7% Hypertonic Saline in Acute Bronchiolitis: A Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: Hypertonic saline (3% and 5%), has been shown to improve clinical severity scores and reduce inpatient length of stay, and was associated with a trend toward lower admission rate in acute bronchiolitis.

WHAT THIS STUDY ADDS: We are not aware of any previous data using 7% hypertonic saline in bronchiolitis. Our results suggest that 7% saline does not lower clinical severity of illness, admission rate, or length of stay, when compared with normal saline.

abstract

BACKGROUND: Research suggests that hypertonic saline (HS) may improve mucous flow in infants with acute bronchiolitis. Data suggest a trend favoring reduced length of hospital stay and improved pulmonary scores with increasing concentration of nebulized solution to 3% and 5% saline as compared with 0.9% saline mixed with epinephrine. To our knowledge, 7% HS has not been previously investigated.

METHODS: We conducted a prospective, double-blind, randomized controlled trial in 101 infants presenting with moderate to severe acute bronchiolitis. Subjects received either 7% saline or 0.9% saline, both with epinephrine. Our primary outcome was a change in bronchiolitis severity score (BSS), obtained before and after treatment, and at the time of disposition from the emergency department (ED). Secondary outcomes measured were hospitalization rate, proportion of admitted patients discharged at 23 hours, and ED and inpatient length of stay.

RESULTS: At baseline, study groups were similar in demographic and clinical characteristics. The decrease in mean BSS was not statistically significant between groups (2.6 vs 2.4 for HS and control groups, respectively). The difference between the groups in proportion of admitted patients (42% in HS versus 49% in normal saline), ED or inpatient length of stay, and proportion of admitted patients discharged at 23 hours was not statistically significant.

CONCLUSIONS: In moderate to severe acute bronchiolitis, inhalation of 7% HS with epinephrine does not appear to confer any clinically significant decrease in BSS when compared with 0.9% saline with epinephrine. Pediatrics 2014;133:e8–e13

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KEY WORDS
7% hypertonic saline, acute bronchiolitis

ABBREVIATIONS
BSS—bronchiolitis severity score
CI—confidence interval
ED—emergency department
HS—hypertonic saline

Dr Jacobs designed the study and the data collection instruments, coordinated and supervised data collection, and drafted the initial manuscript; Dr Foster assisted with randomization and masking of study drug in pharmacy; Dr Wan carried out the initial analyses and reviewed and revised the manuscript; Dr Pershad conceptualized the study design and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Acute viral bronchiolitis is the most common lower respiratory infection in infants and young children; the annual inpatient disease burden exceeds the cost of any respiratory disease in the United States among children younger than 2 years (excluding neonatal care). From 1980 to 1996, the rate of hospitalization for bronchiolitis increased in the United States from 12.9 admissions per 1000 children to 31.2 admissions per 1000 children. However, a recent trend among US children between 2000 and 2009 suggests a significant decline in bronchiolitis hospitalizations to 14.9 per 1000 children. The use of mechanical ventilation and hospital charges for bronchiolitis significantly increased over this same period.

Although several treatment strategies have been investigated, few have been shown to be effective. The mainstay of treatment remains supportive care with supplemental oxygen and hydration as needed. Routine use of corticosteroids or bronchodilators is not recommended. Similarly, in the 2006 bronchiolitis guidelines published by the American Academy of Pediatrics, routine use of bronchodilators is not recommended, although a trial of bronchodilators is listed as an option, based on some evidence that epinephrine may be more efficacious compared with salbutamol and placebo in outpatients. However, conclusive evidence for efficacy of β2-agonist therapy is lacking. Nebulized hypertonic saline (HS) has shown promise as an alternative treatment option. It has been postulated that aerosolized HS hydrates the airway surface liquid, enhances mucociliary clearance by improving mucus flow, reduces edema of the airway wall by absorbing water from the mucosa and submucosa, and causes sputum induction and cough, which can help clear sputum and improve small airway obstruction in acute bronchiolitis.

