

# Hypertonic Saline/Epinephrine Treatment in Hospitalized Infants with Viral Bronchiolitis Reduces Hospitalization Stay: 2 Years Experience

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**Key words:** hypertonic saline, epinephrine, inhalation, viral bronchiolitis, respiratory syncytial virus

## Abstract

**Background:** We recently published preliminary evidence on the effectiveness of hypertonic saline in infants with viral bronchiolitis.

**Objective:** To further establish the efficacy of nebulized hypertonic saline in these infants

**Methods:** In a continuing, second-year randomized, double-blind controlled trial, an additional 41 infants (age  $2.6 \pm 1$  months) hospitalized with viral bronchiolitis were recruited during the winter of 2001–2002. The infants received inhalation of 1.5 mg epinephrine dissolved either in 4 ml normal (0.9%) saline (Group I, n=20) or 4 ml hypertonic (3%) saline (Group II, n=22). The therapy was repeated three times daily until discharge. Pooling our 2 years of experience (2000–2002), a total of 93 hospitalized infants with viral bronchiolitis were recruited; 45 were assigned to Group I and 48 to Group II.

**Results:** The clinical scores at baseline were  $7.6 \pm 0.7$  for Group I vs.  $7.4 \pm 1.3$  for Group II ( $P = NS$ ). However, the clinical scores at days 1 and 2 after inhalation differed significantly between the two groups, invariably favoring Group II:  $7 \pm 1$  vs.  $6.25 \pm 1.1$  ( $P < 0.05$ ),  $6.45 \pm 1$  vs.  $5.35 \pm 1.35$  ( $P < 0.05$ ), respectively. Adding aerosolized 3% saline to 1.5 mg epinephrine reduced the hospitalization stay from  $3.5 \pm 1.7$  days in Group I to  $2.6 \pm 1.4$  in Group II ( $P < 0.05$ ). The pooled data of both years revealed that adding 3% saline to the inhalation mixture decreased hospitalization stay from  $3.6 \pm 1.6$  to  $2.8 \pm 1.3$  days ( $P < 0.05$ ).

**Conclusions:** This second-year experience and our 2 year pooled data analysis strengthen the evidence that the combination of 3% saline/1.5 mg epinephrine benefits hospitalized infants with viral bronchiolitis.

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Acute viral bronchiolitis is an infection of the lower respiratory tract most frequently caused by the respiratory syncytial virus [1]. It is the main cause of hospital admission for respiratory tract illnesses in infants, with an estimated 120,000 children hospitalized with RSV infection in the United States annually [1]. Since one of the physical signs of the disease is wheezing, and considering that 40–50% of the severely infected infants will develop episodes of wheezing years after being infected, physicians have treated the disease with steroids and beta agonists – the treatment of choice for asthma. However, these treatments as well as ribavirin,

the only known anti-RSV agent, are considered controversial and the mainstay of treatment is still hydration and supplemental oxygen [1,2-9].

The pathophysiology of bronchiolitis is quite distinct from that of asthma. Bronchiolitis is an infection of the bronchiolar epithelium, characterized by necrosis and sloughing of epithelial cells, edema, increased secretion of mucus, and peribronchiolar mononuclear infiltration – changes that obstruct flow in the large and small airways, leading to hyperinflation, atelectasis and wheezing [1,2].

Hypertonic saline may theoretically reverse some of these pathophysiologic mechanisms. *In vitro*, the addition of hypertonic saline improves mucus rheologic properties (elasticity and viscosity) and accelerates mucus transport rates [10]. *In vivo*, hypertonic saline inhalation increases the volume of airway surface liquid and increases rates of mucociliary clearance in normal subjects [11].

A preliminary study that we conducted in 53 hospitalized infants with viral bronchiolitis [12] demonstrated the effectiveness of hypertonic saline as a treatment agent. However, since the number of infants studied was relatively small, naturally some physicians still treat this observation with caution. Considering this, as well as the important possible implications of this treatment, and the latest disappointments of epinephrine treatment alone in these infants [8,9], we felt that further confirmation and expansion of the data are needed to readdress the interest of pediatricians in this possible treatment (hypertonic saline plus bronchodilator). We describe a follow-up second year study and a pooled analysis of our 2 years of experience with a total of 93 hospitalized infants recruited in double-blind controlled studies addressing exactly this issue.

