Nebulized hypertonic saline solution for acute bronchiolitis in infants (Review)

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Nebulized hypertonic saline solution for acute bronchiolitis in infants

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ABSTRACT

Background
Airway edema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Nebulized hypertonic saline solution may reduce these pathological changes and decrease airway obstruction.

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

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The 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).

Selection criteria
Randomised controlled trials (RCTs) and quasi-RCTs using nebulized hypertonic saline alone or in conjunction with bronchodilators as an active intervention in infants up to 24 months of age with acute bronchiolitis.

Data collection and analysis
Two review authors (ZL, MRA) independently performed data extraction and study quality assessment. We pooled the data from individual trials using the Cochrane statistical package Review Manager (RevMan).

Main results
We included four trials involving 254 infants with acute viral bronchiolitis (189 inpatients and 65 outpatients) in this review. Patients treated with nebulized 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline (mean difference (MD) -0.94 days, 95% CI -1.48 to -0.40, P = 0.0006). The 3% saline group also had a significantly
lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment (day 1: MD -0.75, 95% CI -1.38 to -0.12, P = 0.02; day 2: MD -1.18, 95% CI -1.97 to -0.39, P = 0.003; day 3: MD -1.28, 95% CI -2.57 to 0.00, P = 0.05). The effect of nebulized hypertonic saline in improving clinical score was greater among outpatients than inpatients. No adverse events related to 3% saline inhalation were reported.

Authors’ conclusions

Current evidence suggests nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis.
**BACKGROUND**

**Description of the condition**

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants (Klassen 1997a). Most cases are viral in origin, with the leading cause being the respiratory syncyial virus (RSV). Other less common pathogens include parainfluenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and Mycoplasma pneumoniae (M. pneumoniae) (Garcia-Garcia 2006; Henderson 1979; Jacques 2006; Rose 1987; Shay 2001).

Virtually all infants are infected by RSV by the age of two years, around 40% to 50% develop involvement of the lower respiratory tract and 1% to 2% develop severe disease leading to hospitalization (Meissner 2003; Rakshi 1994; Shay 1999). In the last decade, an increasing trend in the rate of hospitalization of children with bronchiolitis has been observed in USA and Canada (Njoo 2001; Shay 1999).

In acute bronchiolitis, the principal pathological findings include a peribronchial infiltrate of inflammatory cells, mucosal and submucosal edema, necrosis and desquamation of ciliated epithelial cells, proliferation of cuboidal cells and excess mucus secretion (Panitch 1993; Wohl 1978). The combination of airway wall swelling, sloughing of necrotic debris, increased mucus production and impaired secretion clearance eventually leads to airway obstruction, gas trapping, atelectasis and impaired gas exchange. The diagnosis of acute bronchiolitis is usually based on clinical grounds. Despite the definition of bronchiolitis differing from country to country, it is generally accepted that acute bronchiolitis refers to the first episode of acute wheezing in children less than two years of age, starting after upper respiratory infection (coryza, cough or fever) (Panitch 1993). These criteria for diagnosis of acute bronchiolitis have also been widely used in clinical trials (Bertrand 2001; Klassen 1997b; Schuh 1992; Wainwright 2003; Zhang 2003). Direct fluorescent antibody tests, enzyme immunoassay techniques and cultures of the nasopharyngeal aspirate may be used to identify the causative pathogen.

**Description of the intervention**

The standard treatment for acute bronchiolitis remains supportive care and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant (Panitch 2003; Wohl 2003). There is a lack of convincing evidence for any other therapy. As airway edema and mucus plugging are the predominant pathological features in acute bronchiolitis, any therapeutic modality which can reduce these pathological changes and improve the clearance of airway secretions may be beneficial.

Epinephrine has a theoretical effect on acute bronchiolitis because it contains alpha adrenergic properties which lead to vasoconstriction and reduction of airway edema (Wohl 1978). However, a recent Cochrane review showed that nebulized epinephrine for acute bronchiolitis results in a modest short-term improvement in outpatients, but not among inpatients (Hartling 2006). Inhaled recombinant deoxyribonuclease (rhDNase), a mucolytic agent, has also been tested in hospitalized infants with acute bronchiolitis (Nast 2001). This drug is thought to exert its major effect by enhancing airway secretion clearance. However, no significant effect was observed on clinical severity scores or on the length of hospital stay. Another widely used approach is chest physiotherapy, which is thought to assist infants by enhancing the clearance of secretions and reducing ventilatory effort. However, the current evidence concludes that chest physiotherapy using vibration and percussion techniques does not reduce the length of hospital stay, oxygen requirements or improve the clinical severity score in infants with acute bronchiolitis (Perrotta 2006).

**How the intervention might work**

Hypertonic saline solution has been shown to increase mucociliary clearance in normal subjects, in asthma, bronchiectasis, cystic fibrosis, and sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2007). Hypertonic saline has recently been trialed in patients with acute bronchiolitis (Kuzik 2007; Mandelberg 2003; Sarrell 2002; Tal 2006). The postulated mechanisms of benefit are as follows: 1) hypertonic saline breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion (Ziment 1978); 2) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating secretions and improving mucus rheology (Robinson 1997); 3) hypertonic saline stimulates ciliary beat via the release of prostaglandin E2 (Assouline 1977). Moreover, by absorbing water from the mucosa and submucosa, hypertonic saline solution can increase the local osmolality, thus increasing the rate of transcription, and hence clearance in normal subjects, in asthma, bronchiectasis, cystic fibrosis, and sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2007). Hypertonic saline has recently been trialed in patients with acute bronchiolitis (Kuzik 2007; Mandelberg 2003; Sarrell 2002; Tal 2006). The postulated mechanisms of benefit are as follows: 1) hypertonic saline breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion (Ziment 1978); 2) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating secretions and improving mucus rheology (Robinson 1997); 3) hypertonic saline stimulates ciliary beat via the release of prostaglandin E2 (Assouline 1977). Moreover, by absorbing water from the mucosa and submucosa, hypertonic saline solution can
theoretically reduce edema of the airway wall in infants with acute bronchiolitis (Mandelberg 2003; Sarrell 2002). Hypertonic saline inhalation can also cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction (Mandelberg 2003). The above-mentioned theoretical benefits provide the rationale for the treatment of acute bronchiolitis with nebulized hypertonic saline solution.

