

Is Nebulized Hypertonic Saline Solution an Effective Treatment for Bronchiolitis in Infants?

EBEM Commentator Contact

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals' Evidence-Based Emergency Medicine (EBEM)* series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source of this systematic review abstract is: Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulized hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev.* 2008;(4):CD006458.¹

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review.

OBJECTIVES

To assess the effects of nebulized hypertonic saline solution in infants with acute viral bronchiolitis.

DATA SOURCES

The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2007, issue 4), which contains the Cochrane Acute Respiratory Infections Group Specialized Register; OLDMEDLINE (1951 to 1965); MEDLINE (1966 to November 2007); EMBASE (1974 to November 2007); and LILACS (November 2007).

STUDY SELECTION

The authors included randomized controlled trials and quasi-randomized controlled trials using nebulized hypertonic saline solution alone or in conjunction with bronchodilators as an active intervention in infants up to 24 months of age who had acute bronchiolitis distinguished from asthma by being their first episode of wheezing associated with cough, coryza, and fever.

The primary outcomes were hospital length of stay and admission rates. Secondary outcomes included clinical severity scores, readmission rate, oxygen saturation level, pulse and respiratory rates, time for symptom resolution,

duration of oxygen therapy, pulmonary function test results, and radiologic findings. Known and expected adverse events of medications used were recorded, such as tachycardia, hypertension, pallor, tremors, nausea, vomiting, and acute urinary retention.

DATA EXTRACTION AND ANALYSIS

Two authors independently selected trials for the review. When relevant articles were identified, the authors assessed each independently for satisfaction of inclusion criteria. The methodological quality of all included trials was judged by using the 5-point scoring system of Jadad.² Disagreements between the authors for inclusion/exclusion of trials and quality were resolved by discussion.

The authors combined outcomes from individual trials by using the Cochrane statistical package RevMan 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Norway). Meta-analysis was conducted for hospital length of stay and clinical severity scores; pooled treatment effects were estimated with relative risk for hospitalization rates and mean difference for clinical severity scores and hospital length of stay. Heterogeneity was assessed by visual inspection of graphic presentations and the I^2 statistic. Tests of heterogeneity seek to determine whether the variety of results from different trials in the meta-analysis are due to chance or the result of significant differences in study design such as sampling methods, variations in treatment, or variations in study quality. The I^2 statistic describes the percentage of variation in effect estimates across studies beyond that expected by chance. When $I^2=0\%$, any differences between the study results are probably not important; on the other hand, when I^2 is greater than 50%, substantial heterogeneity may be present and sources of the heterogeneity require exploration. The final decision of an acceptable level of study heterogeneity in a meta-analysis is still a matter of debate.³

MAIN RESULTS

There were 4 double-blind randomized controlled trials involving 254 infants in the review, which included 1

outpatient (n=65) and 3 inpatient (n=189) studies. Participants were between a mean age of 2.6 and 12.5 months, with a range of 10 days to 24 months. Respiratory syncytial virus was found in 69% to 87% of subjects. All the trials used the same intervention of nebulized 3% saline solution, 2 mL in 1 trial and 4 mL in the other 3 trials. Although all 4 trials used 0.9% saline solution in control inhalations, the other components of standard therapy administered to both the control and intervention groups differed among the individual studies. Two trials included 1.5 mg of nebulized epinephrine, 1 trial used 5 mg of nebulized terbutaline, and 1 trial did not require or encourage the addition of any bronchodilators. This clinical heterogeneity as a result of the difference in bronchodilators could not be adjusted for in the analysis. Clinical heterogeneity among the trials was also evident, given that 3 trials delivered inhalations every 8 hours, whereas 1 trial prescribed nebulizers every 2 hours for 3 treatments.

All 3 inpatient studies measured length of stay as the primary outcome, but only 2 trials used the same clinical severity score. The single outpatient trial used hospital admission rate and clinical severity score as outcome measures. All 4 trials were deemed adequate with respect to concealment, blinding, and follow-up; however, only 1 trial reported results by using an intention-to-treat analysis.

Hypertonic saline solution compared with normal saline solution nebulizers significantly reduced hospital length of stay by 25.9%, with a mean decrease of 0.94 days (95% confidence interval 0.40 to 1.48 days), with minimal heterogeneity ($I^2=0.0%$) identified between the 3 inpatient trials. Admission rate was not significantly ($P=.65$) different between the hypertonic and normal saline solution group in the outpatient study. Pretreatment clinical severity scores were comparable between the intervention and control groups for all trials. Pooled clinical severity scores for all trials showed significant improvement for the nebulized hypertonic saline solution groups compared with normal saline solution groups during the first 3 days of treatment. Subgroup analysis of the improvements of clinical severity scores showed substantial heterogeneity ($I^2=59%$) between the in- and outpatient trials. The outpatient trial patients had significantly greater improvement in clinical severity scores compared with the inpatient trial patients, a result that persisted throughout the study period. No adverse events were reported for the hypertonic saline solution group in any of the reviewed trials.

CONCLUSIONS

Nebulized 3% saline solution in combination with β -agonists used in infants with bronchiolitis appears to reduce clinical severity scores and hospital lengths of stay without adverse effects.

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COMMENTARY: CLINICAL IMPLICATION

Bronchiolitis is a common, occasionally severe, viral infection of the lower respiratory tract that affects children younger than 2 years, with a peak incidence between 3 and 6 months. In the United States, the Centers for Disease Control and Prevention estimates that 25 of 1,000 children with bronchiolitis will require hospitalization, and 1% to 2% of these children will require ventilatory support.⁴ The US economic effect of bronchiolitis approaches \$700 million per year.⁵ Worldwide, the World Health Organization estimates that bronchiolitis is responsible for 18,000 to 75,000 hospitalizations, with 90 to 1,900 deaths annually.⁶

Currently, the emergency department (ED) treatment for bronchiolitis is variable and typically consists of a trial of nebulized β_2 -agonists (albuterol, terbutaline, epinephrine) diluted in normal saline solution.⁷ The addition of nebulized or oral corticosteroids does not offer any short- or long-term clinical benefits.^{8,9}

This Cochrane review assessing the effectiveness of nebulized hypertonic saline solution (3%) for bronchiolitis provides some support for use in the inpatient setting, but there was significant statistical ($I^2=59%$) and clinical heterogeneity identified with respect to improvements in clinical severity scores between in- and outpatient trials. Unfortunately, the applicability of the results of this Cochrane review to the acute care setting is limited by the fact that only a single small clinic-based study (n=65) was designed to address the ED-relevant outcome of admission rate and failed to show any difference with nebulized hypertonic saline solution.¹⁰ The fact that in 3 of the studies, including the clinic-based trial, the intervention was administered every 8 hours also highlights problems with application to the ED setting. On the other hand, improvements in the secondary outcomes of studies reporting clinical severity scores were most pronounced in the outpatient setting compared with inpatient settings. One argument for considering the initiation of nebulized 3% saline solution in the ED is that therapies started in the ED may be continued on an inpatient basis when the benefit of decreasing hospital length of stay might be realized. However, future studies need to establish what is a clinically relevant reduction in hospital length of stay.

TAKE-HOME MESSAGE

There is a lack of strong evidence to support routine use of nebulized hypertonic saline solution for infants presenting to the ED with acute bronchiolitis.

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