Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis

Zhengxiu Luo, Enmei Liu, Jian Luo, Subi Li, Fengqiong Zeng, Xiqiang Yang and Zhou Fu
Respiratory Department, Children’s Hospital, Chong Qing Medical University, Chongqing, China

Abstract Background: The objective of this study was to determine the efficacy and safety of nebulized 3% hypertonic saline solution and salbutamol in the treatment of mild to moderate bronchiolitis. Methods: In a randomized controlled trial, 93 infants with mild to moderate bronchiolitis were divided into two groups. The infants received inhalation of 2.5 mg (0.5 mL) salbutamol dissolved in either 4.0 mL normal (0.9%) saline (control group, n = 43) or 4.0 mL hypertonic (3%) saline (treatment group, n = 50). The therapy was repeated three times daily until discharge. Cough, wheezing, pulmonary physical signs, and the length of hospital stay were recorded. Results: Wheezing remission time was 3.8 ± 1.1 days in the control group and 2.7 ± 0.9 days in the treatment group (P < 0.01). Cough remission time was 6.3 ± 0.9 days in the control group and 5.3 ± 0.8 days in the treatment group (P < 0.01). The moist crackles disappeared at 5.4 ± 0.8 days in the treatment group versus 6.2 ± 0.9 days in the control group (P < 0.01). Furthermore, the average length of hospital stay decreased from 7.4 ± 1.5 days in the control group to 6.0 ± 1.2 days in the treatment group (P < 0.01). No obvious adverse effects were observed. Conclusions: Inhalation of nebulized 3% hypertonic saline solution and salbutamol is a safe and effective therapy for patients with mild to moderate bronchiolitis.

Key words bronchiolitis, hypertonic saline solution, salbutamol.

Bibliography

Correspondence: Zhengxiu Luo, MD, Respiratory Center, Children’s Hospital, Chong Qing Medical University, Chongqing, 400014, China. Email: luo Zhengxiu816@163.com

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± 1.6 days. In the control group, there were 43 participants, 26 boys and 17 girls, and the average age and disease course were 5.6 ± 4.5 months and 3.1 ± 1.5 days, respectively. No significant differences existed between the two groups in gender, ages, disease courses or the severity of disease.

1.2 Inclusion criteria
The wheezing infants suffered from viral bronchiolitis for the first time. The patients with bronchiolitis were ranked mild to moderate according to the clinical score system as follows:14 (i) Respiratory rate: 0 points: less than 30 breaths/min; 1 point: 31–45 breaths/min; 2 points: 46–60 breaths/min; 3 points: >60 breaths/min. (ii) Wheezing: 0 points: none; 1 point: terminal inspiration or heard only with stethoscope; 2 points: entire expiration or audible on expiration without stethoscope; 3 points: inspiration and expiration without stethoscope. (iii) Retractions: 0 points: none; 1 point: intercostal only; 2 points: tracheosternal; 3 points: severe with nasal flaring. (iv) General condition: 0 points: normal; 3 points: irritable, lethargic, poor feeding. Referring to the total clinical score, the disease severity can be divided into the following ranks: 0–4.9, mild; 5–8.9, moderate; and 9–12 points, severe disease.

1.3 Exclusion criteria
The exclusion criteria were as follows: age > 24 months, previous episode of wheezing, chronic cardiac and pulmonary disease, immunodeficiency, accompanying respiratory failure, requiring mechanical ventilation, inhaling the nebulized 3% hypertonic saline solution and salbutamol 12 h before treatment, and premature infants born at less than 34 weeks’ gestation.

1.4 Ethics
The study was approved by the ethics and human research committees of the Children’s Hospital, Chongqing Medical University.

2 Methods
2.1 Study design
Each of the two groups received the same supportive and comprehensive treatments, including sputum aspiration and water-electrolyte balance maintenance. Air-compressed nebulizers were obtained (PARI Corporation, Germany). The treatment group received 2.5 mg (0.5 mL) salbutamol dissolved in 4.0 mL hypertonic (3%) saline solution and salbutamol 12 h before treatment, and premature infants born at less than 34 weeks’ gestation.