**Why it is important to do this review**

The hypothesis of this review is that nebulized hypertonic saline solution is beneficial in the management of acute bronchiolitis as assessed by clinically relevant outcomes, both in inpatients and outpatients. The establishment of a therapeutic role for hypertonic saline solution in acute bronchiolitis has relevant clinical implications. This modality may provide a cheap and effective therapy for children with acute bronchiolitis.

**OBJECTIVES**

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

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included randomized controlled trials (RCTs) and quasi-RCTs (where there is alternate allocation to treatment and control groups) in this review. We excluded studies which included patients who had had recurrent wheezing or were intubated and ventilated, and studies which assessed pulmonary function alone.

**Types of participants**

Infants up to 24 months of age with the diagnosis of acute bronchiolitis. Acute bronchiolitis was defined as the first episode of acute wheezing associated with clinical evidence of a viral infection (cough, coryza, or fever). Confirmation of viral etiology was not necessary for study inclusion. We included studies of inpatients or outpatients. We excluded patients with recurrent wheezing.

**Types of interventions**

- Nebulized hypertonic saline alone versus nebulized 0.9% saline
- Nebulized hypertonic saline plus bronchodilator versus nebulized 0.9% saline
- Nebulized hypertonic saline plus bronchodilator versus nebulized 0.9% saline plus same bronchodilator
- Nebulized hypertonic saline plus bronchodilator versus no intervention

Given the very limited number of studies that were identified initially, we added comparison of nebulized hypertonic saline alone versus nebulized 0.9% saline. Hypertonic saline was defined as a concentration of saline greater than or equal to 3%.

**Types of outcome measures**

**Primary outcomes**

Length of hospital stay or time taken to be ready for discharge (inpatients), or rate of hospitalization (outpatients).

**Secondary outcomes**

- Clinical severity scores
- Rate of re-admission to hospital
- Haemoglobin saturation (oximetry)
- Respiratory rate
- Heart rate
- Time for the resolution of symptoms/signs
- Duration of in-hospital oxygen supplementation
- Results of pulmonary function tests
- Radiological findings
- Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, and acute urinary retention)

**Search methods for identification of studies**

**Electronic searches**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The 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). The following search terms were combined with the highly sensitive search strategy as recommended by the Cochrane Collaboration (Dickersin 1994) to search MEDLINE. These terms were adapted to search CENTRAL, EMBASE and LILACS as required.

**MEDLINE (OVID)**

1 exp Bronchiolitis/
2 bronchiolit$.mp.
3 exp Respiratory Syncytial Viruses/
4 exp Respiratory Syncytial Virus Infections/
5 (respiratory syncytial vir$ or RSV).mp.
Selection of studies
Two review authors (LZ, RAM) independently assessed the titles and abstracts of all studies identified by the searches. We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to make a clear decision for their inclusion. We excluded articles that did not meet the inclusion criteria. We noted the reasons for their exclusion (see ‘Characteristics of excluded studies’ table). We resolved any disagreements between the two review authors about study inclusion by discussion.

Data extraction and management
One review author (LZ) extracted study details from the included trials using a standardized data extraction form. These were checked by another review author (RAM). We resolved any disagreements by discussion. We entered the extracted data into RevMan 5 (RevMan 2008). We extracted the following data.

- Study characteristics: publication status, year, country of study, and setting
- Methods: method of allocation, blinding of participants and assessment of outcome, exclusion of participants after randomization, proportion of follow up losses, and intention-to-treat analysis
- Participants: sample size, age, sex, and inclusion and exclusion criteria
- Intervention: concentration of saline, volume of saline, interval of administration, treatment duration, and co-interventions
- Control: nebulized 0.9% saline or nil
- Outcomes: primary and secondary outcomes as described previously

Assessment of risk of bias in included studies
Two review authors (LZ, RAM) independently assessed the methodological quality of all included trials by using the five-point scoring system proposed by Jadad (Jadad 1996). This method evaluates the reported quality of randomization, blinding, and description of withdrawals and drop-outs. We resolved any disagreements between the review authors by discussion. Two review authors (LZ, RAM) also independently ranked quality of allocation concealment by using the Cochrane approach:
Grade A: adequate concealment
Grade B: uncertain
Grade C: clearly inadequate concealment

Assessment of heterogeneity
Due to the small number of included studies the Chi² test was not appropriate to detect heterogeneity. We used fixed-effect models for outcomes without heterogeneity and random-effects models for outcomes with heterogeneity.

Data synthesis
We combined outcomes from individual trials using the Cochrane statistical package RevMan 5 (RevMan 2008). Two numerical outcomes (length of hospital stay and clinical severity score) were suitable for meta-analysis. We calculated the mean difference (MD) and 95% confidence intervals (CI) to estimate the pooled treatment effect. We calculated the Risk Ratio (RR) and 95% CI for one categorical outcome (rate of hospitalization). We assessed homogeneity of effect size between the studies being pooled by visual inspection of graphical presentations and the I² statistic (Higgins 2003).

Sensitivity analysis
We planned sensitivity analyses and examination for publication bias. However, these were not undertaken because of the limited number of included trials. We performed subgroup analysis according to patient status (outpatient versus inpatient).

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
Results of the search
The search of electronic databases retrieved a total of 261 citations. After reviewing the titles and abstracts, we identified seven papers as being potentially relevant, which were reviewed in full text. Four trials met all the criteria for study selection for this review (see 'Characteristics of included studies’ table).

