. In other words, hypertonic saline is effective on the pathophysiologic mechanism of the disease.<sup>6-8</sup>

The aim of this study was to compare the effects of normal saline versus 3% hypertonic saline, used in the management of patients hospitalized due to a first bronchiolitis episode, on the clinical scoring and length of hospital stay.

## METHODS

This study included 46 patients who received inpatient care in Sisli Hamidiye Etfal Education and Research Hospital between October 1, 2014 – May 1, 2015, due to acute first bronchiolitis episode. The aim was to compare the efficacies of normal saline and 3% hypertonic saline solutions used in the treatment of patients between 1-24 months of age and hospitalized for mild and moderate first bronchiolitis episode. Clinical data were retrospectively obtained from patient charts and discharge reports.

Medical history data were analysed for age and sex, natal and postnatal history, nutrition, history of previous illnesses and hospitalizations, presence of atopy, immune deficiency, history of chronic disease such as of the heart and lung, and passive smoking. In addition the educational status of the parents, asthma in first degree relatives, number of people living in the house, presence of pets in the house, and type of heating used in the house were investigated. Once the data on history were recorded, the data on the overall status and physical examination were analysed.

In order to determine the clinical severity of the illness, the Modified Respiratory Assessment Score (MRAS) scores applied in a standard fashion at admission, 48th hour of treatment, and at discharge, were evaluated (Table 1). This score measures the number of respirations per minute, use of assistive respiratory muscles, presence of cyanosis, and auscultatory findings. Based on this scoring system, those patients who had mild and moderate degree of bronchiolitis were included into our study; those with severe attacks were excluded. Length of hospital stay, determined according to standardized discharge criteria, was also recorded. Care was taken to comply with previous studies while adjusting the dosage and intervals of the drugs. Clear inclusion and exclusion criteria were constructed to obtain reliable results.

Those patients with the following criteria were included into the study: scoring was made at admission, at 48th hour of treatment, and discharge; hospitalization was made due to mild and moderate severity first bronchiolitis episode; age was between 1-24 months; RSV rapid antigen test was applied; and salbutamol treatment was administered with 8 hour intervals. Patients under 1 month or above 24 months of age, having a history of an underlying chronic illness (cystic fibrosis, congenital heart disease, immune deficiency syndromes, chronic lung disease), severe bronchiolitis attacks, premature birth (under 37 weeks) history, who received antibiotics, inhalers or systemic corticosteroids during treatment, and

recently treated with steroids or bronchodilators, were excluded.

The charts of 135 patients hospitalized for acute bronchiolitis were retrospectively investigated. Forty six eligible patients were included into the study. Patients who were treated with salbutamol and 3% hypertonic saline combination were placed into the treatment group (Group A), and the remaining patients treated with salbutamol and normal saline combination were placed into the control group (Group B). Length of hospital stay, clinical scores before and after treatment, assessment of reliability, and side effects were compared between the groups. The results of the groups were evaluated after completion of the study.

## Statistical analysis

Complementary statistics included mean, standard deviation, median, minimum-maximum, ratio and frequency values. Distribution of the variables was controlled with the Kolmogorov Smirnov test. Quantitative data analysis was performed with independent sampling t test and Mann Whitney u test. Qualitative data analysis was performed with chi-square test. Repetitive measurements were evaluated with Wilcoxon test/MC nemar test. The SPSS 22.0 software was used for analysis.

## RESULTS

In 46 patients included into the study, 27 were boys (58.6%) and 19 (41.4%) were girls. Mean age was  $7.1 \pm 5.6$  months. RSV antigen positivity, as assessed with the Enzyme Linked Immunosorbent Assay (ELISA) method for RSV direct antigen test, was found in 52.1% of the patients.

There were no differences between Groups A and B with respect to age, distribution of sex, method of childbirth, birth weight, history and length of hospital stay which was showed in Table 2 and preadmission oxygen values and RSV test positivity that was showed in Table 3.

Intergroup comparison showed that the changes in scores at 48 hours and discharge were not significantly different. When the difference between the scores at 48 hours and discharge were evaluated, the change in Group B was significantly greater compared to Group A ( $p=0.003$ ) (Table 4).