All of the infants began treatment within 12 h of admission to the hospital. Patients in each group received three treatments every day, delivered at intervals of 8 h until discharge. Patients were examined at the time of study entry and every day at 08.00–09.00 hours, 16.00–17.00 hours, and 22.00–24.00 hours. All patients’ symptoms (cough, wheezing, hoarse voice, vomiting, diarrhea, general condition) and signs (temperature, respiratory rate, heart rate, retraction, pulmonary signs, heart sounds) were recorded. No detectable difference in color, smell or other physical properties existed between the 0.9% saline solution and the 3% saline solution. The identities of the therapeutic package (0.9% saline solution or 3% saline solution) were not available to the investigators, nurses or parents. The decisions to discharge babies were made during morning rounds by the attending physicians when the patients had had no respiratory symptoms or signs during the past 12 h. The attending physicians were also blind to the therapeutic package.

2.2 Observation and evaluation
We evaluated for cough, wheezing, and pulmonary moist crackles as well as adverse reactions every day at 08.00–09.00 hours, 16.00–17.00 hours, and 22.00–24.00 hours. The day that the cough, wheezing, and pulmonary moist crackles disappeared was recorded. We also recorded the length of the hospital stay.

2.3 Statistical analyses
spss edition 11.5 was used to analyze all the data. χ²-tests were used to compare categorical variables. The mean ± SD (±s) expresses the central tendency of the data. A P-value < 0.05 was considered statistically significant.

Results
Ninety-three infants with bronchiolitis recruited in the trial were assigned to a treatment group or a control group. The two groups did not have statistical differences with respect to gender, age, clinical symptoms or physical exam findings (summarized in Table 1).

Evaluation of therapeutic effects: the treatment group had better outcomes compared to the control group. The time required for wheezing relief as reduced by 1.1 days on average; coughing was reduced by 1.0 day. Meanwhile, the moist crackles vanished 0.8 days earlier. The average length of hospital stay decreased by 1.4 days. All the effects indicated that the treatment group gained improvement compared with the control group (summarized in Table 2). The clinical severity scores at baseline

Table 1 Comparison of basic clinical information between the two groups

<table>
<thead>
<tr>
<th>Basic information</th>
<th>0.9% Saline solution (control group, n 43)</th>
<th>3% Saline solution (treatment group, n 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>65.4</td>
<td>66.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Age (months)</td>
<td>5.6 ± 4.5</td>
<td>6.0 ± 4.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Disease course when hospitalized (days)</td>
<td>3.1 ± 1.5</td>
<td>3.2 ± 1.6</td>
<td>0.80</td>
</tr>
<tr>
<td>Percent of whole-body glucocorticoid usage before admission (%)</td>
<td>31 (72.1%)</td>
<td>36 (72%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Clinical score on admission</td>
<td>5.7 ± 1.3</td>
<td>5.8 ± 1.2</td>
<td>0.63</td>
</tr>
<tr>
<td>Respiratory syncytial virus detection rate(%)</td>
<td>30 (69.7%)</td>
<td>35 (70%)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

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were 5.8 ± 1.2 in the study group and 5.7 ± 1.3 in the control group. The clinical severity scores after inhalation in the study group on the first, second, and third day were 3.4 ± 1.2, 2.2 ± 1.1, and 1.5 ± 0.5, respectively. In the control group, the clinical severity scores after inhalation on the first, second, and third day were 4.9 ± 1.7, 3.8 ± 1.5, and 2.9 ± 0.7, respectively. These declines in clinical scores differed significantly between the two groups on each of these days. However, there was no significant difference in clinical severity scores between the two groups after 72 h of hospitalization (Fig. 1).

Adverse effects: all of the patients completed their respective treatments safely. The coughing and wheezing never worsened over the course of the treatment. No adverse reactions were identified.

Discussion

Bronchiolitis is the most common lower respiratory tract infection in infants and is most frequently caused by the RSV. RSV primarily colonizes the bronchiole, with a diameter of 70–300 μm, pulmonary alveoli, and interstitium. The pathological changes include necrosis of the bronchiole epithelium, lymphocytic infiltration, congestion of the submucosa, edema and glandular proliferation, increased secretion of mucus, and obstruction of the bronchiole. Wheezing is the primary clinical symptom. The primary treatment remains largely supportive with administration of fluids and supplemental oxygen, observation, and mechanical ventilatory support as needed. Other types of treatment remain controversial. Bronchiolitis is characterized by airway plugging with sloughed epithelium, mucus production and edema rather than bronchospasm. Nevertheless, the use of nebulized bronchodilators continues to be common.

