Nebulized 3% Hypertonic Saline Solution Treatment in Hospitalized Infants With Viral Bronchiolitis*

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Objective: **To determine the utility of inhaled hypertonic saline solution to treat infants hospitalized with viral bronchiolitis.**
Design: **Randomized, double-blind, controlled trial. Fifty-two hospitalized infants (mean ± SD age, 2.9 ± 2.1 months) with viral bronchiolitis received either inhalation of epinephrine, 1.5 mg, in 4 mL of 0.9% saline solution (group 1; n = 25) or inhalation of epinephrine, 1.5 mg, in 4 mL of 3% saline solution (group 2; n = 27). This therapy was repeated three times every hospitalization day until discharge.**
Results: **The percentage improvement in the clinical severity scores after inhalation therapy was not significant in group 1 on the first, second, and third days after hospital admission (3.5%, 2%, and 4%, respectively). In group 2, significant improvement was observed on these days (7.3%, 8.9%, and 10%, respectively; $p < 0.001$). Also, the improvement in clinical severity scores differed significantly on each of these days between the two groups. Using 3% saline solution decreased the hospitalization stay by 25%: from 4 ± 1.9 days in group 1 to 3 ± 1.2 days in group 2 ($p < 0.05$).**
Conclusions: **We conclude that in nonasthmatic, nonseverely ill infants hospitalized with viral bronchiolitis, aerosolized 3% saline solution/1.5 mg epinephrine decreases symptoms and length of hospitalization as compared to 0.9% saline solution/1.5 mg epinephrine.**
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Key words: β_2-agonist; epinephrine; hypertonic saline solution; respiratory syncytial virus; viral bronchiolitis

Abbreviations: CF = cystic fibrosis; NS = not significant; RSV = respiratory syncytial virus

Respiratory syncytial virus (RSV) is the chief cause of hospital admission for respiratory tract illness in young children. In the 1980s, an estimated 100,000 children were hospitalized with RSV infection in the United States annually, at a cost of $300 million.[1–3] The magnitude of the cost is understandable, since virtually all children become infected with RSV within 2 years after birth,[1] with 1% requiring hospitalization. Nearly two thirds of the cost related to annual RSV epidemics is attributable to hospitalization.[1,4] Therefore, therapies that reduce hospital days could potentially greatly reduce healthcare expenditures. Despite 4 decades of efforts, there are no effective means to control RSV,[1] and still the mainstay of treatment for RSV infection is supplemental oxygen and hydration.[5] Controversies exist related to the available treatments for acute bronchiolitis.[1,5] Antiviral agents are available, but their use in most patients is controversial and therefore not routinely indicated. The efficacy of ribavirin, the only specific drug available for the treatment of RSV infection,[1] has not been demonstrated conclusively.[1,5–10] 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 β_2-agonists occasionally resulted in a short-term improvement in patients with bronchiolitis, especially when using epinephrine,[13–16] while others failed to show a significant effect.[5,17]

Pathophysiologically, bronchiolitis is an infection of the bronchiolar epithelium, with subsequent pro-

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found submucosal and adventitial edema, increased secretion of mucus, peribronchiolar mononuclear infiltration, 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 by Nasr et al,[19] and had no effect on the length of hospital stay, nor did it improve postinhalation clinical severity scores significantly.

Hypertonic saline solution, by absorbing water from the submucosa, can theoretically reverse some of the submucosal and adventitial edema and decrease the thickness and dryness of the mucous 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 (CF), and in patients with sinonasal diseases.[20–28]

The common practice in our institution is to treat hospitalized babies with acute bronchiolitis with inhalation of epinephrine diluted in normal saline solution. We hypothesized that simply substituting normal saline solution with hypertonic saline solution in the inhalation mixture for delivering epinephrine to these babies may improve clinical severity scores after inhalations and decrease hospitalization stay.

Materials and Methods

Devices

We utilized a nebulizer (Aeromist Nebulizer Set 61400; B&F Medical by Allied; Toledo, OH) routinely available in our ward connected to a source of pressurized oxygen, from the wall, set to a flow rate of 5 L/min. This device has an output of 3 mL in 6 min, an aerodynamic diameter mass medium of 0.5- to 4-μm range, and a geometric SD of 96% of all liquid nebulized. The nebulizers were administered until empty.