In addition to the changes in clinical scores, the lengths of hospital stay were compared. Mean length of hospital stay was  $5.3 \pm 2.0$  days in Group A, and  $4.6 \pm 1.5$  days in Group B, the difference between the groups was not significant ( $p>0.05$ ) (Table 5). In Group B RSV positive patients had shorter length of stay, however this was not significantly different from Group A ( $p>0.05$ ) (Table 5).

## DISCUSSION

Acute bronchiolitis is a contagious disease of infants, often caused by viruses. It affects the lower airways and results from inflammatory narrowing of the bronchioles.<sup>9</sup> It is a significant health problem due its high frequency, possible requirement for hospitalization, and association

with acute or chronic complications. Current treatment includes various treatment alternatives, with bronchodilators, corticosteroids, and antiviral medications being the most common. Bronchiolitis results in significant morbidity, and there is lack of agreement on the efficacies of agents used in management.<sup>3,10-13</sup>

**Table 1: Modified respiratory assessment score.**

Clinical Parameters	Score 0	Score 1	Score 2	Score 3
Respiratory rate (per minute)	<40	40-60	60-70	>70
Use of Accessory Muscles*	None	1 accessory muscle used	2 accessory muscles used	≥3 accessory muscles used
Color / Cyanosis	Pink in room air/no cyanosis	Cyanosed when crying	Pink with oxygen or cyanosed in room air	Cyanosed with oxygen or cardio-respiratory arrest
Auscultatory findings	Normal	Decreased air entry, no rhonchi heard	Decreased air entry, rhonchi heard	Silent chest

\*Accessory muscle usage: suprasternal, subcostal and intercostal retractions; mild bronchiolitis: score 0-4; moderate bronchiolitis: score 5-8; severe bronchiolitis: score 9-12.

**Table 2: Distribution of cases various variables.**

	Group A			Group B			P
	Med.±s.d./ %	Med	(Min-Max)	Med.±s.d./ %	Med	(Min-Max)	
Age (month)	6,8 ± 4.6	6.0	2.0 - 24.0	7.5 ± 6.7	5.0	2.0 - 30.0	0.66
Birth weight	3085 ± 426	3050	2500 - 3900	3088 ± 479	3030	2500 - 4300	0.98
Sex	Male	60.9		56.5			0.76
	Female	39.1		43.5			
Method of childbirth	vaginal delivery	47.8		56.5			0.55
	caesarean	52.2		43.5			
Postnatal history/neonatal intensive care	yes	21.7		13.0			0.43
	no	78.3		87.0			

Group A: Patients treated with normal saline solution; Group B: Patients treated with hypertonic saline solution; Independent sampling t test/Chi-square test.

Although there is no proof to advocate its routine use, nebulized hypertonic saline has emerged as a promising approach in the treatment of acute bronchiolitis. In our study it was seen that salbutamol treatment applied with either normal saline versus 3% hypertonic saline did not show any superiority over each other. Bronchiolitis is common in children under age two, especially around 6 months. Our study included children between ages 1-24 months, and mean age was 7.1± 5.6 months. When it is considered that 80% of bronchiolitis cases are seen in the first year of life, the age distribution in our study was similar to others.<sup>11,14</sup>

**Table 3: Clinical assessment of the cases before treatment.**

	Group A (n=23)	Group B (n=23)	P value
Pre-treatment oxygen value	<92 17.4	26.1	0.475
	≥92 82.6	73.9	
RSV test results	Negative 39.1	56.5	0.238

Group A: Patients treated with normal saline solution; Group B: Patients treated with hypertonic saline solution; Independent sampling t test/Chi-square test.