## Patients and Methods

### Devices

In the winter of 2001–2002 (second study), we used an ultrasonic nebulizer (Omron U1, OMRON Matsusaka Co. Ltd., Japan). This device is as effective as jet nebulizers except when using suspensions [13]. It has an output of 0.25 ml/minute and an aerodynamic mass median diameter of 6  $\mu$ m. The nebulizers were administered until empty.

RSV = respiratory syncytial virus

### Study design

The study comprised a randomized, double-blind controlled trial. Signed informed consent was obtained from the parents of each child and the Helsinki Committee of our hospital approved the study. Forty-four infants who were hospitalized in the Department of Pediatrics at the Wolfson Medical Center for acute viral bronchiolitis during the winter of 2001–2002 were recruited. However, one patient from the control group was excluded from the analysis because of deterioration immediately after the first treatment inhalation, another patient from the control group refused to remain hospitalized and was readmitted the following day, and one patient from the experimental group who required steroid treatment due to low cortisol levels showed a swift recovery. Thus 41 infants were finally included for the analysis. Inclusion criteria were clinical presentation of viral bronchiolitis that led to hospitalization. Exclusion criteria included cardiac disease, chronic respiratory disease, previous wheezing episode, age >12 months, O<sub>2</sub> saturation <85% on room air, obtunded consciousness and/or progressive respiratory failure requiring mechanical ventilation.

The patients were selected in a double-blind randomized fashion. All eligible patients were randomly assigned to one of two groups: Group I received inhalation of 1.5 mg epinephrine in 4 ml normal (0.9%) saline; Group II received inhalation of 1.5 mg epinephrine in 4 ml hypertonic (3%) saline. Patients in each group received three treatments on each day of hospitalization, delivered at 8 hour intervals, until the patient was ready for discharge. Additional inhalations of epinephrine in 0.9% saline, as needed, were recorded and calculated as add-on therapy.

Patients were examined at admission and every day by one of the investigators (G.T.). All patients were enrolled within 24 hours of admission to the hospital. At treatment time and 30 minutes after the beginning of each inhalation session, the following parameters were measured and recorded using the clinical score described by Wang et al. [14]: respiratory rate, wheezing, retraction, and general condition. This scoring system assigns a number from 0 to 3 to each variable with increased severity receiving a higher score. In addition, oxygen saturation on room air was measured on admission. After randomization, the intended therapy was begun. Anteroposterior and lateral chest radiographs were obtained at the time of admission and during hospitalization from infants who showed lack of improvement.

The combination of the therapeutic modality (0.9% saline vs. 3% saline) was not disclosed to the investigator or to the medical personnel. Sight or smell could not distinguish the difference between 0.9% and 3% saline. The code was deposited with the statistician.

Decisions to discharge infants were taken during each morning round by the attending physician based on clinical grounds alone, such as not needing supplemental oxygen, minimal or no chest recession, and feeding adequately without the need for intravenous fluids. The attending physician was 'blinded' as to the combination of the therapeutic modality (0.9% vs. 3% saline).

For the virology studies, a commercial immunochromatographic assay (ImmunoCard STAT! RSV; Meridian Diagnostics

Europe, Bad Homburg, Germany, Catalog no. 750930) for antigen detection was used. The sensitivity of the test is 80–90% [1].

Pooling our 2 years of experience (2000–2002), a total of 93 hospitalized infants with viral bronchiolitis were recruited, of whom 45 were assigned to Group I and 48 to Group II. The inclusion and exclusion criteria were the same for both years.

### Statistics

Two major outcomes of interest were considered: duration of hospitalization and change in clinical score after the 3% saline or 0.9% saline aerosolized inhalations each day (both in combination with 1.5 mg epinephrine). Each variable was visually scanned for normalcy of distribution. As most variables were highly skewed, comparisons were made using the Mann-Whitney non-parametric U test. All continuous variables were examined using the paired or unpaired *t*-test as appropriate. Non-continuous variables (gender and atopy) were examined using the chi-square test. The mean  $\pm$  SD expresses the central tendency of the data. A *P* value < 0.05 for the two-tailed *t*-test was considered statistically significant.