Included studies
All four studies were randomized, double-blind, parallel-group, controlled trials. One study was a multi-center trial involving one hospital in the United Arab Emirates and two hospitals in Canada (Kuzik 2007). The other three studies were conducted by the same group of investigators in Israel (Mandelberg 2003; Sarrell 2002; Tal 2006).

Participants
Outpatients were recruited in one trial (Sarrell 2002) and inpatients were recruited in the other three trials (Kuzik 2007; Mandelberg 2003; Tal 2006). The mean age of participants varied from 2.6 to 12.5 months (range: 10 days to 24 months). The criteria for diagnosis of viral bronchiolitis were clearly defined only by one trial (Kuzik 2007). Virological investigation was available in all four trials and the positive rate for respiratory syncytial virus (RSV) varied from 69% to 87%. Patients with a previous wheezing episode were excluded in all four trials.

Interventions
The concentration of hypertonic saline was defined at 3% in all four trials. The volume of saline for each inhalation was 4 ml in three trials (Kuzik 2007; Mandelberg 2003; Tal 2006) and 2 ml in one trial (Sarrell 2002). Bronchodilators were added to the study solution in three trials; two used 1.5 mg of epinephrine (Mandelberg 2003; Tal 2006) and one used 5 mg of terbutaline (Sarrell 2002). In one trial (Kuzik 2007) the study protocol did not require or encourage the co-administration of bronchodilators with the study solution. However, albuterol was added in 37% of the treatments and racemic epinephrine was added in 23% of the treatments, by attending physicians. Oxygen-driven nebulizers were used for drug deliveries in all but one trial (Tal 2006), in which ultrasonic nebulizers were utilized. Inhaled therapies were delivered at eight-hour intervals in three trials (Mandelberg 2003; Sarrell 2002; Tal 2006). In one trial (Kuzik 2007), the treatment was administered every two hours for three doses, followed by every four hours for five doses, and then every six hours. The duration of the treatment was five days for outpatients. For inpatients, the treatment was delivered until discharge.

Outcome measures
All three inpatient trials (Kuzik 2007; Mandelberg 2003; Tal 2006) used length of hospital stay as the primary outcome measure. The same clinical severity score was used by two trials as the secondary outcome measure. This clinical score was initially described by Wang (Wang 1992), grading respiratory rate, wheezing, retraction, and general condition from 0 to 3, with increased severity receiving a higher score. For outpatients (Sarrell 2002) rate of hospitalization and clinical severity score were used as the outcome measures. Side effects associated with inhaled therapies were reported in all four trials.

Risk of bias in included studies
The method of randomization was explicitly described and was adequate in one trial (Kuzik 2007). In the other three trials (Mandelberg 2003; Sarrell 2002; Tal 2006), the authors were requested to provide details regarding the method of randomization and they were judged as adequate. None of the four trials had described allocation concealment. After assessing information provided on request by the trial authors, allocation concealment was judged to be adequate in all four trials. The methods for double-blinding and the description of withdrawals/drop-outs were described and were appropriate in all four trials. One trial (Kuzik 2007) used analysis on an intention-to-treat basis. The Jadad score was five for all four trials.

Effects of interventions
Four RCTs involving 254 infants with viral bronchiolitis (189 inpatients and 65 outpatients) compared nebulized 3% saline to nebulized 0.9% saline.

1. Length of hospital stay
All three inpatient trials (Kuzik 2007; Mandelberg 2003; Tal 2006), with a total of 189 infants, demonstrated a benefit of nebulized 3% saline in reducing the duration of hospitalization. The pooled results show that infants treated with nebulized 3% saline had a statistically significant shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline, with a MD of -0.94 days (95% CI -1.48 to -0.40, P = 0.0006). This represents a 25.9% reduction from the mean length of hospital stay in the 0.9% saline group.

2. Rate of hospitalization
One outpatient trial (n = 70) (Sarrell 2002) used the rate of hospitalization as an outcome. This trial failed to demonstrate the efficacy of nebulized 3% saline in reducing the risk of hospitalization (RR 0.67, 95% CI 0.12 to 3.75, P = 0.65).

3. Clinical severity score
One outpatient (Sarrell 2002) and two inpatient trials (Mandelberg 2003; Tal 2006) used clinical severity score as an outcome. All three trials compared the post-inhalation clinical scores.
between infants treated with nebulized 3% saline and those treated with nebulized 0.9% saline on the first three days of treatment. We obtained the original data on clinical severity score of these three trials from the trial authors. The baseline clinical scores were comparable between the two groups in all three trials. On the first day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed that the 3% saline group had a statistically significant lower post-inhalation clinical score compared to the 0.9% saline group, with a MD of -1.28 (95% CI -1.92 to -0.64, P < 0.0001). However, the differences between the two groups did not reach statistical significance for 93 inpatients included in two trials (Mandelberg 2003; Tal 2006), with a MD of -0.48 (95% CI -1.10 to 0.14, P = 0.13). The pooled results from the three trials demonstrate a significantly lower post-inhalation clinical score favoring treatment with nebulized 3% saline over nebulized 0.9% saline on the first day of treatment, with a MD of -0.75 (95% CI -1.38 to -0.12, P = 0.02). This difference represents a 11.2% reduction from the mean clinical score in the 0.9% saline group. On the second day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed a lower post-inhalation clinical score in the 3% saline group compared to the 0.9% saline group, with a MD of -2.0 (95% CI -2.92 to -1.08, P < 0.0001). The difference was smaller, but statistically significant between the two groups among 89 inpatients (Mandelberg 2003; Tal 2006), with a MD of -0.85 (95% CI -1.42 to -0.28, P = 0.004). The pooled results from these three trials demonstrate benefit of nebulized 3% saline in reducing the post-inhalation clinical score on the second day of treatment, with a MD of -1.18 (95% CI -1.97 to -0.39, P = 0.003). This difference represents a 20% reduction from the mean clinical score in the 0.9% saline group. On the third day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed a lower post-inhalation clinical score in the 3% saline group, with a MD of -2.64 (95% CI -3.85 to -1.43, P < 0.0001). However, the two inpatient trials (n = 71) (Mandelberg 2003; Tal 2006) failed to show a statistically significant difference between the two groups in terms of post-inhalation clinical score (MD -0.69, 95% CI -1.42 to 0.04, P = 0.06). The pooled results from these two trials demonstrate benefit of nebulized 3% saline in reducing the post-inhalation clinical score on the third day of treatment. However, the results are of borderline statistical significance (MD -1.28, 95% CI -2.57 to 0.00, P = 0.05).