Study Design

This was a randomized, double-blind, controlled trial. Signed informed consent was obtained from the parents of each child, and the human ethics committee (Helsinki) of our hospital approved the study. Fifty-three infants who were hospitalized in the Edith Wolfson Medical Center for acute viral bronchiolitis during the winter of 2000–2001 were recruited. Inclusion criteria were clinical presentation of viral bronchiolitis with temperatures $> 38°C$ that lead to hospitalization. Exclusion criteria were as follows: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, saturation $< 85\%$ on room air, obtunded consciousness, and/or progressive respiratory failure requiring mechanical ventilation.

The patients were recruited sequentially and were randomized in a double-blind fashion. However, eight potentially eligible patients were excluded because their parents did not agree to sign the informed consent: three patients intended for the 3% saline solution group, and five patients intended for 0.9% saline solution group. All eligible patients were randomly assigned to one of two groups: group 1 received inhalation of epinephrine, 1.5 mg, in 4 mL of 0.9% saline solution; group 2 received inhalation of epinephrine, 1.5 mg, in 4 mL of 3% saline solution. Patients in each group received three treatments for every day of hospital stay delivered at intervals of 8 h, until the patient was ready for discharge. Additional inhalations as needed of epinephrine in 0.9% saline solution were recorded and calculated as add-on therapy.

Patients were examined at the study entry and every day. All patients were enrolled within 24 h of admission to the hospital. At treatment time and 30 min after the beginning of each inhalation session, the following parameters were measured and recorded using a clinical severity 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, as follows: respiratory rate, < 30 breaths/min, 31 to 45 breaths/min, 46 to 60 breaths/min, or > 60 breaths/min; wheezing, none, terminal expiratory or only with stethoscopy, or inspiration and expiration without stethoscope; retraction, none, intercostal only, tracheosternal, or severe with nasal flaring; and general condition, 0 point for normal, and 3 points for irritable, lethargic, or poor feeding. After randomization, the intended therapy was begun. Anteroposterior and lateral chest radiographs were obtained at the time of hospital admission and 3 days afterwards. The radiograph assessment 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 or medical personnel. No detectable difference in color, smell, or other physical properties existed between 0.9% saline solution and 3% saline solution. The code was deposited with the statistician.

The decisions to discharge babies were made at morning rounds by the attending physician, based on clinical grounds alone. The attending physician was blinded to the combination of the therapeutic package (0.9% saline solution vs 3% saline solution).

Antigen detection was performed using a commercial immunochromatographic assay (ImmunoCard STAT! RSV; Meridian Diagnostics Europe; Bad Homburg, Germany). The sensitivity of the test is 80 to 90%.[1]

Statistical Methods

Two major outcomes of interest were considered: duration of hospitalization, and the change in clinical severity score after the 3% saline solution/0.9% saline solution (with epinephrine) inhalations each day. Other minor outcomes were pulse rate, saturation on room air, radiograph assessment score, and number of add-on treatments. Each variable was visually scanned for normalcy of distribution. Only age and hospitalization days were highly skewed. These variables therefore were log transformed prior to analysis. All continuous variables were examined using the paired or unpaired t test as appropriate. Noncontinuous variables (sex and atopy) were examined using the χ^2 test. After log transformation, days of illness at hospital admission were regressed against days of hospitalization to examine the linear correlation between them using the least-squares method. The mean ± SD expresses the central tendency of the data. The mean ± SE was used in the graphs. To examine the change in clinical severity score after the inhalations, paired t tests were carried out for each day in each treatment group separately. For this analysis, a p value < 0.006 for two-tailed t test was considered significant due to multiple comparisons. Otherwise, $p < 0.05$ was considered statistically significant.

Results

Fifty-three previously healthy infants with viral bronchiolitis were enrolled in the study between December 2000 and March 2001. Their mean age was 2.9 ± 2.1 months (range, 0.5 to 12 months). One patient from group 1 was excluded from the analysis because of deterioration immediately after the first treatment inhalation, which required mechanical ventilation; this deterioration was attributed to inhalation of epinephrine. Of the 52 infants who took part in the study analysis, 25 infants were enrolled to receive epinephrine, 1.5 mL (1.5 mg), in 4 mL of 0.9% saline solution as a wet nebulized aerosol (group 1), and 27 infants received epinephrine, 1.5 mL (1.5 mg), in 4 mL of 3% saline solution administered in the same manner as above (group 2). The two groups had similar clinical characteristics and variables at baseline. Using the immunochromatographic assays, 47 of 52 infants (87%) were RSV positive. The positive rate for RSV in group 2 was 23 of 27 infants (85%) and in group 1 was 22 of 25 infants (88%), p = not significant (NS).