A 2008 Cochrane database systematic review stated that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis. Since this review, additional studies have evaluated HS in infants with bronchiolitis: 1 in an ambulatory setting, 3 in an emergency department (ED), and 5 in hospitalized patients. All of these studies have shown a reduction in pulmonary severity scores and/or a trend toward reduced admission rates in the HS group. Of note, all investigations to date have shown HS to be safe, with no patients experiencing decreased oxygen saturation, apnea, or cyanosis after administration of the medication.

We are unaware of any study examining the role of 7% HS in the ED setting for treating bronchiolitis. Our primary hypothesis was that the higher concentration of saline (7% HS) with epinephrine administered in the ED would confer a greater and more sustained decrease in bronchiolitis severity score (BSS) for infants and young children with acute bronchiolitis and, secondarily, decrease hospitalization rate, increase the discharge rate after a 23-hour inpatient hospital stay, and decrease hospital length of stay.

METHODS

Study Design

A double-blind, randomized, comparative, controlled trial was conducted in the ED of an urban tertiary care center, with an annual census of 70 000 patient visits. The institutional review board approved the study.

Patient Selection

Informed consent was obtained from a parent or legal guardian of each patient enrolled in the study. Patients age 6 weeks to ≤18 months presenting to the ED between October and March over a 2-year period (2010–2012) with bronchiolitis (defined as viral respiratory illness and first episode of wheeze) and a BSS of ≥4 were eligible for the study. Exclusion criteria were a previous history of wheezing, any use of bronchodilators within 2 hours of presentation, gestational age ≤34 weeks, history of congenital heart disease or chronic pulmonary or chronic renal disease, oxygen saturation of ≤85% at the time of recruitment, severe disease requiring ICU admission, or inability to obtain informed consent. Depending on the availability of the principal investigator (a pediatric emergency medicine fellow), a convenience sample was used to recruit patients. The ED physicians and staff were notified of the fellow’s hours of availability by way of a call schedule that was posted in the ED.

Study Protocol

Eligible patients were randomized to 1 of 2 groups in blocks of 10. The control group received an aerosol of 0.5 mL 2.25% racemic epinephrine with 3 mL 0.9% saline, and the study group received 0.5 mL 2.25% racemic epinephrine with 3 mL 7% HS.

The treating clinician in the ED contacted the principal investigator who enrolled the participants within an hour of an eligible patient’s arrival. Caregiver consent was obtained before administration of inhaled therapy. The pharmacy department maintained a box in the ED holding sequentially numbered, previously randomized concealed envelopes containing either the study (7% HS) or control (0.9% saline) medication. After initial screening and assessment and after consent was obtained, the patient was administered the medication via nebulization driven by 6 L per minute O2 flow. Research personnel, including the investigators, the treating physician, and staff who performed the BSS were kept blinded throughout the process.
BSSs were recorded before, immediately after, and 4 hours after administering the aerosol. If the patient was admitted or discharged before 4 hours, the second posttreatment score was recorded at the time of disposition. The treating ED clinician determined the final disposition of the patient. If admitted, the patient continued to receive aerosols containing the same designated medication every 6 hours until discharge or 24 hours after the admission. Disposition was ascertained by reviewing the electronic medical record for the time the order for discharge was written by the treating clinician. Our protocol did not require any specific criteria for discharge.

A standardized data sheet was completed after enrollment and during each patient's stay in the ED or inpatient ward. Any cointerventions, such as additional bronchodilators, supplemental oxygen, intravenous fluids, or deep nasal suction, were at the discretion of the treating clinician. The clinician was free to withdraw the patient from the study if clinical deterioration warranted escalation of care or if adverse effects related to the medication were observed.

Outcome Measures

The BSS is an objective respiratory assessment tool that has been previously validated (Table 1). We used a modified BSS, which has been used in our institution since 2006, to assess severity of illness in acute bronchiolitis (Table 2). A change in the modified BSS was the primary outcome.