4. Adverse events

No adverse events related to 3% saline inhalation were reported in any of the four trials. Two trials (Mandelberg 2003; Sarrell 2002) reported that pulse rate did not differ, on any day of the treatment, between the 3% saline group and the 0.9% saline group. One trial (Mandelberg 2003) did not find a significant difference between the two groups in terms of room air saturation of oxyhemoglobin throughout the study period. Although one trial (Kuzik 2007) reported that five infants were withdrawn at the parents’ request because of perceived adverse effects of the therapy, only two of these infants were treated with 3% saline inhalation. One two month old male infant was withdrawn because of vigorous crying during his third inhalation (3% saline alone) and again at his fifth inhalation (3% saline + racemic epinephrine). The other three month old female infant was withdrawn because of agitation after her second inhalation (3% saline + albuterol). There were no other associated changes in respiratory status or clinical condition in these two infants and they were eventually discharged on day six and day two.

DISCUSSION

Summary of main results

In this review, the length of hospital stay was defined as the primary outcome to measure the efficacy of nebulized hypertonic saline among inpatients with viral bronchiolitis. Despite differences in inhalation mixture and delivery intervals across the studies, the effect sizes of the treatment with 3% saline inhalation reported by three independent studies (Kuzik 2007; Mandelberg 2003; Tal 2006) were similar. That is, there was approximately a one-day reduction in the duration of hospitalization. The pooled results from these three trials demonstrate that nebulized 3% saline could produce a reduction of 0.94 days in the mean length of hospital stay. This represents a 25.9% reduction from the mean length of hospitalization in the normal saline group. Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalization, this reduction may be considered clinically relevant and may potentially have a positive economic impact.

The benefit of nebulized hypertonic saline in reducing the rate of hospitalization was assessed by one outpatient trial (Sarrell 2002). This study showed a 33% reduction in the risk of hospitalization among outpatient treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation. However, this reduction was not statistically significant. Low statistical power due to a small sample size may have contributed to this negative result. Further large RCTs are required to evaluate the efficacy of nebulized 3% saline in preventing hospitalization among outpatients with viral bronchiolitis.

Clinical score is generally considered a relatively objective instrument to assess the severity of illness. There are two clinical severity scoring systems more commonly used by randomized trials involving infants with viral bronchiolitis. One is a Respiratory Distress Assessment Instrument (RDAI) which assesses chest retractions and auscultatory findings, and provides a score ranging from 0 to 17, with a higher score indicating more severe respiratory distress (Lowell 1987). The other scoring system, initially described by Wang, assesses respiratory rate, wheezing, retractions, and general condition, providing a score ranging from 0 to 12, with increased severity receiving a higher score (Wang 1992). In this review, three...
trials utilized the clinical severity score system proposed by Wang. The pooled results from these three trials (one outpatient and two inpatient) demonstrate a statistically significant lower mean post-inhalation score among infants treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation in the first two days of treatment. The magnitude of reduction in the severity score produced by 3% saline inhalation may be considered clinically relevant because it represents a reduction of up to 20% from the mean clinical score in the 0.9% saline group. However, the benefit of nebulized 3% saline in improving clinical score on the third day of treatment was of borderline statistical significance. Low statistical power due to insufficient sample size may have contributed to this finding. Moreover, the subgroup analysis showed significant heterogeneity, regarding effect sizes of treatment with 3% saline inhalation, between outpatients and inpatients. Among outpatients, nebulized 3% saline produced a greater reduction in clinical severity score than nebulized 0.9% saline on each of the first three days of treatment. In contrast, the effect size of treatment with 3% saline inhalation was smaller among inpatients and the reduction in clinical score reached statistical significance only on the second day of treatment, but not on the first and the third days of treatment. A less favorable treatment response among inpatients than among outpatients was also observed in another Cochrane review which evaluated the efficacy of nebulized epinephrine in infants with viral bronchiolitis (Kuzik 2007). A greater severity of illness was postulated as the possible factor contributing to a smaller treatment effect size among inpatients with viral bronchiolitis.

The potential side effects, principally acute bronchospasm, remain a concern with nebulized hypertonic saline. This review included 128 infants receiving 3% saline in repeated doses and no significant adverse events were reported. In three trials (Mandelberg 2003; Sarrell 2002; Tal 2006), the patients received hypertonic saline inhalation in conjunction with bronchodilators. In one trial (Kuzik 2007), the study protocol defined the use of nebulized 3% saline alone, but bronchodilators were added into the study solution in 60% of the treatments by attending physicians. Therefore, this review could not provide valid evidence regarding the safety of nebulized 3% saline alone in infants with viral bronchiolitis. Given the possibility of acute bronchospasm induced by hypertonic saline in asthmatics and the difficulty in distinguishing between asthma and viral bronchiolitis in infants, it would seem reasonable to administer hypertonic saline in conjunction with bronchodilators to avoid any possible bronchoconstrictive effect. The safety of nebulized hypertonic saline, even in higher concentration (5% to 7%), has recently been reported in another Cochrane review of 143 cystic fibrosis patients (Wark 2007), which attributed the good safety profile of the therapy to the co-administration of hypertonic saline with bronchodilators.

