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Comparing the Efficacy of 7%, 3% and 0.9% Saline in Moderate to Severe Bronchiolitis in Infants

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Background: There is no standard treatment option in acute bronchiolitis. 3-7% hypertonic saline (HS) seems to be the effective treatment choice for reducing the hospitalization day.
Aims: To compare the effect of nebulized 7% HS/salbutamol and 3% HS/salbutamol to 0.9% saline/salbutamol. The primary outcome measure was the effect of study drugs on the length of hospital stay (LOS). Secondary outcome measures were safety and efficacy in reducing the clinical severity score (CSS) at the 24 hours of the study.
Study Design: Prospective, double-blinded randomized clinical study.
Methods: The study consists of 104 infants. Groups were constituted according to the treatment they received: These are, group A – 0.9% saline/salbutamol, group B -3% HS/salbutamol and group C-7% HS/salbutamol. Heart beat, Bronchiolitis CSS and oxygen saturation of the patients were determined before and after nebulization. The patients were monitored for adverse reactions.
Results: Length of hospital stay in group A, B and C were as follows; 72.0 (20-288) hours in group A, 64.0 (12-168) hours in group B and 60.0 (12-264) hours in group C. No significant differences was observed among three groups ($p>0.05$).
Conclusion: 7% HS and 3% HS does not have any effect to decrease LOS for infants with bronchiolitis.
Keywords: Bronchiolitis, hypertonic saline, infant

Bronchiolitis is the most frequent viral lower respiratory tract infection seen in infancy period characterized by cough, wheezing and tachypnea. Bronchiolitis is the major reason of infant hospitalization in both developed and developing countries. Although it is common there is no current standard treatment. Supportive care is the only evidence based treatment option (1,2). Many studies focused on testing the effects of bronchodilators such as β2-agonsits (3), epinephrine (4), glucocorticoids (5) and magnesium sulfate (6) with controversial results.

There exists the first necrosis of the respiratory epithelium in bronchiolitis. Following by the fact that, exaggerated mucus production occurs due to the proliferation of goblet cells. On the other hand epithelial regeneration with nonciliated cells happens thus decreasing mucociliary clearance. Lymphocytic infiltration may result in submucosal edema (7). Johnson et al. (7) demonstrated that, airway obstruction in bronchiolitis was because of epithelial and inflammatory cell debris. And they did not observe bronchial smooth muscle constriction. This can explain why bronchodilator therapy is not effective in bronchiolitis. Thus the ideal treatment has to decrease submucosal edema and improve mucociliary clearance by restoring the elasticity and viscosity of the mucus. In the last decade, 3% and 5% hypertonic saline (HS) studied in infants with bronchiolitis with good results (8-14). In the light of cystic fibrosis studies, it was shown that 7% HS increases mucociliary clearance and decreases epithelial edema (15-17). Thus,

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recently 7% HS has been studied in infants with bronchiolitis (18,19). But the effect of 7 % HS treatment to the bronchiolitis outcome is still dilemma.

We aimed to determine the effectiveness of nebulized %7 HS plus salbutamol with comparing it with 3% HS plus salbutamol and 0.9% saline plus salbutamol in infants having moderate to severe bronchiolitis. The primary outcome measure was the effect of study drugs on the length of hospital stay (LOS). Secondary outcome measures were safety and efficacy in reducing the clinical severity score (CSS) at the 24 hours of the study.

MATERIALS AND METHODS

This double-blinded, prospective clinical trial was conducted between January 2014 and May 2014 in the Pediatric hospital. Inclusion criteria were as follows: age 1- 24 months, a history of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation, first wheezing episode, and a CSS of ≥4. Bronchiolitis was diagnosed on clinical grounds. The CSS was defined as described previously by Wang et al. (20) in Table 1. Exclusion criteria were as follows: infants with CSS <4, oxygen saturation (SaO_2) <80% in room air, chronic cardiopulmonary or neurological disease, premature birth, birth weight <2500 g, history of recurrent wheezing episodes, proven immune deficiency, age <1 month or >2 years, proven or suspected acute bacterial infection, previous treatment with bronchodilators or corticosteroids, the presence of symptoms >7 days, consolidation or atelectasis on a chest roentgenogram. The primary physicians (AO, ZK, UA, EK, AO, YAT, and AFK) who manage the patients treated the consequent patients with the study drugs ordinarily without knowing the given drugs. The randomization of the given drug was performed according to the age, sex, and CCS distributions of the patients with a computer program. Other authors (SK, AS, FE and MK) evaluated the CCS and outcome of the patients at the end of the study. Signed informed consent was obtained from the parents of each infant. Local Ethics Committee approved the study.