The mean duration of hospitalization was 3.5 ± 1.6 days for the whole population, and it differed significantly between the two groups: 4 ± 1.9 days in group 1 and 3 ± 1.2 days in group 2 (Table 1) [$p < 0.05$]. Days of illness prior to hospital admission (as obtained by history taking) were 3 ± 1.6 days in group 1 vs 3.9 ± 2.9 days in group 2. This could theoretically affect the hospital stay. Therefore, after log transformation, days of illness at hospital admission were regressed against days of hospitalization to examine the linear association between them using the least-squares method. This association was not significant ($r = 0.14$, $p = 0.3$) and indicated that variation in days of illness at hospital admission accounted for only 2% (r^2) of the variation in days of hospitalization. The percentage of infants remaining in the hospital each day for each group is shown in Figure 1.

Table 1—*Baseline Clinical Characteristics*

Characteristics	0.9% Saline Solution (Group 1; n = 25)	3% Saline Solution (Group 2; n = 27)	p Value
Age, mo	2.6 ± 1.9	3 ± 1.2	NS
Female/male gender	9/15	12/15	NS
Baseline clinical severity scores	8.08 ± 1.3	8.29 ± 1.35	NS
Baseline radiograph scores	3.9 ± 2.32	3.52 ± 2.49	NS
Days of illness at hospital admission, No.	3 ± 1.6	3.9 ± 2.9	NS
Baseline saturation, %	94.7 ± 3.3	93.8 ± 3.2	NS

The clinical severity scores at baseline were 8.08 ± 1.3 in group 1 and 8.29 ± 1.3 in group 2 (p = NS). The percentage fall of the clinical severity score after inhalation therapy was NS in group 1 on the first, second, and third days after hospital admission (3.5%, 2%, and 4%, respectively). In group 2, significant differences were observed on each of the first 3 days (7.3%, 8.9%, and 10%, respectively; $p < 0.001$) [Fig 2]. Also, these falls in clinical scores differed significantly between the two groups on each of these days.

The radiograph assessment scores at baseline were 3.9 ± 2.32 in group 1 and 3.52 ± 2.49 in group 2 (p = NS). The second radiograph assessment score improved in both groups (3.43 ± 2.35 in group 1 and 3.38 ± 2.28 in group 2), but it did not reach significance. There was no significant difference between the groups.

No adverse effects were observed. Pulse rate and the room air saturation of oxyhemoglobin did not differ at any day between the two groups. In the first 3 days, there was a trend for more add-on inhalation therapy needed per day for group 1 (1.2 ± 0.9 as compared to 0.9 ± 0.7 for group 2). However, this did not reach significance according to the two-tailed test (p = 0.1; p = 0.05 for one-tailed test). Analysis of intention to treat showed that two patients in group 1 and no patients in group 2 required mechanical ventilation. However, as mentioned above, one of these patients was excluded from the analysis.

Discussion

Our study indicates that by substituting normal saline solution with hypertonic saline in the inhalation mixture for delivering epinephrine to hospitalized infants with viral bronchiolitis, the in-hospital stay was reduced by 25%, from 4 days in the 0.9% saline solution group (group 1) to 3 days in the 3% saline solution group (group 2). This possible effect could bear an important economic and clinical impact worldwide; in the United States, > 100,000 children are hospitalized annually at a cost of $300 million.[1–3] Decreasing this burden by almost 25% could theoretically save nearly $75 million annually in the United States alone.