### Results

Forty-one previously healthy infants with viral bronchiolitis, age  $2.6 \pm 1$  months (range 1–5 months), were enrolled in the study between December 2001 and March 2002. Of the 41 infants who took part in the study, 20 received 1.5 ml (1.5 mg) epinephrine in 4 ml of 0.9% saline as a wet nebulized aerosol (Group I) and 21 received 1.5 ml (1.5 mg) epinephrine in 4 ml of 3% saline, administered as above (Group II). At baseline, the two groups had similar clinical characteristics and variables [Table 1]. Using the immunochromatographic assays, 33 of the 41 patients (80%) were RSV-positive. The positive rates for RSV were 15/20 (75%) for Group I and 18/21 (86%) for Group II (not significant).

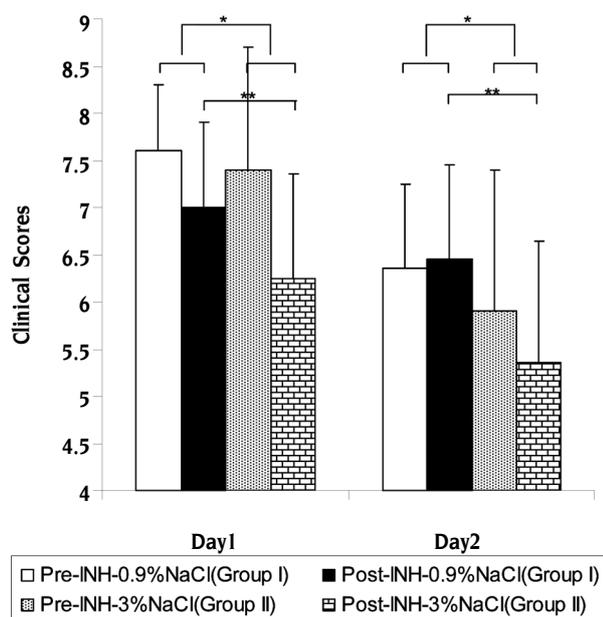
The mean hospitalization stay was  $3 \pm 1.6$  days for the whole population. This parameter differed significantly between the two groups, being  $3.5 \pm 1.7$  days for Group I and  $2.6 \pm 1.4$  for Group II [Table 2] (*P* < 0.05). The clinical scores at baseline were  $7.6 \pm 0.7$  for Group I and  $7.4 \pm 1.6$  for Group II (NS) [Figure 1]. The fall in clinical scores during the first 2 days after the inhalation

**Table 1.** Baseline clinical characteristics

	0.9% saline Group I (n = 20)	3% saline Group II (n = 21)	Significance
Age (months)	2.3 $\pm$ 0.7	2.8 $\pm$ 1.2	NS
Female/Male	7/13	11/10	NS
Baseline clinical score	7.6 $\pm$ 0.7	7.4 $\pm$ 1.4	NS
Days of illness at admission	4.5 $\pm$ 2.2	4.0 $\pm$ 2.2	NS
Saturation on admission on room air (%)	92.9 $\pm$ 2.9	93.3 $\pm$ 1.9	NS

**Table 2.** Duration of hospitalization (days)

	0.9% saline Group I (n = 20)	3% saline Group II (n = 21)	<i>P</i>
Days	3.5 $\pm$ 1.7	2.6 $\pm$ 1.4	0.018



**Figure 1.** Clinical severity scores in Group I and Group II pre- and post-inhalations

\* The fall in clinical scores after inhalations in the first 2 days significantly favored the 3% NaCl/epinephrine Group II versus 0.9 NaCl/epinephrine Group I.

\*\* The post-inhalation scores in the first 2 days significantly favored Group II versus group I.

