Nebulized 5% or 3% Hypertonic or 0.9% Saline for Treating Acute Bronchiolitis in Infants

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Objective To compare the efficacy and safety of 5%, 3%, and 0.9% saline solution for treating acute bronchiolitis in the prehospital setting.

Study design This was a double-blind trial including consecutive infants aged <18 months treated in an urban urgent care setting. A total of 165 patients were randomized to receive nebulized 5%, 3%, or 0.9% (normal) saline with epinephrine every 4 hours. The primary efficacy outcome was bronchiolitis severity score improvement at 48 hours ($\chi^2$ analysis). Scores and oxygen saturation immediately before and after each treatment were recorded to assess safety.

Results A total of 187 previously healthy infants (median age, 3.1 months) diagnosed with bronchiolitis were enrolled. Positivity for respiratory syncytial virus was similar in the 3 treatment groups (mean, 56%). At 48 hours, the mean severity score for the 5% saline group was 3.69 ± 1.09, and that for the 0.9% saline group was 4.12 ± 1.11 ($P = .04$; difference, 0.43, 95% confidence interval for the difference, 0.02-0.88). The mean severity score for the 3% saline group was intermediate at 4.00 ± 1.22. Revisit rates after discharge were similar in the 3 treatment groups. No adverse reactions or other safety concerns were identified.

Conclusions Nebulization with 5% hypertonic saline is safe, can be widely generalizable, and may be superior to current treatment for early outpatient treatment of bronchiolitis. (J Pediatr 2010;157:630-4).

Bronchiolitis is among the most common and serious lower respiratory tract infections in young children, affecting mainly infants aged 2-5 months.1,2 Incidence peaks between December and March.3,4 In the United States in 2002, 149,000 patients with bronchiolitis required hospitalization, with a mean hospital stay of 3.3 days and admission costs of $500 million.5 In Qatar in 2008, about 4600 patients made about 6100 visits to pediatric emergency centers for bronchiolitis; 20% of these patients were hospitalized.

The mainstay of treatment remains supportive care, with supplemental oxygen and hydration if needed, and a trial of bronchodilator therapy (albuterol/salbutamol or epinephrine) as an option.6-8 Using the bronchiolitis severity score to assess patients over time, inhaled 3% hypertonic saline with epinephrine administered by nebulization every 6-8 hours has been found to improve the bronchiolitis severity score and reduce the length of hospital stay in hospitalized patients when compared with 0.9% saline with epinephrine;9-13 this treatment is not routinely recommended, however.8 In patients with cystic fibrosis, hypertonic saline concentration of 3%, 7%, and 12% have shown promise in a dose-response pattern for improving mucociliary clearance and maintaining lung function compared with 0.9% saline.14,15 Cough and chest tightness at the time of hypertonic saline administration were reported in those patients, however.

Early, prehospital intervention for bronchiolitis with a safe, effective, and inexpensive agent might save lives, reduce complications and hospitalizations, and be applicable for use worldwide, including small communities where hospital care is not available. We reasoned that a hypertonic saline concentration >3% could be safe and more efficacious, alleviating severe symptoms and avoiding the need for hospitalization in some instances. To build on the therapeutic benefit of 3% saline for inpatients with acute bronchiolitis,9-13 we applied the dose-response and safety data from stable patients with cystic fibrosis, cautiously focusing on 5% rather than higher concentrations for our infant patients. We compared 5% saline with 3% saline and 0.9% (normal) saline in terms of efficacy and safety in treating acute bronchiolitis in the outpatient, early treatment setting.

### Methods

We conducted a double-blinded, randomized, parallel-group clinical trial to compare the efficacy and safety of 5% and 3% hypertonic saline versus 0.9% (normal) saline for the treatment of acute bronchiolitis. The study was con-
duced between September 2007 and December 2008 in the short-stay unit of the Pediatric Emergency Center of Hamad General Hospital, the only pediatric emergency facility in Qatar. The center serves an average of 200 000 patients annually and manages 42 beds in a short-stay unit. Patients admitted to the unit are assessed at least every 6 hours by a pediatrician to determine readiness for discharge. The length of stay in the unit for bronchiolitis ranges from 6 to 168 hours.

Infants aged ≤18 months presenting to the unit for the treatment of moderate to severe viral bronchiolitis were eligible for the study. Inclusion criteria were a prodromal history consistent with viral upper respiratory tract infection followed by wheezing and/or crackles on auscultation and a Wang bronchiolitis severity score of ≥4 (Table I; available at www.jpeds.com) on presentation.

Patients were excluded from the study if they had one or more of the following characteristics: born at ≤34 weeks’ gestation, previous history of wheezing, steroid use within 48 hours of presentation, obtundation and progressive respiratory failure requiring intensive care unit (ICU) admission, history of apnea within 24 hours before presentation, oxygen saturation ≤85% on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease, or immunodeficiency. The 6 attending physicians covering the 18 beds in the respiratory section of the short-stay unit were trained on using the Wang bronchiolitis severity score and its practical application on 4 patients with bronchiolitis before the start of the study. Written informed consent, sought from a parent or legal guardian as soon as the patient was admitted to the unit, was obtained for every participant. The study was approved by the hospital’s Institutional Review Board.