Before study enrollment, we assessed correlation between the modified BSS and the BSS published by Wang et al. We assumed that these 2 measures are highly correlated, as high as correlation coefficient (r) = 0.85. The null hypothesis was that they were not as highly correlated, and could be r ≤ 0.75. Assuming 5% significance level and 90% power, the estimated sample size was 46 patients. The correlation between the BSS and the modified BSS was high, with an r = 0.91 (P < .0001). Secondary outcome measures included hospitalization rate, discharge rate at 23 hours (observation status), and length of hospital stay.

### Statistical Analysis

Using retrospective data from patients with a diagnosis of acute bronchiolitis who presented to our ED in 2010, we determined an SD of 3.4 in BSS. The sample size was calculated on the basis of an anticipated difference in BSS of 2 points between the study and control groups. Assuming a power of 80%, α of 0.05, and a 2-tailed test, estimated sample size was 47 patients per study group. Continuous variables were examined by using Student t test. Dichotomous variables were examined by using the X² or Fisher exact test.

### RESULTS

#### Patient Characteristics

A total of 113 participants were approached for consent. Of these, 101 patients were enrolled into the study. 52 in the study group and 49 in the control group (Fig 1). Failure to recruit resulted from either refusal to consent or because the guardian’s primary language was other than English. The 2 groups were similar in all clinical and historical characteristics except that more patients in the control group had a family history of atopic disease than did those in the study group (67% vs 46%; Table 3). The difference in proportion of patients in the study and control groups who received albuterol (13% vs 18%; P = .5) and/or supplemental oxygen (12% vs 25%; P = .08) as cointerventions was not statistically significant.

#### Clinical Outcomes

Although both groups demonstrated a decrease in BSS from baseline to ED disposition, the difference in BSS between the 2 groups was not statistically significant. No difference emerged after 24 hours of inpatient treatment (Table 4).

There was no difference in proportion of patients admitted from the ED, discharged at 23 hours after admission, or inpatient length of stay between the 2 groups (Table 5). Neither group had any adverse effects.

Interobserver variability was assessed by having 2 groups of nurses and respiratory therapists record a BSS on a sample of 20 patients with bronchiolitis. The Cohen κ statistic for level of agreement was 0.94.

### DISCUSSION

Inhaled 7% HS with epinephrine was no better than normal saline with epinephrine in improvement of clinical score in patients with moderate to severe bronchiolitis. Further, there did not appear to be a decrease in admission rate, a lower discharge rate after 23 hours’ observation, or decrease in hospital length of stay.
Our results are mixed when compared with other studies evaluating lower concentrations of nebulized HS to treat bronchiolitis. Most showed a reduction in either respiratory distress scores or hospital length of stay in the HS group; others failed to show any statistical difference between the 2 groups in terms of their primary outcomes. Two of these studies, albeit underpowered, demonstrated a difference that favored HS but did not reach statistical significance. When limiting the comparison with studies initiated in the ED, Al-Ansari et al evaluated 5% HS and showed a lower mean severity score at 48 hours compared with normal saline (NS) (3.89 ± 1.09 vs 4.12 ± 1.11, \( P = .04 \); difference, 0.43; 95% confidence interval [CI] for the difference 0.02 to 0.88). In contrast, Grewal et al demonstrated no change in mean respiratory score from baseline to 120 minutes (study group 4.39 versus control group 5.13; difference 0.74; CI −1.45 to 2.93).

Our results seem to be consistent with previous data on use of HS in patients with cystic fibrosis. Studies of infants with cystic fibrosis have shown that 7% HS is well tolerated and safe in this age group, although ineffective in reducing pulmonary exacerbations or improving lung function. Although higher concentrations of saline have shown promise in a dose response pattern for improving mucociliary clearance and maintaining lung function in patients with cystic fibrosis, the safety and efficacy of inhaled therapy in patients younger than 6 years has been established only with 7% HS. Hence, we elected to study the role of 7% HS in our trial.