therapy differed significantly between the two groups, favoring the experimental group:  $0.6 \pm 0.9$  in Group I vs.  $1.15 \pm 0.7$  in Group II ( $P = 0.046$ ),  $-0.1 \pm 0.7$  in Group I vs.  $0.55 \pm 0.9$  in Group II ( $P = 0.02$ ) [Figure 1]. Moreover, the post-inhalation clinical scores on days 1 and 2 after inhalation differed significantly between the two groups, invariably favoring Group II:  $7 \pm 1$  vs.  $6.25 \pm 1.1$  ( $P < 0.05$ ),  $6.45 \pm 1$  vs.  $5.35 \pm 1.3$  ( $P < 0.05$ ), respectively [Figure 1]. There were fewer add-on inhalations in the experimental hypertonic saline group, but this was not statistically significant. The numbers of add-on inhalations for Groups I and II for the first, second and third hospitalization days were as follows:  $1.5 \pm 1.2$  vs.  $1.4 \pm 0.82$ ,  $1.25 \pm 0.85$  vs.  $1.1 \pm 0.47$  and  $1.18 \pm 0.98$  vs.  $0.93 \pm 0.25$ , respectively. Eight patients from Group I and 5 from Group II underwent a second chest X-ray due to lack of improvement. Interestingly, three patients in Group I but none in Group II showed atelectasis on the second X-ray. No adverse effects were observed in patients in either of the groups.

#### Analysis of the pooled data (meta-analysis)

Altogether, 93 patients participated in our two studies, of whom 48 were in the control group (epinephrine/0.9% saline combination) and 45 in the experimental group (epinephrine/3% saline combination). Patients in the two groups had similar clinical characteristics and variables at baseline. The mean duration of hospitalization was  $3.2 \pm 1.5$  days for the whole population, differing significantly between the two groups:  $3.6 \pm 1.7$  days for

Group I and  $2.8 \pm 1.3$  days for Group II ( $P < 0.05$ ). The clinical scores at baseline were  $7.9 \pm 1.1$  for the control group and  $7.9 \pm 1.4$  for the experimental group ( $P = \text{NS}$ ). The fall in scores during the first 2 days after the inhalation therapy differed significantly between the two groups, favoring the experimental group.

#### Discussion

We believe that 3% hypertonic saline is indeed an active drug in acute viral bronchiolitis. This is based on our recent observations that an inhaled epinephrine/hypertonic saline combination is significantly effective in bronchiolitis, while inhaled epinephrine/normal saline combination did not have a statistically significant effect [12]. Moreover, hypertonic saline has recently been proven to be an active drug even in normal volunteers, increasing the volume of airway surface liquid and increasing rates of mucociliary clearance [11]. The results of the present study further strengthen our previous finding that delivering bronchodilators with hypertonic saline to infants with RSV bronchiolitis is an effective therapeutic modality [12,15].

The second randomized, double-blind, controlled trial in hospitalized infants with viral bronchiolitis compared the effect of hypertonic 3% saline/epinephrine inhalation mixture to that of 0.9% saline in the same mixture. This is the second year that our findings have revealed a significant reduction in hospitalization stay following treatment with hypertonic 3% saline. Of the other clinical outcomes, the fall in values differed significantly between the two groups during the first 2 days after treatment, favoring the experimental group, as was demonstrated in the previous study [12]. Moreover, pooling the data of our 2 year experience, and with a total of 93 hospitalized infants with RSV bronchiolitis, more significantly establishes the efficacy of nebulized hypertonic saline in infants hospitalized with viral bronchiolitis.

Our findings are not confined to hospitalized infants only, as shown recently for ambulatory children with viral bronchiolitis [15]. According to these findings, the combination of hypertonic saline and terbutaline was more effective in decreasing symptoms compared to terbutaline alone [15]. The present study and the 2 years pooled data did not address the mechanism by which hypertonic saline has reduced the number of hospitalization days and improved the clinical score. However, the mechanism by which hypertonic saline acts on the respiratory tract epithelium and on sputum rheology has been studied extensively, *in vitro* and *in vivo*, although not in bronchiolitis. Scheffer and colleagues [16] demonstrated *in vitro* that the addition of hypertonic 3% saline markedly reduced sputum viscosity. In cystic fibrosis patients, Dasgupta et al. [17] demonstrated that hypertonic saline had a greater effect than DNase on mucus clarity *in vitro*. King and co-workers [18] demonstrated that hypertonic saline reduced the viscoelasticity of sputum, compared to 0.9% saline. Other studies have demonstrated that hypertonic saline inhalation increased mucus secretion and clearance in patients with chronic bronchitis [19]. Sood and associates [11] demonstrated that hypertonic saline inhalations increase mucociliary clearance in normal volunteers, specifically through a cough-independent mechanism. The effect of hypertonic saline is not confined to the ciliated

epithelium and mucus rheology. Hypertonic saline has also been implicated in modulating the inflammatory response. Ciesla et al. [20] demonstrated a decreased inflammatory response of polymorphonuclear leukocytes after pretreatment with hypertonic saline. Arbabi and team [21] demonstrated that prostacyclin, an agent with the potential to inhibit formation of thromboxane and the adhesion of leukocytes to endothelial cells, is produced in response to hypertonic saline and lipopolysaccharide.