Study Procedures

Patients were examined on presentation in the Pediatric Emergency Center’s examination area, and those needing further treatment or observation were admitted to the short-stay unit. Patients with bronchiolitis were assessed for study eligibility within 2 hours of the initial physician assessment. In patients for whom consent was obtained, plain chest radiography was performed, and nasopharyngeal swabs were taken for detection of respiratory syncytial virus (RSV) (RSV Respi-Strip; Coris Bioconcept, Gembloux, Belgium). Then a computer-generated list of random numbers was used by the enrolling physicians in consecutive order to identify a sealed envelope containing 1 of 3 codes identifying 1 of 3 different 500-mL bags of sterilely prepared blinded study solution containing 5%, 3%, or 0.9% saline, prepared fresh each morning by a pharmacist blinded to patient assignment.

Patients received 5 mL of the study nebulization mixed with 1.5 mL of epinephrine in a double-blinded fashion on enrollment and every 4 hours thereafter until they were ready for discharge. Inhaled medications were delivered through a tight-fitting face mask by pressurized oxygen with the flow meter set at 10 L/min. Additional nebulized epinephrine (5 mL) delivered in the same way could be administered with blinded study solution at a maximum frequency of every hour, and additional treatment (eg, supplementary oxygen, hydration) could be given at the discretion of the treating physician. Patients were withdrawn from the study if oxygen saturation within 30 min after nebulization fell below 85% on room air or if clinical deterioration was deemed to warrant hospital admission.

A patients could be discharged when the treating physician determined she or he did not need supplementary oxygen, was feeding adequately without intravenous fluids, and had minimal or absent wheezing, crackles, and chest retractions, provided that oxygen saturation was ≥94% and the severity score was <4. However, quite frequently, the actual time of discharge was determined based on social factors, such as availability and consensus of family members. At discharge, patients were sent home with an albuterol metered-dose inhaler with an appropriately sized Aerochamber and mask attachment (Forest Laboratories, Dublin, Ireland). Daily telephone follow-up by a study nurse was mandatory for 1 week after discharge. A patient could return to the Pediatric Emergency Center earlier if desired or necessary.

Study Measurements and Outcomes

Immediately before each scheduled nebulization (initial and every 4 hours), immediately after, and 2 hours after, the following measurements were collected for each patient: bronchiolitis severity score, oxygen saturation on room air, and heart rate. The primary efficacy outcome in this double-blinded study was mean prenebulization bronchiolitis severity score for each treatment group at 48 hours. Secondary outcomes were the severity scores at 24 hours and trend over time to 72 hours, 2-hour postnebulization severity scores trending over time, and safety measures. The latter included severity scores and oxygen saturation levels immediately before versus after nebulization, number of patients requiring ICU admission, number requiring readmission to the short-stay unit, and the number revisiting the Pediatric Emergency Center in the week after discharge.

Statistical Analysis

We predicted a dose response with a superior (lower) severity score at 48 hours for patients not already discharged in the 5% saline group compared with the 0.9% saline group, with an intermediate value for the 3% saline group. We also predicted that mean scores starting at about 16 hours after the start of treatment would confirm this relationship. We predicted that by 72 hours, the group mean differences would disappear, due to relatively refractory illness among remaining patients regardless of saline group assignment. Given that pervious studies of hospitalized patients with bronchiolitis had severity scores of ~7, we estimated that our less ill outpatients’ mean severity scores would be ~6. We felt that a 10% improvement in severity score at 48 hours for not-yet-discharged patients randomized to the 5% saline group compared with the 0.9% saline group would be clinically significant. Assuming that the 0.9% saline group remained at a score of 6, a reduction to 5.4 for the 5% saline group and
to an intermediate value for the 3% saline group would confirm our hypothesis. We calculated descriptive statistics (mean, standard deviation and frequency) with percentages for relevant variables, using χ² tests for categorical variables and one-way analysis of variance with post hoc Bonferroni correction for continuous variables. We used SPSS 14.0 statistical packages (SPSS Inc., Chicago, Illinois) for all data entry and analysis.

We calculated that having 45 patients per group would provide 80% power to show a mean severity score improvement of 10% for the 5% saline group versus the 0.9% saline group, assuming a standard deviation of about 1 for each mean severity score. We did not intend to definitively compare the 5% and 3% saline groups. To account for patients discharged before the 48-hour time point, we added 10 patients to each group, for a sample size of 55 patients per group. Patients properly enrolled with outcome data at 48 hours were included in the analysis.

Results

A total of 187 previously healthy infants diagnosed with viral bronchiolitis, median age 3.1 months (range, 9 days to 14.7 months), were enrolled in the study. Sixteen infants were excluded from the analysis; 9 should have been excluded from enrollment (4 born at ≤34 weeks’ gestational age, 2 with a history of apnea with cyanosis before enrollment, 1 with previously known severe laryngomalacia, and 2 who had received steroids within 24 hours before enrollment), 1 infant was enrolled twice in the study (the second enrollment was excluded from the analysis), and 6 infants were electively removed by their parents. Of the 171 infants remaining, 57 were randomized to receive 3% hypertonic saline, and 56 to receive 0.9% saline. Subjects’ baseline characteristics before enrollment were similar in the 3 treatment arms (Table II).

