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

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Chest 2002;122;2015-2020
DOI: 10.1378/chest.122.6.2015

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.**

(CHEST 2002; 122:2015–2020)

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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Manuscript received October 11, 2001; revision accepted May 21, 2002.

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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]

independent samples was used to compare means by treatment group for each variable. Noncontinuous variables were examined using the χ^2 test. The mean ± SD was used to express the central tendency of the data. The mean ± SE was used in the graphs. To examine the change in CS scores after the inhalations, for each day in each treatment group separately, a p value < 0.005 was considered significant due to multiple comparisons. Otherwise, $p < 0.05$ was considered statistically significant.

Results

Seventy previously healthy infants with viral bronchiolitis were enrolled in the study between December 2000 and March 2001. Their mean age was 12.5 ± 6 months (range, 3 to 24 months). Sixty-five infants completed the study. Five infants (7.1%) were hospitalized and therefore excluded from further evaluation. Of the 65 infants who took part in the final study analysis, 32 infants received 0.9% saline solution (0.5 mL [5 mg] terbutaline in 2 mL of 0.9% saline solution as a wet nebulized aerosol [0.9% saline solution; group 1]) and 33 infants received 0.5 mL [5 mg] terbutaline in 2 mL of 3% saline solution administered in the same manner as above (treatment; group 2). The two groups had similar clinical characteristics and variables at baseline (Table 2). Using the immunochromatographic assays, 52 of 65 infants (80%) were RSV positive. In fact, the positive rate for RSV in the 0.9% saline solution-treated group (group 1) was 25 of 32 infants (78%) and in the treatment group (group 2) was 27 of 33 infants (82%; p = not significant [NS]).

On the first day of treatment, the CS scores at baseline were 6.4 ± 1.8 in group 1 and 6.6 ± 1.5 in group 2 (NS). After the baseline measurement on day 1, the CS score before inhalation therapy was significantly better (lower) in the group 2 on the second, third, fourth, and fifth days of treatment (3.9 ± 1.5, 2.1 ± 2.2, 1.1 ± 2.2, and 0.9 ± 2.2, respectively) as compared to (5.2 ± 1.9, 4.8 ± 2.3, 3.8 ± 2.5, and 2.9 ± 2.7, respectively) group 1 ($p < 0.005$) [Fig 1]. Also, the CS score after the inhalation treatments differed significantly, in favor of the group 2 as compared to the group 1, on each of the treatment days (Fig 1). Most of the effect occurred on the first 2 days of treatment. On the first day, the improvements in CS score after inhalation treatments differed significantly between the two groups ($p < 0.005$). On the second day, improvements in CS score after inhalation treatments were higher in the group 2 as compared to group 1 ($p = 0.01$, Fig 1).

The RA score at baseline was 2.7 ± 2.3 in group 1, and 2.1 ± 2.4 in group 2 (NS). The second RA score improved in both groups and was 1.6 ± 2.3 in group 1 and 1.5 ± 2.2 in group 2 (NS). These results did not differ significantly at any time between the two groups.

No adverse effects were observed. Pulse rate did not differ on any day between the two groups. Analysis of intention to treat was not different from the above and also showed that three patients of the group 1 and two patients of the group 2 required hospitalization (NS).

Table 2—*Baseline Clinical Characteristics

Characteristics	Group 1, Control (0.9% Saline Solution, n = 32)	Group 2, Treatment (3% Saline Solution, n = 33)	p Value
Age, mo	12.3 ± 1.1	12.7 ± 0.9	NS
Female/male gender, No.	14/18	15/18	NS
Day care attendance, %	87	88	NS
Baseline CS score	6.4 ± 1.8	6.6 ± 1.5	NS
Baseline RA score	2.7 ± 2.1	2.3 ± 2.4	NS

*Data are presented as mean ± SE unless otherwise indicated.