The researchers observed the infants and assigned the CSS. Children meeting inclusion criteria were invited to participate in the study. Data were collected using standardized forms to document history and physical exam. Each child's age, gender, hospitalization, CSS, respiratory rate, SaO_2 in room air (determined by bedside monitor (Suresigns VM6, Philips; Andover, USA), and heart rate were recorded. Chest X-rays were performed. Proven asthma in parents and siblings, passive smoking, positive atophy history were questioned before the study. Serum sodium levels were investigated before and after treatment. All eligible patients were randomly assigned to one of the three groups: group A (n=35) received inhalation of salbutamol (Ventolin, Glaxo Smithkline; Middlesex, UK), 0.15 mg/kg plus 2.5 mL 0.9% saline (Neofleks 0.9%, Türktıpsan; Ankara, Turkey) solution; group B (n=35) received inhalation of salbutamol 0.15 mg/kg plus 2.5 mL 3% saline (Neofleks 3%, Türktıpsan; Ankara, Turkey) solution; group C (n=34) received inhalation of salbutamol 0.15 mg/kg plus 2.5 mL 7% saline solution (prepared in hospital pharmacy); the procedure was performed on two occasions at 30 min intervals at the admission and repeated for 6 hours interval until discharge. 1mg/kg steroid were administered for 3 days to all patients whom CSS≥10 after 1 hour of the initial treatment. The patients were monitored for hypotension, tachycardia, tremor, bronchospasm and cough during nebulization during each dose was administered. The patients are discharged if CSS <4, SaO_2 >92% in room air for 4 hours and no feeding difficulty. LOS calculated from first dose of study medication until clinical decision to discharge.

All statistical analysis was performed by using the SPSS (SPSS PC Ver. 22; IBM Corp.; Armonk, New York, USA). The normality of data distribution was assessed by the Shapiro-Wilk test. In case of normal distribution, differences among the three groups were tested with one-way analysis of variance and in case of abnormal distribution; the Kruskal-Wallis test was used. For repeated measures in the same group, Wilcoxon analyses were used. The relationships in categorical variables were analyzed with Chi-square test of exact methods. Findings of $p<0.05$ were taken to indicate significant differences.

RESULTS

The power of the study was 50%. One hundred and four patients were enrolled in the study. Two patients in the group

TABLE 1. Clinical severity score (20)

	1 point	2 point	3 point
Respiratory ratebreaths/min	31-45	46-60	>60
Wheezing	at terminal expiration using a stethoscope	during the entire expiration or audible on expiration without stethoscope	inspiratory and expiratory wheezing without stethoscope
Retraction	intercostal	tracheosternal	severe retraction with nasal flaring
General condition	normal	stable	irritability, lethargy and poor appetite

TABLE 2. General baseline characteristics of the study groups

	Group A n=35	Group B n=35	Group C n=34	P
Age months Median (min-max)	7.6 (1-18)	7.6 (2-23)	7.7 (1-24)	0.994
Gender (m/f)	14/21	14/21	14/20	0.999
Passive smoking	14 (40%)	14 (40%)	16 (47%)	0.800
Positive atophy history	6 (17.2%)	4 (11.4%)	4 (11.8%)	0.820
Proven asthma in parents and siblings	5 (14.3%)	7 (20.0%)	2 (5.9%)	0.247
Sodium mEq/L Before treatment	n: 29 136.8±2.1	n: 23 137.2±2.9	n: 22 136.8±2.3	0.920
Sodium mEq/L After treatment	n: 21 138.1±2.2	n: 20 138.6±2.1	n: 17 138.0±2.0	0.692
CSS 0	6.97±1.72	7.17±1.90	7.26±1.72	0.778
Heart rate	147.3±13.7	148.7±17.8	152.0±10.9	0.448
LOS hours	72.0 (20-288)	64.0 (12-168)	60.0 (12-264)	0.760
Steroid requirement	16 (45.7%)	16 (45.7%)	22 (64.7%)	0.195

CSS: clinical severity score; LOS: length of stay; m: male; f: female

TABLE 3. Outcome characteristics of the study groups

	Group A n=35	Group B n=35	Group C n=34	P
CSS 0	7.0±1.7	7.2±1.9	7.3±1.7	0.778
CSS 1	5.8±1.9^{+}	6.2±1.8^{+}	6.6±2.0	0.271
CSS 24	4.6±1.7^{+*}	4.2±1.3^{+*}	4.7±1.1^{+*}	0.165

CSS: clinical severity score
$^{+}$p<0.001 in group A and B; when compared with baseline values
*p<0.001 in all groups when compared with 0 and 1 h values

C were subsequently withdrawn because of deteriorated clinical status. Gender, age, baseline CSS and heart rates, baseline sodium levels, history of atophy and proven asthma in parents and siblings were similar in each group. Baseline characteristics of three groups were showed in Table 2. Length of hospital stay in group A, B and C were similar in each group. We did not find remarkable differences among three groups (p>0.05). Steroid requirement and serum sodium levels were similar in all groups (Table 2).