The inhalation therapy was administrated via jet nebulizers in all but one trial (Tal 2006), in which ultrasonic nebulizers were used. Theoretically, there are some differences in the physical properties of aerosols produced by jet nebulizers and ultrasonic nebulizers, which may affect their therapeutical efficacies. On the one hand, ultrasonic nebulizers induce sputum more efficiently than jet nebulizers. On the other hand, jet nebulizers generate aerosols with smaller aerodynamic mass median diameter which may more easily reach smaller bronchi and bronchioles. This review could not provide direct evidence regarding the impact of the physical properties of aerosols generated by different types of nebulizers, on the efficacy of inhaled hypertonic saline in infants with viral bronchiolitis. However, at least one trial (Tal 2006) demonstrated that both jet nebulizers and ultrasonic nebulizers are an efficient method of delivery of hypertonic saline in these patients. Further studies are required to compare the efficacy of nebulized hypertonic saline delivered by different nebulizers in infants with viral bronchiolitis.

The delivery interval of nebulized hypertonic saline was eight hours in three trials (Mandelberg 2003; Sarrell 2002; Tal 2006), but more frequent deliveries were administrated in one trial (Kuzik 2007). No significant difference was observed between the studies, regarding effect sizes of treatment with 3% saline inhalation delivered at different intervals, on the reduction of length of hospital stay. However, the optimal delivery intervals of nebulized hypertonic saline in infants with viral bronchiolitis still need to be established by further studies.

Quality of the evidence

All four included trials had high overall quality, with Jadad scores of five. However, some methodological limitations should be taken into account in the interpretation of the results of this review. Firstly, three trials (Mandelberg 2003; Sarrell 2002; Tal 2006) did not use analysis on an intention-to-treat basis. This analysis strategy aims to maintain the unbiased group comparison afforded by randomization and to deal with the problem of non-compliance and protocol deviation. As the number of patients withdrawn after randomization was small in these three trials, the lack of application of an intention-to-treat principle was unlikely to cause significant bias. Secondly, the sample size of this review was relatively small and the statistical power of the study might be sufficient for some but not for other outcome measures. This limitation may explain why this review could confirm the efficacy of nebulized hypertonic saline in reducing the length of hospital stay but failed to demonstrate consistently the benefit of this therapy in improving the clinical severity score in the first three days of treatment, among inpatients with viral bronchiolitis. This review also might not have enough power to assess the efficacy of nebulized hypertonic saline in preventing hospitalization among outpatients with viral bronchiolitis.

Authors’ conclusions

Nebulized hypertonic saline solution for acute bronchiolitis in infants (Review)
Implications for practice

Nebulized 3% saline produces a 25.9% reduction (0.94 days) in the mean length of hospital stay, compared to nebulized normal saline, among infants hospitalized with viral bronchiolitis. This therapy also significantly reduces clinical severity score, principally among outpatients with viral bronchiolitis. Given the clinically relevant benefit and good safety profile, nebulized 3% saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with viral bronchiolitis.

Implications for research

Further large RCTs, preferably multi-centered, are still required to evaluate the effectiveness of nebulized hypertonic saline in infants with viral bronchiolitis, principally to verify the benefit of this therapy in improving clinical score among inpatients and in reducing the risk of hospitalization among outpatients. The optimal delivery intervals and concentration of saline, and the most effective delivery devices remain to be determined. The mechanism of action of nebulized hypertonic saline in patients with viral bronchiolitis also needs to be addressed by further studies.

Acknowledgements

Thanks to Ruth Foxlee and Sarah Thorning for help in defining the search strategy and in running the literature search. Thanks also to Libby Lissiman for assistance in the early stages of this review and to the Cochrane ARI Group, especially Liz Dooley, for ongoing assistance. The authors wish to thank the following people for commenting on the draft review: Hayley Edmonds, Avigdor Mandelberg, Federico Martinón Torres, Sree Nair and Meenu Singh.

References

References to studies included in this review

Kuzik 2007 {published data only}

Mandelberg 2003 {published data only}

Sarrell 2002 {published data only}

Tal 2006 {published data only}

References to studies excluded from this review

Amirav 2005 {published data only}

Guomo 2007 {published data only}
Nebulized hypertonic saline solution for acute bronchiolitis in infants (Review)

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**Tribastone 2003** (published data only)


**Additional references**

**Assouline 1977**


**Bertrand 2001**


**Daviskas 1996**


**Dickersin 1994**


**Garcia-Garcia 2006**


**Hartling 2006**


**Henderson 1979**


**Higgins 2003**


**Jacques 2006**


**Jadad 1996**


**Kellert 2005**


**Klassen 1997a**


**Klassen 1997b**


**Lowell 1987**


**Meissner 2003**


**Nasr 2001**


**Njoo 2001**


**Panitch 1993**


**Panitch 2003**


**Perrotta 2006**

Perrotta C, Ortiz Z, Roque M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004873.pub3]

**Rakshi 1994**


**RevMan 2008**


**Robinson 1997**


**Rose 1987**


**Schuh 1992**


**Shay 1999**

Shay 2001

Shoseyov 1998

Wainwright 2003

Wang 1992

Wark 2007

Wohl 1978

Wohl 2003

Zhang 2003

Ziment 1978

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

**Kuzik 2007**

| Methods | Design: randomized, double-blind, parallel-group, controlled trial  
| Randomization: computer-based randomization program  
| Blinding: double-blind  
| Withdrawals/drop-outs: 2 patients from the hypertonic saline (HS) group and 3 from the normal saline (NS) group were withdrawn at parental request because of perceived adverse effects of therapy.  
| Jadad score: 5 |