Discussion

Our study shows that simply by substituting normal saline solution with hypertonic saline solution in the inhalation mixture for delivering terbutaline to ambulatory infants with mild-to-moderate viral bronchiolitis, we could decrease symptoms on every day of treatment (Fig 1). On the first and second days of treatment, we also demonstrated a significant immediate postinhalation improvement in CS score after terbutaline inhalation in hypertonic 3% saline solution as compared to terbutaline in 0.9% saline solution (Fig 1). Overall, the basic CS score before inhalation improved (decreased) significantly each day until discharge. After the first baseline score on the first day, significant differences were demonstrated for the basic preinhalation CS score between the two groups (Fig 1). Considering this, it is obvious that the main effect responsible for the significant differences throughout the study between the two groups stems from the great improvement taking place, on the first and probably on the second days of treatment (Fig 1). One possible explanation points to the relatively, already mild CS score after the great improvement on the first and second days, so that no further significant differences were possible between the two groups (Fig 1). The exact duration of the effect of one hypertonic saline solution inhalation and therefore its continuing impact on CS score is not known. Nevertheless, in our patient population with relatively mild RSV bronchiolitis, three such inhalations every day were enough to demonstrate a

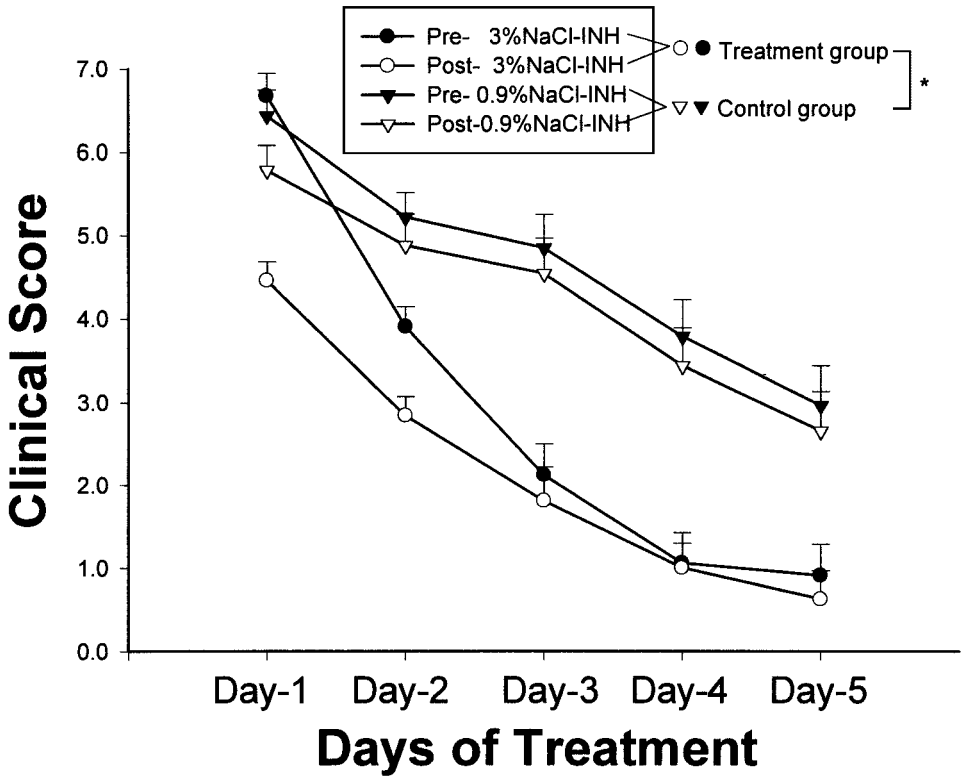

FIGURE 1. After the baseline measurement on the first day, the CS score differed significantly between the two groups: terbutaline/3% NaCl (treatment group) vs terbutaline/0.9% NaCl (control group). *$p < 0.005$. INH = inhalation.

significantly better CS score for the treatment group over the control group throughout the study.

This observation may not be the case in treating RSV-infected infants with a more severe CS score. The rate of hospitalization (two patients in the treatment group and three patients in the control group) did not reach significance. Given the relatively low rate of hospitalization in our population (7%), a very much larger population than ours would have been required to elucidate this issue. It would be interesting whether more hospitalization could be prevented if more severely affected ambulatory infants were to receive this treatment.