The use of inhaled hypertonic saline solution in the treatment of viral bronchiolitis in hospitalized infants was first reported in 2003 and strengthened with the publication of a 2-year extension of the original study. These authors demonstrated that nebulized 3% hypertonic saline solution and epinephrine treatment in hospitalized infants with viral bronchiolitis decreases the clinical symptoms, shortens the length of hospitalization, and reduces the clinical severity score. A Cochrane review states that nebulized hypertonic saline with bronchodilators was considered an effective and safe treatment for infants with viral bronchiolitis. Here we demonstrate a similar result: inhalation of nebulized 3% hypertonic saline/salbutamol solution decreases the clinical symptoms and shortens the length of hospital stay. The clinical severity scores decreased more significantly in the study group than in the control group within 72 h of hospitalization. It took less time to relieve symptoms and pulmonary signs: one day on average for wheezing and cough alleviation, and two days for pulmonary moist crackles. The length of hospital stay was reduced by 1.5 days. In our study, patients were discharged when they had had no respiratory symptoms or signs during the past 12 h, while in other studies the discharge criteria were clinical score < 4 and SaO2 of at least 95% in room air for 4 h. Therefore, the mean length of stay in our study is longer than other studies in which the length of stay is typically 3–6 days. Some researchers demonstrated that, in vivo, nebulized hypertonic saline improves mucociliary clearance, and that hypertonic saline improved mucus clearance in vitro more than rhDNase. It has previously been shown that inhalation of a 6.0% to 10% solution of hypertonic saline significantly improved mucous clearance in a group of adult patients with cystic fibrosis. The mechanism underlying was postulated: inducing the water into the airway by the osmotic flow, changing the mucus rheology, breaking the ionic bonds within the mucin gel, thereby reducing the effective degree of cross linking and lowering the viscosity and elasticity; raising the ion concentration to form a shield so as to limit the repulsion; inducing the macromolecules to enter the slime layer to aid the clearance. Tomooka et al. hypothesized that hypertonic saline improves nasal symptoms via (i) decreasing mucosal edema; (ii) decreasing inflammatory mediators; (iii)

Table 2 Comparison of symptoms, signs, and hospital time between the two groups (X ± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Wheezing</th>
<th>Cough</th>
<th>Pulmonary moist crackles</th>
<th>Hospital time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>50</td>
<td>2.7 ± 0.9</td>
<td>5.3 ± 0.8</td>
<td>5.4 ± 0.8</td>
<td>6.0 ± 1.2</td>
</tr>
<tr>
<td>Control group</td>
<td>43</td>
<td>3.8 ± 1.1</td>
<td>6.3 ± 0.9</td>
<td>6.2 ± 0.9</td>
<td>7.4 ± 1.5</td>
</tr>
<tr>
<td>t-value</td>
<td></td>
<td>5.29</td>
<td>5.49</td>
<td>4.51</td>
<td>4.97</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

![Fig. 1](image) Clinical scores versus hospitalization days in the (●) study group and the (■) control group.
mechanically clearing inspissated mucus; and (iv) improving mucociliary function. In this trial, we did not detect the concrete mechanisms. It is presumed that the hypertonic saline can alleviate the mucosal edema, improve mucociliary function, and promote the elimination of mucus, thereby reducing the adhesion of virus and consequent airway inflammation reaction as well as the risk of a secondary bacterial infection. However, further investigation is needed to verify these assumptions.

Our previous work inferred that inhalation of nebulized hypertonic saline is safe for asthmatic children to induce sputum. In this trial, we showed that inhalation of nebulized hypertonic saline/salbutamol has an excellent safety profile for treating bronchiolitis in infants. All 50 patients finished the entire treatment without bronchospasm, cough or wheezing aggravation.

In conclusion, we demonstrate that the combination of nebulization of hypertonic saline solution and salbutamol is an effective and safe treatment for infants with mild to moderate bronchiolitis. It relieves the clinical symptoms and improves the pulmonary signs faster, shortens the length of hospital stay, and is economical as well, and therefore it is a worthwhile treatment approach.

References


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