| Participants | Setting: inpatient wards of 3 regional tertiary care hospitals, 1 in United Arab Emirates and 2 in Canada  
| Eligible: not stated  
| Randomized: 47 HS group; 49 NS group  
| Completed: 45 HS group; 46 NS group  
| Gender (male): 59%  
| Age: mean age 4.7 months, range 10 days to 18 months  
| Inclusion criteria: infants with diagnosis of moderately severe bronchiolitis, which required a history of a preceding viral upper respiratory infection, the presence of wheezing or crackles on chest auscultation, plus either an oxygen saturation of < 94% in room air or RDAI score of >= 4  
| Exclusion criteria: previous episode of wheezing, chronic cardiopulmonary disease or immunodeficiency, critical illness at presentation requiring admission to intensive care, the use of nebulized HS within the previous 12 hours, or premature birth (gestational age <= 34 weeks) |

| Interventions | Test group: nebulized 3% hypertonic saline (4 ml)  
| Control group: nebulized 0.9% normal saline (4 ml). The treatment was given every 2 hours for 3 doses, |
Kuzik 2007

(Continued)

followed by every 4 hours for 5 doses, followed by every 6 hours until discharge. All inhaled therapies were delivered to a settled infant from a standard oxygen-driven hospital nebulizer through a tight-fitting face-mask, or head box, whichever was better tolerated by the infant.

Outcomes

Length of hospital stay

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - adequate</td>
</tr>
</tbody>
</table>

Mandelberg 2003

Methods

Design: randomized, double-blind, parallel-group, controlled trial
Randomization: randomization in blocks of 4, using an online randomizer
Blinding: double-blind
Withdrawals/drop-outs: 9 patients were withdrawn. 8 because of parental refusal (3 from the 3% saline group and 5 from the 0.9% saline group) and 1 because of clinical deterioration (from the 0.9% saline group).
Jadad score: 5

Participants

Setting: inpatient ward, the Edith Wolfson Medical Center, Israel
Eligible: 61
Randomized: 31 (0.9% saline group); 30 (3% saline group)
Completed: 25 HS group; 27 NS group
Gender (male): 57.7%
Age: mean age 2.9 months, range 0.5 to 12 months
Inclusion criteria: infants with clinical presentation of viral bronchiolitis with temperatures > 38ºC that lead to hospitalization
Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, oxygen saturation < 85% in room air, obtunded consciousness, and/or progressive respiratory failure requiring mechanical ventilation

Interventions

Test group: nebulized 3% saline solution (4 ml) plus 1.5 mg epinephrine
Control group: nebulized 0.9% saline solution (4 ml) plus 1.5 mg epinephrine. The treatment was given 3 times/day at intervals of 8 hours, until the patient was ready for discharge. All inhaled treatments were delivered using a nebulizer (Aeromist Nebulizer Set 61400; B&F Medical by Allied; Toledo, OH) connected to a source of pressurized oxygen at a flow rate of 5 L/min

Outcomes

Length of hospital stay
Change in clinical severity score
Others: pulse rate, saturation on room air, radiograph assessment score, and number of add-on treatments

Notes

Risk of bias
Sarrell 2002

Methods
Design: randomized, double-blind, parallel-group, controlled trial
Randomization: randomization in blocks of 4, using an online randomizer
Blinding: double-blind
Withdrawals/drop-outs: 5 patients were withdrawn, but the reasons were not stated
Jadad score: 5

Participants
Setting: The Pediatrics and Adolescent Ambulatory Community Clinic of General Health Services of Petach-Tikva, Israel
Eligible: not stated
Randomized: 70
Completed: 32 (0.9% saline group); 33 (3% saline group)
Gender (male): 59%
Age: mean age 12.5 months, range 3 to 24 months
Inclusion criteria: infants with clinical presentation of mild-to-moderate viral bronchiolitis
Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age >= 24 months, oxygen saturation < 96% on room air, and need for hospitalization

Interventions
Test group: nebulized 3% saline solution (2 ml) plus 5 mg (0.5 ml) terbutaline
Control group: nebulized 0.9% saline solution (2 ml) plus 5 mg (0.5 ml) terbutaline. The treatment was given 3 times/day at intervals of 8 hours for 5 days

Outcomes
Change in clinical severity score
Hospitalization rate
Others: radiograph assessment score, pulse rate, and tremor

Notes
Risk of bias

Tal 2006

Methods
Design: randomized, double-blind, parallel-group, controlled trial
Randomization: randomization in blocks of 4, using an online randomizer
Blinding: double-blind
Withdrawals/drop-outs: 2 patients from the 0.9% saline group were withdrawn, 1 because of clinical deterioration and another because of parental refusal. 1 patient from the 3% saline group was withdrawn because of protocol violation.

Jadad score: 5

Participants
Setting: inpatient ward, the Wolfson Medical Center, Israel
Eligible: unclear
Randomized: 22 (0.9% saline group); 22 (3% saline group)
Completed: 20 (0.9% saline group); 21 (3% saline group)
Gender (male): 56.1%
Age: mean age 2.6 months, range 1 to 5 months
Inclusion criteria: infants with clinical presentation of viral bronchiolitis that led to hospitalization
Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, oxygen saturation < 85% on room air, obtunded consciousness, and/or progressive respiratory failure requiring mechanical ventilation

Interventions
Test group: nebulized 3% saline solution (4 ml) plus 1.5 mg epinephrine
Control group: nebulized 0.9% saline solution (4 ml) plus 1.5 mg epinephrine. The treatment was given 3 times/day at intervals of 8 hours, until the patient was ready for discharge. All inhaled treatments were delivered using an ultrasonic nebulizer (Omron UI, OMRON Matsusaka Co. Ltd., Japan)

Outcomes
Length of hospital stay
Change in clinical severity score

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

*HS = hypertonic saline
NS = normal saline
### Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amirav 2005</td>
<td>Study of drug delivery (hood versus face-mask)</td>
</tr>
<tr>
<td>Guomo 2007</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Tribastone 2003</td>
<td>Summary of Sarrell 2002</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. 3% saline versus 0.9% saline