Clinical severity scores at 1 hour and 24 hour were better in group A and B when compared with baseline scores. CSS at 24 hour was better in group C when compared with baseline and 1 hour scores (p<0.05). We did not observe significant differences for CSS at 24 hour when three groups are compared with each other (p>0.05) (Table 3).

All patients were followed for occasional side effects of the study drugs such as tachycardia, tremor, bronchospasm and cough during the nebulization. We did not obtain any side effects in group A and B. In group C, bronchospasm was observed in two patients and cough during the nebulization was observed in two patients too. And in one patient both bronchospasm and cough during the nebulization was observed.

DISCUSSION

In this double-blinded prospective trial, the LOS was not significantly different among three groups. In a recent study Nenna et al. (19) treated 39 bronchiolitis either by 7% HS plus hyaluronic acid or 0.9 saline. They administered 2.5 cc 7% HS twice a day for three days. They found that LOS was 0.7 days shorter in 7% HS group. Our results were opposed with Nenna's findings. On the other hand, Jacobs et al. (18) treated 101 bronchiolitis with 7% HS plus epinephrine or 0.9% saline plus epinephrine in the emergency department and they concluded that 7% HS did not show any clinically significant decrease in CSS. The fact that they did not calculate the LOS limited study. We in turn, found that CSS at the 24 hour was not better in 7% HS group.

In a Cochrane database review, inhaled 3% HS treatment makes a 1.2 day decrease in the mean LOS and this treatment option reduces CSS. And finally, they recommended 3% HS effective and safe treatment option (21). In our trial, median LOS was not different among three groups. Al-Ansari et al. (14) conducted a double-blinded, randomized clinical trial in infants with bronchiolitis in the emergency department. They prescribed 3.5 mL 5% HS, 3% HS and 0.9% saline with epinephrine every four hours for two days in a short stay unit of pediatric emergency department. Their primary outcome was CSS at 48 hour and they concluded that 5% HS is ef-

fective to reduce CSS at 48 hour. LOS was shorter in both 5% HS and 3% HS group when compared with 0.9% saline group (1.56±1.38 days for the 5% HS group, 1.4±1.41 days for the 3% HS group and 1.88±1.76 days for the 0.9% saline group). In a recent multicenter study Everard et al. (22) compared 3% HS and placebo and they concluded that nebulised HS is not effective treatment option in acute bronchiolitis. Recently, Teunissen et al. (23) reported a multicenter trial with 247 patients. Study solutions are prescribed with epinephrine three times a day until discharge with 4 mL total volume. They compared 6% and 3% HS in bronchiolitis in a randomized controlled trial and they concluded that nebulization with 3% or 6% HS did not reduce LOS and duration of supplemental oxygen saturation in moderate to severe bronchiolitis. They concluded that 0.9% saline might not be a good control group. Our findings were similar with Everard (22) and Teunissen (23) results. In one study, nebulization with a high volume of normal saline was as effective as that of a lower volume of 3% HS (24). In vivo "the change in airway surface liquid and the improvement in mucus clearance after 0.9% saline or HS inhalation is probably a direct effect of the total mass of sodium chloride added to the airway surface" (25). Thus, total mass of sodium chloride prescribed to the bronchioles seems to have therapeutic effects in the disease course rather than volume.

Studies show that, 3-7% HS may have some beneficial effects to the natural course of bronchiolitis. But as mentioned above, some trials have paradoxical results. This opposite situation might be due to the dosage, volume and duration of the HS. On the other hand natural course and pathophysiology of the bronchiolitis might be different with various viral agents. And probably various viruses give different results to the HS therapy.

In cystic fibrosis studies, some adverse effects associated with HS treatment were reported. The most common side effects are increased cough, chest tightness, bronchospasm, throat irritation and a temporary decline in FEV_1 (26,27). In this trial, we added salbutamol to prevent possible bronchial constriction. We examined adverse events in 5 (14.7%) patients in 7% HS group. These adverse events were cough and bronchospasm. But none of the patients stop the medication because of the side effects. Hypernatremia might be occasional side effect of HS treatment and as a result of our investigation of the patients we could not examine this side effect in the patients.

Some limitations are found in this trial. First, the number of children in the study group was limited. Secondly, because there is no standard in the literature for the treatment with 5-7% HS, the dosage and volume of the 7% HS in this study is not standard. And finally the viral agents are absent in this trial.

In conclusion, both 3% and 7% HS do not have any effect to decrease LOS in infants with bronchiolitis. Further multicenter studies with different dosage and volume of HS (mass of sodium chloride) and probably with the same viruses and sodium chloride free placebo are needed to provide more data.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University.

Informed Consent: Written informed consent was obtained from patients' parents who participitated to the study.

Peer-review: Externally peer-reviewed.

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