This study demonstrated a significantly better improvement in clinical severity score after epinephrine inhalation in hypertonic 3% saline solution as compared to epinephrine in 0.9% saline solution (Fig 2). The clinical severity scores before inhalation decreased progressively in a significant way each day until discharge. No significant differences were demonstrated for the preinhalation clinical severity scores between the two groups (Fig 2). One possible

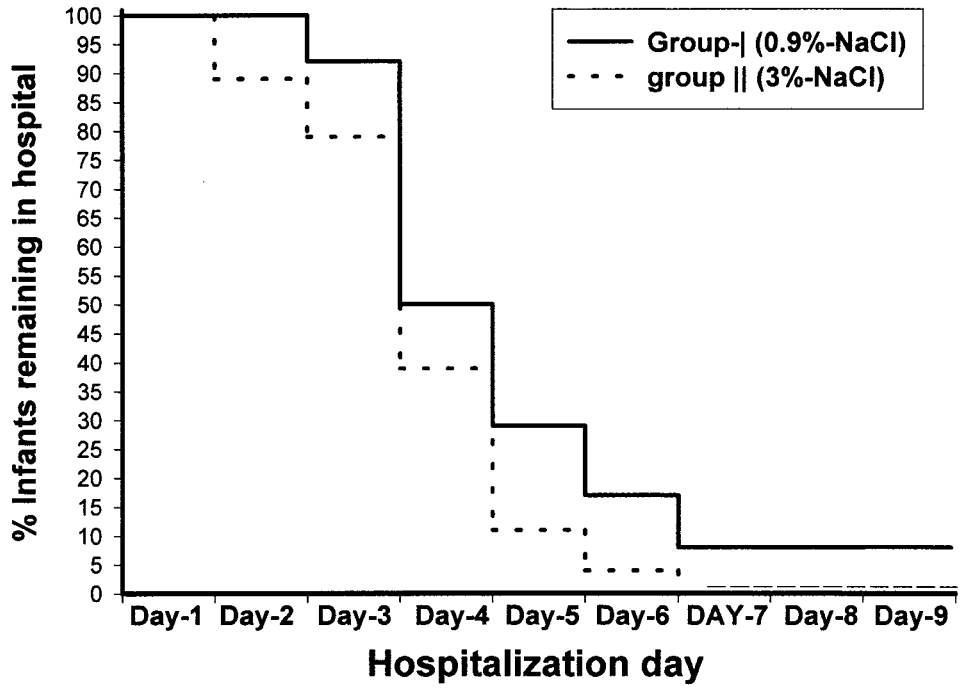

FIGURE 1. The percentage of infants remaining in the hospital each day for each group.

explanation to this observation points to lower percentage of infants remaining hospitalized in the 3% saline solution group as compared to the 0.9% saline solution group. As more infants with lower (better) clinical severity scores were discharged from group 2 than from group 1, the average clinical severity score of group 2, now including relatively more sick patients, would resemble the clinical severity score of group 1 (Fig 1). Another possible explanation is that the acute effect of the hypertonic saline solution on symptoms (clinical severity) is shorter than the intervals between inhalations, so that the favorable decline in clinical severity score after each inhalation does not persist overnight and is not apparent on the next morning before the next inhalation. The exact duration of the effect of one hypertonic saline solution inhalation and therefore its continuing impact on clinical severity score is not known and should be investigated further. Conceivably, more inhalations should be tried before assuming a maximal dose/effect of hypertonic 3% saline solution inhalations in infants hospitalized with bronchiolitis. In our patient population, the three-times-daily dose and subsequent duration of effect proved to be sufficient to shorten hospital stay significantly (Fig 1).

The precise pathophysiologic mechanism of hypertonic saline solution action specifically in bronchiolitis has not been investigated in this study. However, some mechanisms have been studied and proposed for the favorable action of hypertonic saline solution on the respiratory epithelium and the mucociliary transport. 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 concentration, (3) mechanically clearing inspissated mucus, and (4) improvement in 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 CF patients nebulized hypertonic saline solution of $\geq 3\%$ concentration improves mucociliary clearance immediately after administration with possible long-term beneficial effect.[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]; (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]; and (3) hypertonic saline solution increases the ionic