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Length of hospital stay (days)</td>
<td>3</td>
<td>189</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.94 [-1.48, -0.40]</td>
</tr>
<tr>
<td>2 Clinical severity score (post-treatment) at day 1</td>
<td>3</td>
<td>158</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.75 [-1.38, -0.12]</td>
</tr>
<tr>
<td>2.1 Outpatients</td>
<td>1</td>
<td>65</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.28 [-1.92, -0.64]</td>
</tr>
<tr>
<td>2.2 Inpatients</td>
<td>2</td>
<td>93</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.48 [-1.10, 0.14]</td>
</tr>
<tr>
<td>3 Clinical severity score (post-treatment) at day 2</td>
<td>3</td>
<td>154</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-1.18 [-1.97, -0.39]</td>
</tr>
<tr>
<td>3.1 Outpatients</td>
<td>1</td>
<td>65</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>0.00 [-2.92, -1.08]</td>
</tr>
<tr>
<td>3.2 Inpatients</td>
<td>2</td>
<td>89</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.85 [-1.42, -0.28]</td>
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<tr>
<td>4 Clinical severity score (post-treatment) at day 3</td>
<td>3</td>
<td>136</td>
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<tr>
<td>4.1 Outpatients</td>
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<td>4.2 Inpatients</td>
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<td>71</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.69 [-1.42, 0.04]</td>
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<tr>
<td>5 Rate of hospitalization</td>
<td>1</td>
<td>70</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.12, 3.75]</td>
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</table>

### Analysis 1.1. Comparison 1 3% saline versus 0.9% saline, Outcome 1 Length of hospital stay (days).

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants
Comparison: 1 3% saline versus 0.9% saline
Outcome: 1 Length of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference (IV, Fixed, 95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelberg 2003</td>
<td>27</td>
<td>25</td>
<td>-1.00 [-1.87, -0.13]</td>
<td>38.1 %</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>21</td>
<td>20</td>
<td>-0.90 [-1.86, 0.06]</td>
<td>31.6 %</td>
</tr>
<tr>
<td>Kuzik 2007</td>
<td>47</td>
<td>49</td>
<td>-0.90 [-1.88, 0.08]</td>
<td>30.3 %</td>
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<tr>
<td>Total (95% CI)</td>
<td>95</td>
<td>94</td>
<td>100.0 %</td>
<td>-0.94 [-1.48, -0.40]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² = 0.0%
Test for overall effect: Z = 3.42 (P = 0.00063)
Analysis 1.2. Comparison 1 3% saline versus 0.9% saline, Outcome 2 Clinical severity score (post-treatment) at day 1.

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants
Comparison: 1 3% saline versus 0.9% saline
Outcome: 2 Clinical severity score (post-treatment) at day 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Mean(SD))</td>
<td>N (Mean(SD))</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1 Outpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>33 (4.36 (1.05))</td>
<td>32 (5.64 (1.54))</td>
<td>-1.28 [-1.92, -0.64]</td>
<td>35.5 %</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>32</td>
<td>-1.28 [-1.92, -0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 3.90$ ($P = 0.000095$)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>2 Inpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mandelberg 2003</td>
<td>27 (7.7 (1.5))</td>
<td>25 (7.81 (1.49))</td>
<td>-0.11 [-0.92, 0.70]</td>
<td>29.0 %</td>
<td></td>
</tr>
<tr>
<td>Tal 2006</td>
<td>21 (6.25 (1.1))</td>
<td>20 (7 (1))</td>
<td>-0.75 [-1.39, -0.11]</td>
<td>35.5 %</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>48</td>
<td>45</td>
<td>-0.48 [-1.10, 0.14]</td>
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<tr>
<td>Total (95% CI)</td>
<td>81</td>
<td>77</td>
<td>-0.75 [-1.38, -0.12]</td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.06; \chi^2 = 1.46, df = 1$ ($P = 0.23$); $I^2 = 32%$</td>
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<td>Test for overall effect: $Z = 1.52$ ($P = 0.13$)</td>
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</tbody>
</table>

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants
Comparison: 1 3% saline versus 0.9% saline
Outcome: 2 Clinical severity score (post-treatment) at day 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Mean(SD))</td>
<td>N (Mean(SD))</td>
<td>IV, Random, 95% CI</td>
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</tr>
<tr>
<td>1 Outpatients</td>
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</tr>
<tr>
<td>Sarrell 2002</td>
<td>33 (4.36 (1.05))</td>
<td>32 (5.64 (1.54))</td>
<td>-1.28 [-1.92, -0.64]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>32</td>
<td>-1.28 [-1.92, -0.64]</td>
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<tr>
<td>Heterogeneity: not applicable</td>
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<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 3.90$ ($P = 0.000095$)</td>
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</tbody>
</table>
### Analysis 1.3. Comparison of 3% saline versus 0.9% saline, Outcome 3 Clinical severity score (post-treatment) at day 2.

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline N</th>
<th>Mean(SD)</th>
<th>0.9% saline N</th>
<th>Mean(SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>33</td>
<td>2.77 (1.3)</td>
<td>32</td>
<td>4.77 (2.31)</td>
<td>-2.00</td>
<td>30.8 %</td>
<td>-2.00 [-2.92, -1.08]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>33</td>
<td>32</td>
<td>30.8 %</td>
<td>-2.00 [-2.92, -1.08]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 4.28 (P = 0.000018)</td>
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</tr>
<tr>
<td><strong>Inpatients</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>24</td>
<td>6.41 (1.4)</td>
<td>25</td>
<td>6.92 (1.62)</td>
<td>-0.51</td>
<td>32.7 %</td>
<td>-0.51 [-1.36, 0.34]</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>20</td>
<td>5.35 (1.3)</td>
<td>20</td>
<td>6.45 (1)</td>
<td>-1.10</td>
<td>36.5 %</td>
<td>-1.10 [-1.82, -0.38]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>44</td>
<td>45</td>
<td>69.2 %</td>
<td>-0.85 [-1.42, -0.28]</td>
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<td>Heterogeneity: Tau² = 0.01; Ch² = 1.08, df = 1 (P = 0.30); I² = 8%</td>
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<td>Test for overall effect: Z = 2.91 (P = 0.0036)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>77</td>
<td>77</td>
<td>100.0 %</td>
<td>-1.18 [-1.97, -0.39]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.31; Ch² = 5.53, df = 2 (P = 0.06); I² = 64%</td>
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<tr>
<td>Test for overall effect: Z = 2.93 (P = 0.0033)</td>
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</tbody>
</table>
### Comparison: 3% saline versus 0.9% saline