The variable results from studies conducted in the ED and outpatient setting with HS may be related to frequency of administration of the study drug and duration of therapy. We speculate that this may also explain the failure of our study to demonstrate a difference from baseline to ED disposition or after 24 hours of inpatient treatment with 7% HS. This hypothesis is supported by inpatient studies that showed a decrease in either severity scores and/or hospital length of stay when HS was given more frequently from admission until discharge. However, in both inpatient and outpatient studies, an improvement in clinical scores was observed by study day. Moreover, because bronchiolitis tends to be a self-limiting illness, we felt that any improvement noted after 24 hours of supportive care might reflect the natural course of disease. The challenge in comparing these trials with our results is the heterogeneity of study design, respiratory assessment tools, and frequency and duration of inhaled therapy.

Our study had several limitations. We elected to evaluate change in bronchiolitis score as our primary outcome. As others have suggested, it is unclear if this is a pertinent outcome in the context of a disease like viral bronchiolitis.

### TABLE 2 Modified BSS

<table>
<thead>
<tr>
<th>Points</th>
<th>Respiratory rate, breaths/minute</th>
<th>Breath sounds</th>
<th>Work of breathing</th>
<th>Oxygen saturation</th>
<th>Mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;40</td>
<td>Clear</td>
<td>None/mild</td>
<td>≥95% on room air</td>
<td>Awake and alert</td>
</tr>
<tr>
<td>1</td>
<td>40–50</td>
<td>End-expiratory wheeze/crackles</td>
<td>Subcostal, intercostal</td>
<td>92% to 94% on room air</td>
<td>Fussy but consolable</td>
</tr>
<tr>
<td>2</td>
<td>50–60</td>
<td>Full expiratory wheeze/crackles</td>
<td>Subcostal, intercostal, supraclavicular</td>
<td>90% to 95% on &lt;40% FIO₂</td>
<td>Fussy and inconsolable</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 80</td>
<td>Inspiratory/expiratory wheeze/crackles</td>
<td>Global</td>
<td>&lt; 90% on &gt;40% FIO₂</td>
<td>Lethargic</td>
</tr>
</tbody>
</table>

FIO₂, fraction of inspired oxygen.
admission rate, discharge rate at 23 hours, hospital length of stay, and safety profile, our study was not powerd for these outcomes.

The decision to discharge the patient was at the discretion of the treating clinician. Our protocol did not require that the patient meet specific discharge criteria nor did we specifically address readiness to discharge versus actual departure time. This may have led to variability in timing of patient disposition.

It has been suggested that by combining HS with inhaled epinephrine, the presence of a confounding bronchodilator may have resulted in drug interaction that could mask the benefits of HS. We elected to include epinephrine because of its proven efficacy in acute bronchiolitis and to mitigate against the theoretical risk of exacerbating bronchospasm with the higher concentration of HS. Further, most of the previous studies in bronchiolitis have used similar models, by using HS combined with a bronchodilator to demonstrate a clinical improvement. However, HS appears to be safe when used alone to treat infants with bronchiolitis, and because patients with asthma or recurrent wheezing (a subgroup that may benefit from steroids) were systematically excluded, we do not believe that this was a significant confounder. Of note, none of the participants in our study had received inhaled or oral corticosteroids.

Although informed consent was obtained before administration of inhaled therapy, we were unable to provide comparative information on time from admission to enrollment. Finally, although randomization ensured that the 2 groups were similar, because a convenience sample was assessed, we cannot exclude enrollment bias.