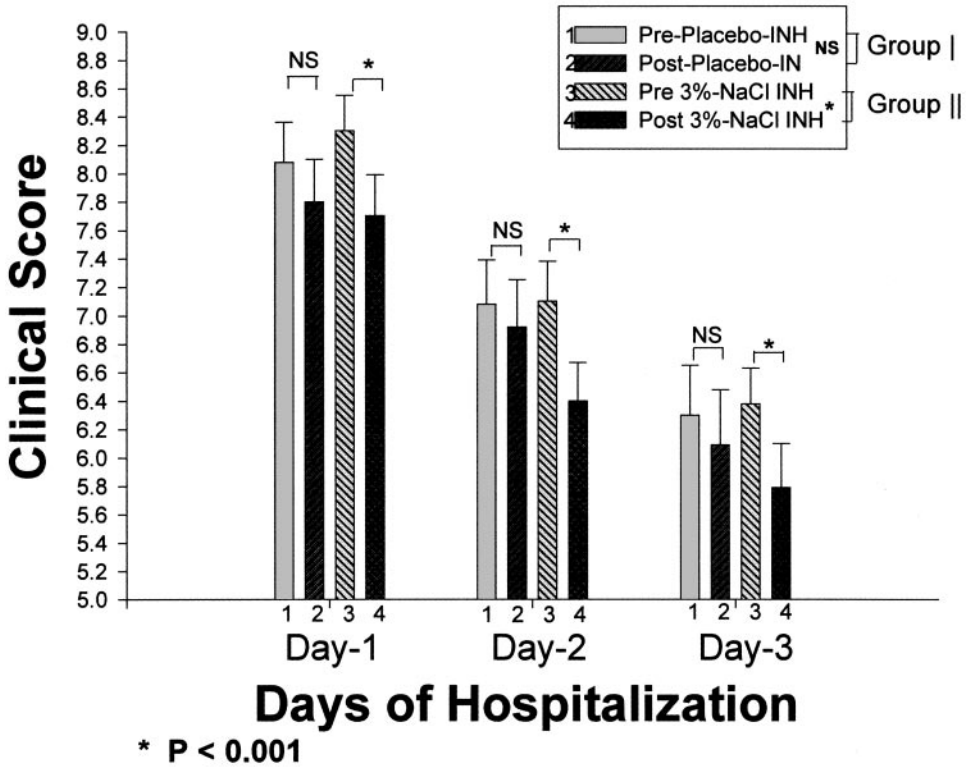

FIGURE 2. The clinical severity scores in group 1 and group 2. The fall of the clinical score after the inhalation therapy was NS in group 1 on the first, second, and third days after hospital admission. In group 2, significant differences were observed on each of the first 3 days ($p < 0.001$). Also, these falls in clinical scores differed significantly between the two groups on each of these days. IN, INH = inhalation.

concentration of the mucus and causes a conformational change by shielding the negative charges and thereby reducing repulsion. This would result in a more compact mucus macromolecule that would allow more effective clearance.[24] However, as rheologic properties of CF sputum differ from that of RSV bronchiolitis, any direct extrapolation of these mechanisms to infants with bronchiolitis should be taken with caution, until examined specifically in RSV bronchiolitis. Interestingly, it has been shown in different models that using 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 infectious 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] Taking this into consideration, the exact contribution and importance of each of these possible mechanisms waits to be documented in viral bronchiolitis in animal or *in vitro* studies. It is possible that in our study, an improvement in mucociliary transport and a better elimination of intracellular debris may have reduced viral load and decreased ongoing inflammation within the airways. This might have reduced opportunity for secondary bacterial overgrowth and thereby may contribute to the favorable effect of decreasing postinhalation therapy clinical severity score and shortening hospital stay as noted (Figs 1, 2). Finally, hypertonic saline solution inhalation can cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway function in infants with bronchiolitis.

Our patient population included only hospitalized infants < 12 months old (mean age, 2.9 ± 2.1 months). However, the extent of RSV bronchiolitis is much wider. Virtually all children become infected with RSV within 2 years after birth, and the histologic evidence of recovery reveals that complete restoration of ciliated epithelial cells requires 4 to 8 weeks in correlation with the common clinical findings of prolonged cough, wheezing, and altered pulmonary function.[1,35]

Safety Issues

We used a relatively low concentration of 3% hypertonic saline solution in order to decrease the possible negative effect of a higher concentrations (> 7% saline solution) on the ciliary beat frequency and to decrease risk of bronchospasm.[36] We always administered hypertonic saline solution in conjunction with epinephrine solution in order to avoid any possible bronchoconstriction effect. In our study, we found no such detrimental effect. This is in concordance with excellent safety profile reported by Wark and McDonald[20] and others,[21–26] 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 faster rate of discharge from the hospital and a significant posttreatment improvement in clinical severity score, we conclude that 3% saline solution/1.5 mg epinephrine is more effective than normal saline solution/epinephrine in a nonseverely ill infant population hospitalized with acute bronchiolitis. Additionally, there was no difference in safety profile.

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