**Outcome:** Clinical severity score (post-treatment) at day 2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
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<td>Mean(SD)</td>
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<tr>
<td><strong>Outpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>33</td>
<td>2.77 (1.3)</td>
<td>32</td>
<td>4.77 (2.31)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td>32</td>
<td></td>
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<tr>
<td><strong>Heterogeneity:</strong> not applicable</td>
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<tr>
<td>Test for overall effect: Z = 4.28 (P = 0.000018)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td><strong>Inpatients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>24</td>
<td>6.41 (1.4)</td>
<td>25</td>
<td>6.92 (1.62)</td>
</tr>
<tr>
<td>Tal 2006</td>
<td>20</td>
<td>5.35 (1.3)</td>
<td>20</td>
<td>6.45 (1)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>44</td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.01; Ch² = 1.08, df = 1 (P = 0.30); I² =8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.91 (P = 0.0036)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 1.4. Comparison 1 3% saline versus 0.9% saline, Outcome 4 Clinical severity score (post-treatment) at day 3.

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants
Comparison: 1 3% saline versus 0.9% saline
Outcome: 4 Clinical severity score (post-treatment) at day 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean(SD)</td>
<td>N  Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td>N,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Outpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>33 1.77 (2.4)</td>
<td>32 4.41 (2.57)</td>
<td>-2.64 [-3.85, -1.43]</td>
<td>31.6 %</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>32</td>
<td>-2.64 [-3.85, -1.43]</td>
<td>31.6 %</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.28 (P = 0.000019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Inpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tal 2006</td>
<td>13 4.7 (1.5)</td>
<td>14 5.72 (1)</td>
<td>-1.02 [-1.99, -0.05]</td>
<td>35.1 %</td>
<td></td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>21 5.81 (1.68)</td>
<td>23 6.08 (2.03)</td>
<td>-0.27 [-1.37, 0.83]</td>
<td>33.3 %</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34</td>
<td>37</td>
<td>-0.69 [-1.42, 0.04]</td>
<td>68.4 %</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>67</td>
<td>69</td>
<td>-1.28 [-2.57, 0.00]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.32); I² =1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.86 (P = 0.063)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants
Comparison: 1 3% saline versus 0.9% saline
Outcome: 4 Clinical severity score (post-treatment) at day 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean(SD)</td>
<td>N  Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td>N,Random,95% CI</td>
<td></td>
</tr>
<tr>
<td>1 Outpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>33 1.77 (2.4)</td>
<td>32 4.41 (2.57)</td>
<td>-2.64 [-3.85, -1.43]</td>
<td>31.6 %</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>33</td>
<td>32</td>
<td>-2.64 [-3.85, -1.43]</td>
<td>31.6 %</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.28 (P = 0.000019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Review: Nebulized hyper tonic saline solution for acute bronchiolitis in infants
Comparison: 3% saline versus 0.9% saline
Outcome: Clinical severity score (post-treatment) at day 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV</td>
</tr>
<tr>
<td>2 Inpatients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tal 2006</td>
<td>13</td>
<td>4.7 (1.5)</td>
<td>14</td>
<td>5.72 (1)</td>
</tr>
<tr>
<td>Mandelberg 2003</td>
<td>21</td>
<td>5.81 (1.68)</td>
<td>23</td>
<td>6.08 (2.03)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34</td>
<td>37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.32); I² = 1%
Test for overall effect: Z = 1.86 (P = 0.063)

Analysis 1.5. Comparison 1 3% saline versus 0.9% saline, Outcome 5 Rate of hospitalization.

Review: Nebulized hyper tonic saline solution for acute bronchiolitis in infants
Comparison: 3% saline versus 0.9% saline
Outcome: Rate of hospitalization

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>3% saline</th>
<th>0.9% saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarrell 2002</td>
<td>2/35</td>
<td>3/35</td>
<td>100.0 %</td>
<td>0.67 [0.12, 3.75]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>35</td>
<td>35</td>
<td></td>
<td>100.0 %</td>
<td>0.67 [0.12, 3.75]</td>
</tr>
</tbody>
</table>

Total events: 2 (3% saline), 3 (0.9% saline)
Heterogeneity: not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

WHAT'S NEW

Last assessed as up-to-date: 12 November 2007

Date | Event | Description
--- | --- | ---
18 February 2008 | Amended | Converted to new review format.
13 November 2007 | New search has been performed | Searches conducted.
CONTRIBUTIONS OF AUTHORS

Linjie Zhang (LZ) conceived the idea and wrote the draft protocol and review.

LZ and Raúl A Mendoza-Sassi (RAM) were responsible for study selection, quality assessment, data collection and data analysis.

RAM, Claire Wainwright (CW) and Terry P Klassen (TPK) provided input for writing the protocol and review.

The final version of the review was approved by all authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Departamento Materno-Infantil, Universidade Federal do Rio Grande, Brazil.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the very limited number of studies that were identified initially, we added comparison of nebulized hypertonic saline alone versus nebulized 0.9% saline. Hypertonic saline was defined as a concentration of saline greater than or equal to 3%. We also clarified the population according to the age and changed the title to specify infants.