**Table 4: Prediction of modified respiratory assessment score.**

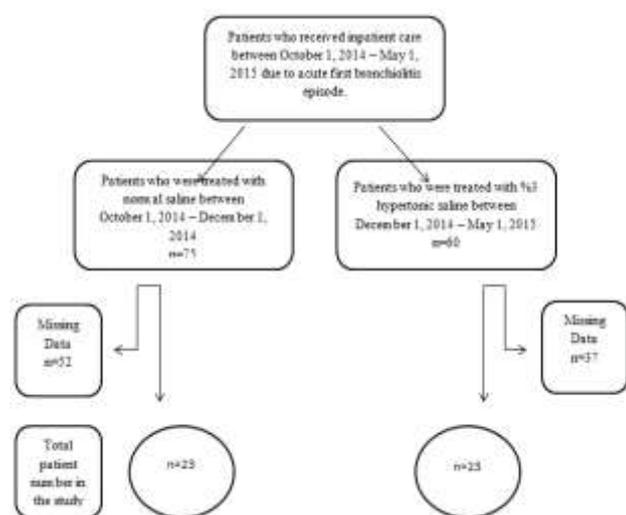
MRAS	Group A Mean ± sd	Group B Mean ± sd	P value
Admission	6.1 ± 0.9	5.6 ± 1.0	0.140
after 48 hr	4.3 ± 1.3	3.7 ± 1.1	0.144
discharge	2.0 ± 1.2	2.3 ± 0.8	0.831
Admission/after 48 hr hospitalization	-1.83 ± 1.11	1.87 ± 0.97	0.747
Admission /discharge	-4.09 ± 1.28	-3.35 ± 1.11	0.067
48 hr hospitalization / discharge	-2.26 ± 0.92	-1.48 ± 0.79	0.003

**Table 5: Comparison of length of hospital stay considering RSV positivity.**

	Group A Mean±sd	Group B Mean±sd	P
Mean length of stay	5.3 ± 2.0	4.6 ± 1.5	0.225
Mean length of stay of RSV negative ones	4.4 ± 1.9	4.8 ± 1.9	0.761
Mean length of stay of RSV positive ones	5.8 ± 2.0	4.4 ± 0.8	0.067

Mann-Whitney U Test

Bronchiolitis is more frequent in boys, with a tendency to follow a more severe course in them.<sup>9,11</sup> Boys had a higher ratio (58.6%) in our study also, however disease severity was not significantly different between the two sexes.



**Figure 1: Flow diagram of study selection.**

The most common cause of acute bronchiolitis is RSV. Because it is the most common isolated agent in hospitalized children (50-90%), those patients who underwent RSV direct antigen test with the ELISA method were included into the study. The positivity rate in our study was 52.1%, similar to previous reports.<sup>4</sup> Thus, unnecessary uses of antibiotics were avoided, and nasocomial spread was prevented by isolation of the patients.

The first study on the use on hypertonic saline in patients receiving ambulatory hypertonic saline treatment was performed by Sarell et al. In this study, nebulized 3% hypertonic saline was compared with normal saline (0.9% NaCl). Clinical evaluation at 48 hours of treatment showed a more rapid symptomatic improvement in the group treated with 3% saline.<sup>7</sup>

In 2003, Mandelberg et al performed a study on 53 infants with mild or moderate bronchiolitis, and found that 3% hypertonic saline provided both clinical improvement and significant decrease in the length of stay.<sup>15</sup> Although the study revealed significantly better outcomes with respect to the efficacy of hypertonic saline, suspicion was raised on the reliability of the study due to the insufficient study population. Therefore in 2006, the same investigators conducted a more comprehensive study on 93 patients, with a longer follow up. The length of hospital stay decreased from 3.6±1.6 days to 2.8±1.3 days, with a difference of 22%. These results supported the findings of the previous study, and it was reemphasized that 3% hypertonic saline decreased the symptoms and shortened the length of stay.<sup>16</sup>

Kuzik et al conducted a similar study; however they applied a different method. The 3% hypertonic saline was used in combination with a bronchodilating agent three times a day in previous studies and our study, whereas in that study by Kuzik et al, it was used both alone (in 38% part of the treatment); or in combination with albuterol (37% part of the treatment), epinephrine (23% part of the treatment), and inhaled steroid (3% part of the treatment), with shorter intervals. Normal saline treated group served as the control. The study included 96 patients, and a 26% reduction in the length of hospital stay was attained. Based on these, 3% hypertonic saline was reported as a safe and economic treatment. However, the lack of a post treatment clinical scoring, application of the treatments with different frequencies than other previous studies, and the possibility of the results to be influenced from other medications are the weaknesses of the study.<sup>8</sup>