Efficacy

Figure 1 shows bronchiolitis severity scores from baseline to 72 hours. At the primary outcome time point of 48 hours, the mean severity score for the 5% saline group was 3.69 ± 1.09, and that for the 0.9% saline group was 4.12 ± 1.11 (P = .04; difference, 0.43; 95% confidence interval for the difference, 0.02-0.88). The mean severity score for the 3% saline group was intermediate, at 4.00 ± 1.22. At 24 hours after randomization, the mean severity score for the 5% saline group was 3.75 ± 1.27, and that for the 0.9% saline group was 3.97 ± 1.40 (P = .38). The mean severity score for the 3% saline group at 24 hours was 4.00 ± 0.98. Figure 1 shows a consistent trend favoring 5% saline starting about 8 hours after randomization and continuing to 72 hours.

Additional epinephrine doses were prescribed for 3 infants (5.3%) in the 5% saline group, 1 infant (1.7%) in the 3% saline group, and 3 infants (5.4%) in the 0.9% saline group (P = .53).

Follow-Up

The mean length of stay was 1.56 ± 1.38 days for the 5% saline group, 1.4 ± 1.41 days for the 3% saline group, and 1.88 ± 1.76 days for the 0.9% saline group (P = .36). Time to discharge for the 3 groups is displayed in Figure 2. Three infants (1.6%) were lost to follow-up after discharge, 2 in the 5% saline group and 1 in the 0.9% saline group.

The rate of revisits to the Pediatric Emergency Center in the 7 days after discharge was high and similar in the 3 treatment groups: 35 (61%) in the 5% saline group, 35 (59%) in the 3% saline group, and 35 (63%) in the 0.9% saline group (P = .91). Short-stay readmission was required for 10 infants (18%) in the 5% saline group, 8 infants (14%) in the 3% saline group, and 7 infants (13%) in the 0.9% saline group (P = .73). One infant in the 0.9% saline group required a 2-day stay in the ICU during a hospital admission in the week after the study visit. Antibiotic usage was similar in the 3 groups: 19% in the 5% saline group, 22% in the 3% saline group, and 18% in the 0.9% saline group. No study subjects received corticosteroid therapy.

Safety

No patient was withdrawn from the study because of apnea, cyanosis, or decreased oxygen saturation. No patient required hospital or ICU admission during their study visit for bronchiolitis. Severity scores immediately after and immediately before nebulization and oxygen saturations immediately after and immediately before nebulization were

<table>
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<th>Table II. Baseline characteristics of enrolled infants</th>
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<tr>
<td>Characteristics</td>
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<td>Vireal pneumonia</td>
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obtained for each patient at baseline and 24, 48, and 72 hours after study entry, and the difference between the each set of prenebulization and postnebulization values was calculated to explore whether nebulization negatively affected either measurement in any of the treatment groups. The results were similar among the 3 groups and demonstrated no evidence of toxicity.

Discussion

In our study group, nebulization with 5% hypertonic saline proved superior to 0.9% saline for improving the bronchiolitis severity score in patients with viral bronchiolitis in the early treatment setting, and possibly superior to 3% saline as well. If our results are confirmed, we believe this simple, inexpensive, easily applied, safe, and apparently effective treatment could be generalized for use worldwide in clinics, infirmaries, and hospitals caring for pediatric patients. Bronchiolitis morbidity1,17 might be minimized by systematic introduction of this helpful early intervention. However, a multicenter trial with a larger sample size and relevant clinical outcome is needed to confirm and extend our results.

Grewal et al18 reported no difference in efficacy between nebulized 3% and 0.9% saline in the emergency department at 2 hours after randomization. Our study found no differences that early. Grewal et al did find a difference in hospitalization rate that was clinically significant, but not statistically significant due to their limited sample size.18

Our study has some limitations. The relatively small number of patients enrolled does not allow us to distinguish the efficacy of 3% saline and 5% saline in a definitive way. In addition, although our primary measure was the calculated bronchiolitis severity score, objectively determined by physical examination and blinded with respect to treatment assignment, this is not the only measure that determines clinical (as opposed to social) readiness for discharge from the infirmary. This instrument has been previously validated for its relationship to disease improvement, interobserver, intraobserver, and intrasubject variation, however.16,19 Finally, it is possible that some of our patients had early presentation of asthma rather than acute bronchiolitis. We tried to limit the likelihood of enrolling subjects with asthma by following strict inclusion criteria. The proportion of our patients with a positive RSV assay was similar to that reported for other bronchiolitis populations1 and is higher than what would be expected for asthma. Moreover, if asthma were prevalent among our patients, then we would have expected to see worsening of clinical symptoms on exposure to hypertonic saline.

We conclude that nebulization with 5% hypertonic saline is safe and may be superior to current treatment for early infirmary outpatient treatment of bronchiolitis. Planning for a multicenter trial to explore the clinical benefit of this therapy with a larger sample size is underway.

References

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