TABLE 3 Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HS, n = 52</th>
<th>Normal Saline, n = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo, mean ± SD</td>
<td>6.0 ± 3.9</td>
<td>5.6 ± 3.3</td>
</tr>
<tr>
<td>Gender: male</td>
<td>36/52 (69%)</td>
<td>28/49 (57%)</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD</td>
<td>7.5 ± 2.1</td>
<td>7.4 ± 2.0</td>
</tr>
<tr>
<td>Duration of symptoms, d, mean ± SD</td>
<td>3.4 ± 1.7</td>
<td>3.4 ± 1.6</td>
</tr>
<tr>
<td>RSV positive</td>
<td>26/38 (68%)</td>
<td>15/30 (50%)</td>
</tr>
<tr>
<td>Baseline BSS score, mean ± SD</td>
<td>5.8 ± 1.5</td>
<td>5.7 ± 1.8</td>
</tr>
<tr>
<td>Albuterol use</td>
<td>7/52 (13%)</td>
<td>9/49 (18%)</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>6/52 (12%)</td>
<td>12/48 (25%)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>24/52 (46%)</td>
<td>33/49 (67%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>13/52 (25%)</td>
<td>15/49 (27%)</td>
</tr>
</tbody>
</table>

TABLE 4 Primary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>HS, 7%</th>
<th>Normal Saline, 0.9%</th>
<th>Difference, P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in BSS at ED disposition (mean ± SD)</td>
<td>2.6 ± 1.9</td>
<td>2.4 ± 2.3</td>
<td>0.21, P = .61 (0.61 to 1.03)</td>
</tr>
<tr>
<td>Change in BSS after first nebulized treatment in ED disposition (mean ± SD)</td>
<td>2.06 ± 1.7</td>
<td>2.0 ± 1.9</td>
<td>0.06, P = .87 (0.67 to 0.78)</td>
</tr>
<tr>
<td>Change in BSS for admitted patients at 24 h (mean ± SD)</td>
<td>3.1 ± 2.5</td>
<td>3.7 ± 1.9</td>
<td>−0.6, P = .37 (−2.0 to 0.78)</td>
</tr>
</tbody>
</table>

TABLE 5 Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>HS, n = 52</th>
<th>Normal Saline, n = 49</th>
<th>P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in ED, h, mean ± SD</td>
<td>4.1 ± 0.9</td>
<td>3.9 ± 4.0</td>
<td>.8</td>
</tr>
<tr>
<td>Proportion of patients admitted</td>
<td>22/52 (42%)</td>
<td>24/49 (49%)</td>
<td>OR = 0.76 (0.35–1.7)</td>
</tr>
<tr>
<td>Proportion of patients discharged at 24 h</td>
<td>3/21 (14%)</td>
<td>3/23 (13%)</td>
<td>OR = 1.1 (0.2–6.2)</td>
</tr>
</tbody>
</table>

OR, odds ratio.

TABLE 6 Supplemental Oxygen

<table>
<thead>
<tr>
<th></th>
<th>HS, n = 52</th>
<th>Normal Saline, n = 49</th>
<th>P Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms, d, mean ± SD</td>
<td>3.4 ± 1.7</td>
<td>3.4 ± 1.6</td>
<td>0.06, P = .87 (0.67 to 0.78)</td>
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<td>3.7 ± 1.9</td>
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</tr>
</tbody>
</table>

Although we intended to recruit infants with severe bronchiolitis, our study population primarily included children with moderate disease. Hence, our study cannot exclude potential benefit of inhaled 7% HS in infants with severe illness. We also did not specify previous corticosteroid use as an exclusion criterion. Because corticosteroids have not been shown to be beneficial in bronchiolitis, and because patients with asthma or recurrent wheezing (a subgroup that may benefit from steroids) were systematically excluded, we do not believe that this was a significant confounder. Of note, none of the participants in our study had received inhaled or oral corticosteroids.

Our study demonstrated no additional clinical benefit from inhaled 7% HS with epinephrine when compared with normal saline with epinephrine. Although 7% HS appears safe, future, larger studies should focus on the safety and efficacy of HS when administered alone versus when combined with epinephrine.

CONCLUSIONS

Our study demonstrated no additional clinical benefit from inhaled 7% HS with epinephrine when compared with normal saline with epinephrine. Although 7% HS appears safe, future, larger studies should focus on the safety and efficacy of HS when administered alone versus when combined with epinephrine.
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