Zhang et al. performed a meta-analysis of 4 randomized studies published before 2008 (189 hospitalized, and 65 outpatient cases), and concluded that 3% hypertonic saline shortened the length of stay, and provided a rapid improvement in clinical scores, especially in outpatient cases. The amount of 3% hypertonic saline was 2 ml in one study, and 4 ml in the other 3 studies. Normal saline was preferred as the comparison solution in all the

studies, and dosages of the bronchodilators used were different. The patients took 3 nebulas per day in 3 of the studies, and 9 nebulas per day in one. Also, the clinical weight scales used were different.<sup>17</sup> Therefore, the results were not found to be acceptable or reliable due to the clinical heterogeneity and variable application regimes.

A review of the recent studies shows persistence of the controversies on the optimum dose and dose intervals. In 2013 Mahesh Kumar et al. published a study in which they compared 3% hypertonic saline with normal saline on 40 patients in India. The study population was similar to ours, and the study was performed on a group of patients hospitalized with the first bronchiolitis episode. Hypertonic saline was combined with salbutamol; however it was applied with 6 hour intervals. The results were similar to our study; 3% hypertonic saline had no statistically significant effect on the clinical score and length of hospital stay. This condition was attributed to the relatively limited number of patients in the study, their small mean age (60% of them under 6 months), and relatively lower clinical scores.<sup>18</sup> Another study performed in India and published in 2012 had similar characteristics, and the patients were treated with 4 hour intervals until discharge, however the results did not change.<sup>19</sup>

In our study, patients who received normal or 3% hypertonic saline were compared with respect to the length of hospital stay and clinical improvement. Similar to the two studies by Mandelberg et al, the patients received these study solutions three times a day, in combination with a bronchodilator and in a nebulized form. The results of our study did not show any superiority of the 3% hypertonic saline compared to normal saline. Also comparison of patients' positive and negative for RSV with respect to the treatments they received did not reveal any significant difference in the length of hospital stay. There are few studies on this subject; Martin et al. obtained similar results in their study published in 2013, they did not find a significant effect of 3% hypertonic saline on the length of hospital stay in RSV positive patients. However, they found that 3% hypertonic saline decreased the oxygen requirement in RSV positive patients.<sup>20</sup> Because our study included those patients with mild or moderately severe bronchiolitis episodes and who did not need oxygen, such an assessment was not made. Our study is retrospective, performed with the data on the charts. Missing data and our inability to organize the study in the manner we wished are the most significant limitations of our study.

Comparison of 7 studies (581 patients) that investigated the efficacy of hypertonic saline showed that hypertonic saline was applied together with a bronchodilator in 6 of them. Two of these studies used beta-2 agonist as the bronchodilators, as in our study. Three of the studies used epinephrine, and one study used both epinephrine and beta-2 agonist.<sup>13,17</sup> In the other study, 60% of the total treatment was combined with a bronchodilator. Patients

with a history of asthma or recurrent wheezing were excluded from our study, similar to the above mentioned studies. Also, our solutions were combined with salbutamol to prevent reflex bronchospasm. There were no side effects.

## CONCLUSION

The findings of our study showed that when compared to normal saline, 3% hypertonic saline did not provide a superior symptomatic recovery, and did not significantly reduce the length of hospital stay in patients hospitalized for mild-moderate moderate attacks. Also, comparison of RSV positive and negative patients with respect to the treatments they received did not show a significant difference. Studies which investigated the efficacy of hypertonic saline in the management of bronchiolitis revealed controversial outcomes. In addition, questions on the use of hypertonic saline, including optimum saline concentration, ideal dosage and dosing interval are still unanswered.

There were no undesired effects related to the use of hypertonic saline. Based on previous studies, hypertonic saline can be used safely only together with a bronchodilator; despite the lack of information on the most appropriate combination, there is no reliable evidence on its use alone. Further studies, in which the drug is used alone, are needed to better understand the side effect profile and prove the safety.

In conclusion, multicenter, placebo controlled, standardized studies that involve large patient series, utilize clinical scores, and have long term follow up are needed in order to prove the efficacy of treatment. Since there is a limited number of a study regarding the role of hypertonic saline in the treatment of bronchiolitis, we believe that the results of our study will enlighten the future studies.

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