The precise pathophysiologic mechanism of hypertonic saline solution action specifically in bronchiolitis has not been investigated. However, some mechanisms have been studied and proposed for the favorable action of hypertonic saline solution on the respiratory epithelium and the mucociliary transport, *in vitro*, in normal subjects and in other inflammatory diseases. Hypertonic saline solution has been shown to enhance mucociliary clearance *in vivo*.[27] Moreover, hypertonic saline solution had a greater effect on mucus clearability *in vitro* than deoxyribonuclease.[27] Tomooka et al[28] suggested four mechanisms for the favorable effect of hypertonic saline solution in a study of patients suffering from sinonasal diseases: (1) decreasing mucosal edema, (2) decreasing inflammatory mediators concentrations, (3) mechanically clearing inspissated mucus (possibly by cough), and (4) improving overall mucociliary function and transport. A current review and meta-analysis of the literature including seven high-quality, selected, recent randomized controlled studies, concluded that in patients with cystic fibrosis (CF), nebulized hypertonic saline solution improves mucociliary clearance immediately after administration, with a possible long-term beneficial effect in CF.[20–27] The postulated molecular mechanism of the favorable effect of hypertonic saline solution on the mucus membrane and mucus transport in patients with CF according to these articles was as follows: (1) hypertonic saline solution induces an osmotic flow of water into mucus layer, rehydrating secretions and thereby improving mucus rheology[24]; and (2) hypertonic saline solution breaks the ionic bonds within the mucus gel, which could reduce the degree of cross-linking and entanglement and lower viscosity and elasticity.[20] Interestingly, it has been shown in different models that a much higher concentration than we used (7.5% hypertonic saline solution) can potentially reduce lung damage by suppressing neutrophil activation.[31–33]

Pathophysiologically, viral bronchiolitis is an infec-

tious inflammation of the whole respiratory mucosal epithelium, although more pronounced in small bronchioles.[34] This leads to tissue edema and mucus production, resulting in thick mucus plaques within the airway lumen and increase in intraluminal DNA concentration due to lysis of inflammatory and sloughed respiratory epithelial cells.[19,34] DNA is a polyanion macromolecule that further increases the viscosity and adhesiveness of lung secretions.[19,34] Taking this into consideration, the exact contribution and importance of each of these possible mechanisms waits to be documented in viral bronchiolitis in animal studies or *in vitro*. It is possible that in our study, an improvement the mucociliary transport and a better elimination of intracellular debris may have reduced viral load and milder ongoing inflammation within the airways. This might decrease in opportunity for secondary bacterial overgrowth and thereby may contribute to the favorable effect of decreasing post-inhalation therapy CS score (Fig 1).

Our patient population included only infants < 24 months old (mean age, 12.5 ± 1 months). However, the burden of RSV bronchiolitis is much wider. RSV infections and burden are now recognized as important pathogens in adults[1] and are significant and often unrecognized causes of lower respiratory tract infection in both elderly and immunosuppressed patients.[35] As an example, RSV was isolated as frequently as influenza A in elderly institutionalized patients with an "influenza-like illness" and was associated with increased mortality compared to influenza A.[36] Therefore it would be most interesting to evaluate the effect of this new treatment modality in treating older adults as well, especially in immunocompromised patients, since the mortality of RSV infection approaches 100% in this patient population.[1]

In our study, the RA score parameter tested did not show any favorable advantage for the tested group over 0.9% saline solution. It is probable that RA score measurements are not sensitive enough to detect early improvements in bronchiolitis, especially as in our study, when taken in a double-blinded fashion of previous history of the CS of the disease, each patient's group assignment, and the time the radiograph was obtained.[30,37] In addition, 3 days from the first to the second radiograph may not be enough time to show RA score improvement, as radiographic changes can lag after clinical improvements.

Safety Issues

We used a relatively low concentration of hypertonic saline solution in order to decrease the possible negative effect of a higher concentration (> 7% saline solution) on the ciliary beat frequency and to decrease risk of bronchospasm.[38] We always administered hypertonic saline in conjunction with terbutaline solution in order to avoid any possible bronchoconstriction effect. In our study, we found no such detrimental effect. This is in concordance with the excellent safety profile reported by Wark and McDonald[20] and others,[20–26] who found no reports of bronchospasm in 143 reviewed patients with relatively severe CF treated with hypertonic saline solution inhalations. They attributed this reassuring observation to the cotreatment of the hypertonic saline solution inhalations with β-agonists.

Conclusion

On the basis of a significantly improvement in CS score over control (0.9% saline solution), we conclude that the combination of hypertonic saline solution 3%/terbutaline is an effective medication for ambulatory infants with relatively mild acute bronchiolitis. This treatment has an excellent safety profile when compared to terbutaline diluted in normal saline solution.

ACKNOWLEDGMENT: Mona Boaz, MSc, biostatistician of the Edith Wolfson Medical Center, Holon, advised on statistics.

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