In our previous study in the winter of 2000–2001, we utilized a jet nebulizer (in contrast to the ultrasonic nebulizers in the winter of 2001–2002). It appears that the nebulizer itself has an impact on sputum expectoration as described by Popov et al. [22] who showed that sputum induction was higher using ultrasonic nebulizers compared to jet nebulizers. The jet nebulizer that we utilized in the winter of 2001–2002 generates aerosol with a smaller aerodynamic mass median diameter (0.5–4  $\mu\text{m}$ ) [12,15] as compared to 6  $\mu\text{m}$  diameter with the ultrasonic nebulizer. On the one hand, aerosol with a smaller aerodynamic mass median diameter reaches smaller bronchi and bronchioles, but ultrasonic nebulizers induce sputum more efficiently than jet nebulizers on the other. In addition, the inflammation and mucus secretions in acute viral bronchiolitis are not confined to the smaller bronchioles but are distributed throughout the respiratory system epithelium from the nose to the smallest bronchioles. Thus, the different mass median diameters of the two nebulizers, and the different aerosol nebulization technique, could yield different outcomes affecting different locations along the respiratory airways. Nevertheless, using both types of nebulizers to deliver the 3% saline/epinephrine aerosol mixture favored our patients in the same direction. It is possible that using a different ultrasonic nebulizer that generates smaller particles than ours will prove to be even more effective in acute viral bronchiolitis (unpublished data).

### Safety issues

We used a relatively low concentration of 3% saline in order to decrease the possible negative effects of higher concentrations [12,15]. In fact, the safety of an even higher concentration of 7% hypertonic saline with beta-2 agonists in cystic fibrosis patients was recently documented [23]. Hypertonic saline alone, not backed up with beta-2 agonists, can cause bronchoconstriction especially in asthmatic. Since some of the bronchiolitic infants may be asthmatics, we always administered hypertonic saline in conjunction with epinephrine to avoid any possible bronchoconstriction effect. In our 2 year experience, we found no such detrimental effect using beta-2 agonist/hypertonic saline mixtures. Moreover, considering safety issues, including this work, we now have good published experience in treating 207 bronchiolitic infants with beta-2 agonist/hypertonic saline mixtures [12,15,24]. This is in concordance with the excellent safety profile reported by Wark and McDonald [25], who found no reports of bronchospasm in a review of 143 relatively severe cystic fibrosis patients treated with hypertonic saline inhalations. They attributed this reassuring observation to the co-treatment using hypertonic saline inhalations with beta-2 agonists.

### Study limitations

The decision to discharge infants were taken at each morning's rounds by the attending physician based on clinical grounds, such as not needing supplemental oxygen, minimal or no chest recession, and feeding adequately, without the need for intravenous fluids. However, the time until the child was ready for discharge according to these criteria was not recorded and this is indeed a weakness of our study. Nevertheless, although the decision to discharge a child may have been affected by other administrative and social factors unrelated to the condition of the child, the attending physician was 'blinded' as to the therapeutic modality combination (0.9% vs. 3% saline), so that both groups were affected equally by these factors and any strong difference demonstrated between the groups is still valid. In fact, the total length of hospitalization that we measured is an important outcome in "real life."

### Conclusions

Considering the disappointment of many treatments for RSV bronchiolitis and especially the latest disappointments of epinephrine treatment in these infants [8,9], it is of paramount importance for pediatricians to be aware of and more confident in a simple, seemingly efficient and safe treatment for RSV bronchiolitis – the main cause of hospital admission for respiratory tract illnesses in infants [1].

Both our second year study by itself, repeating the same results, and the analysis of 2 years experience, establish further confidence in aerosolized 3% saline/1.5 mg epinephrine treatment to decrease symptoms in infants with acute viral bronchiolitis and shorten hospitalization stay. More research with higher saline concentrations and more frequent inhalation of hypertonic saline is warranted to further clarify this potential treatment modality. This treatment has an excellent safety profile.

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