Nebulized 3% Hypertonic Saline Solution Treatment in Ambulatory Children With Viral Bronchiolitis Decreases Symptoms*

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Objective: **To determine the utility of inhaled hypertonic saline solution to treat ambulatory infants with viral bronchiolitis.**

Design: **Randomized, double-blind, controlled trial. Sixty-five ambulatory infants (mean ± SD age, 12.5 ± 6 months) with viral bronchiolitis received either of the following: inhalation of 0.5 mL (5 mg) terbutaline added to 2 mL of 0.9% saline solution as a wet nebulized aerosol (control; group 1; n = 32) or 0.5 mL (5 mg) terbutaline added to 2 mL of 3% saline solution administered in the same manner as above (treatment; group 2; n = 33). This therapy was repeated three times every day for 5 days.**

Results: **The clinical severity (CS) scores at baseline on the first day of treatment were 6.4 ± 1.8 in group 1 and 6.6 ± 1.5 in group 2 (not significant). After the first day, the CS score was significantly lower (better) in group 2 as compared to group 1 on each of the treatment days ($p < 0.005$; Fig 1). On the first day, the percentage decrease in the CS score after inhalation therapy was significantly better for group 2 (33%) than for group 1 (13%) [$p < 0.005$; Fig 1]. On the second day, the percentage improvement was better in the hypertonic saline solution-treated patients (group 2) as compared to the 0.9% saline solution-treated patients (group 1) [$p = 0.01$; Fig 1].**

Conclusions: **We conclude that in nonasthmatic, nonseverely ill ambulatory infants with viral bronchiolitis, aerosolized 3% saline solution plus 5 mg terbutaline is effective in decreasing symptoms as compared to 0.9% saline solution plus 5 mg terbutaline.**

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Key words: ambulatory; β_2-agonist; hypertonic saline solution; respiratory syncytial virus; terbutaline; viral bronchiolitis

Abbreviations: CF = cystic fibrosis; CS = clinical severity; NS = not significant; RA = radiograph assessment; RSV = respiratory syncytial virus

Virtually all children acquire respiratory syncytial virus (RSV) infection within 2 years after birth[1–3]; only 1% require hospitalization.[1,4] Therefore, therapies that decrease symptoms and morbidity in ambulatory children with RSV bronchiolitis are of benefit and could potentially reduce health-care expenditures. Despite 4 decades of efforts, there are no effective means to control RSV.[1] Currently, controversies exist over the available treatments for acute bronchiolitis.[1,5] Antiviral agents such as ribavirin are available, but their use in most patients is controversial and therefore not indicated, especially in ambulatory patients.[5–10] Most of the studies using glucocorticoids in the treatment of bronchiolitis denied a positive therapeutic effect in previously normal children with bronchiolitis.[5,11,12] The use of adrenergic agonists occasionally resulted in a short-term improvement in patients with bronchiolitis,[13–16] while others failed to show a significant effect.[5,17]

Pathophysiologically, bronchiolitis is an infection of the bronchiolar epithelium, with subsequent profound submucosal and adventitial edema, increased secretion of mucus, peribronchiolar mononuclear infiltration,

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and epithelial cell necrosis. These changes obstruct flow in the small airways, leading to hyperinflation, atelectasis, and wheezing.[1,5,18] A single inhalation of recombinant human deoxyribonuclease has been recently used as a mucolytic agent in RSV bronchiolitis with some success.[19] However, this expensive drug was administered only once to each baby tested and had no effect on the length of hospital stay, nor did it improve post-inhalation therapy clinical severity (CS) scores significantly.[19] A more cost-effective drug is urgently needed for this purpose.

Hypertonic saline solution, by absorbing water from the submucosa, can theoretically reverse some of the submucosal and adventitial edema and improve the clearance of the thick mucus plaques inside the bronchiolar lumen. It has been shown to increase mucociliary transit time in various situations: *in vitro*, in normal subjects, in patients with cystic fibrosis, and in patients with sinonasal diseases.[20–28]

In our region, the current standard inhalation therapy of ambulatory babies with acute bronchiolitis consists of β_2-agonists—terbutaline or albuterol—diluted in normal saline solution. We hypothesized that simply substituting normal saline solution for hypertonic saline solution in the inhalation mixture for delivering terbutaline to these babies may improve CS scores after inhalations and decrease hospitalization rates.

Materials and Methods

This was a randomized, double-blinded, controlled trial. Signed informed consent was obtained from the parents of each child, and the human ethics committee of our hospital approved the study according to the principles of the Declaration of Helsinki. Seventy infants who presented to the Pediatrics and Adolescent Ambulatory Community Clinic of General Health Services of Petach-Tikva for acute viral bronchiolitis during the winter of 2000–2001 were recruited. The inclusion criterion was clinical presentation of mild-to-moderate viral bronchiolitis. Exclusion criteria were as follows: cardiac illness, chronic respiratory disease, previous wheezing episode, age > 24 months, oxygen saturation $< 96\%$ on room air, and need for hospitalization.

The patients were selected in a double-blind, randomized fashion. All eligible patients were randomly assigned to one of two groups: group 1 (control) received inhalation of 0.5 mL (5 mg) terbutaline in 2 mL of 0.9% saline solution as a wet nebulized aerosol, and group 2 (treatment) received 0.5 mL (5 mg) terbutaline in 2 mL of 3% saline solution administered in the same manner as above. The final concentration of NaCl was 2.6% in the group 2. Patients in each group received three treatments every day, delivered at intervals of 8 h for 5 days. Patients were examined on entry and every morning by the investigator (E.M.S.) at treatment time and 30 min after the beginning of the inhalation session. The following parameters were measured and recorded using a CS score described by Wang et al.[29] This scoring system assigns a number from 0 to 3 to each variable with increased severity receiving a higher score (Table 1). After randomization, the intended therapy was begun. Patients returned to the clinic—The Pediatrics and Adolescent Ambulatory Community Clinic of General Health Services—once every morning and were examined at the clinic; the inhalation treatments were administered by the study nurse according to the study protocol. On the first day of the study, the nurse gave the parents the therapeutic package (0.9% normal saline solution or 3% saline solution) and instructed them carefully how to administer the other two inhalation treatments at home. At least once a day, the investigator phoned the parents to advise them and to ensure proper compliance in delivering the treatments according to the protocol.

Anteroposterior and lateral chest radiographs were obtained on the first day of treatment and 3 days afterwards. The radiograph assessment (RA) score described by Nasr et al[19,30] was utilized.

The combination of the therapeutic package (0.9% normal saline solution vs 3% saline solution) was not available to the investigator, nor to the medical personnel or the parents. The code was deposited with the statistician. Virology studies were antigen detection for RSV; a commercial immunochromatographic assay (ImmunoCard STAT! RSV; Meridian Diagnostics Europe; Bad Homberg, Germany) was used. The sensitivity of the test is 80 to 90%.[1]

Statistical Methods

Two major outcomes of interest were considered: (1) the difference in the decline in CS scores from baseline between the two groups every day, and the change in CS scores after the hypertonic saline solution/0.9% saline solution inhalations each day; and (2) the difference in hospitalization rate between the two groups. Other minor outcomes were RA score, pulse rate, and tremor. Continuous variables were visually scanned for normalcy of distribution. Only the subtraction of posttreatment observation from pretreatment observation each day was highly skewed, and the Mann-Whitney *U* test was used. The two-tailed *t* test for

Table 1—*CS Scores

Variables	Score			
	0	1	2	3
Respiratory rate, breaths/min	< 30	31–45	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			Irritable, lethargic, poor feeding

*From Wang et al.[29]