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

Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP

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[Intervention Review]

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* 2010, Issue 2), which contains the Cochrane Acute Respiratory Infections Group Specialized Register, OLDMEDLINE (1951 to 1965), MEDLINE (1966 to May Week 4, 2010), EMBASE (1974 to June 2010) and LILACS (1985 to June 2010).

Selection criteria

Randomized 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 independently performed data extraction and study quality assessment. We performed meta-analyses using the Cochrane statistical package RevMan 5. We used the random-effects model for meta-analyses. We used mean difference (MD) and risk ratio (RR) as effect size metrics.

Main results

We included seven trials (581 infants) with mild to moderate acute viral bronchiolitis (282 inpatients, 65 outpatients and 234 emergency department patients). Patients treated with nebulized 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline (MD -1.16 days, 95% CI -1.55 to -0.77, P < 0.00001). 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 -0.95, 95%

CI -1.52 to -0.39, P = 0.0009; day 2: MD -1.31, 95% CI -1.87 to -0.75, P < 0.00001; day 3: MD -1.31, 95% CI -2.01 to -0.61, P = 0.0003). The effects of improving clinical score were observed in both outpatients and inpatients. Two emergency department-based trials failed to show significant short-term effects (30 to 120 minutes) of up to two doses of nebulized hypertonic saline in improving clinical score and oxygen saturation. No significant 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 among infants hospitalized with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.

PLAIN LANGUAGE SUMMARY

Nebulized hypertonic saline solution for acute bronchiolitis in infants

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants, but the standard treatment remains supportive care. This review was conducted to assess the effects of 3% saline solution administered via nebulizer, which can increase clearance of mucus, in these patients. We included seven randomized trials involving 581 infants with mild to moderate bronchiolitis. Meta-analysis suggests that nebulized 3% saline may significantly reduce the length of hospital stay among infants hospitalized for non-severe acute bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations. No significant short-term effects (30 to 120 minutes) of one to two doses of nebulized hypertonic saline were observed among emergency department patients; however, more trials are needed to address this question. There were no significant adverse effects noted with nebulized hypertonic saline when administered along with bronchodilators.

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 syncytial 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). Over the last few decades, an increasing trend in the rate of hospitalization of children with bronchiolitis has been observed in the USA and Canada (Langley 2003; 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 as a viral 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 (Nasr 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).

Hypertonic saline has been recently introduced as a treatment for infants with acute bronchiolitis. Most of randomized trials demonstrate that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis (Luo 2010; Mandelberg 2003; Sarrell 2002; Tal 2006).

How the intervention might work

Hypertonic saline solution has been shown to increase mucociliary clearance in normal patients, in asthma, bronchiectasis, cystic fibrosis and sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2007). Such benefits would also be expected in infants with acute bronchiolitis (Mandelberg 2010). The postulated mechanisms of benefit are as follows: 1) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance (Mandelberg 2010; Robinson 1997); 2) 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); 3) hypertonic saline stimulates cilial 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; Mandelberg 2010; 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

1. Nebulized hypertonic saline alone versus nebulized 0.9% saline
2. Nebulized hypertonic saline plus bronchodilator versus nebulized 0.9% saline
3. Nebulized hypertonic saline plus bronchodilator versus nebulized 0.9% saline plus same bronchodilator
4. Nebulized hypertonic saline alone or plus bronchodilator versus no intervention

Given the very limited number of studies that were identified initially, we added the 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

1. Clinical severity scores
2. Rate of readmission to hospital
3. Hemoglobin saturation (oximetry)
4. Respiratory rate
5. Heart rate
6. Time for the resolution of symptoms/signs
7. Duration of in-hospital oxygen supplementation
8. Results of pulmonary function tests
9. Radiological findings
10. Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting and acute urinary retention)

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 2), which contains the Cochrane Acute Respiratory Infections Group Specialized Register, OLDMEDLINE (1951 to 1965), MEDLINE (1966 to May Week 4, 2010), EMBASE (1974 to June 2010) and LILACS (1985 to June 2010). See Appendix 1 for details of the previous search.

We used the following search strategy to search MEDLINE and CENTRAL. As there were so few search results we used no filter to identify randomized trials in MEDLINE. We adapted the search terms to search Embase. com (Appendix 2) and LILACS (Appendix 3).

MEDLINE (OVID)

1 exp Bronchiolitis/
2 bronchiolit*.tw.
3 respiratory syncytial viruses/ or respiratory syncytial virus, human/
4 Respiratory Syncytial Virus Infections/
5 (respiratory syncytial virus* or rsv).tw.
6 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
7 Parainfluenza Virus 2, Human/
8 Respirovirus Infections/
9 Adenovirus Infections, Human/
10 Rhinovirus/
11 Influenza, Human/
12 exp influenzavirus a/ or exp influenzavirus b/
13 (parainfluenza* or respirovirus* or adenovirus* or rhinovirus* or influenza*).tw.
14 or/1-13
15 Saline Solution, Hypertonic/
16 (hypertonic adj3 (saline or solution*)).tw.
17 Sodium Chloride/
18 (sodium chloride or saline).tw.
19 or/15-18
20 exp "Nebulizers and Vaporizers"/
21 (nebuli* or vapour* or vapour* or atomi*).tw.
22 Administration, Inhalation/
23 inhal*.tw.
24 Aerosols/
25 aerosol*.tw.
26 or/20-25
27 14 and 19 and 26

There were no language or publication restrictions.

Data collection and analysis

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.

1. Study characteristics: publication status, year, country of study and setting
2. 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

3. Participants: sample size, age, sex, and inclusion and exclusion criteria

4. Intervention: concentration of saline, volume of saline, interval of administration, treatment duration and co-interventions

5. Control: nebulized 0.9% saline or nil

6. Outcomes: primary and secondary outcomes as described previously

Assessment of risk of bias in included studies

Two review authors (LZ, RAM) independently assessed the potential risk of bias in included studies according to the Cochrane Collaboration's recommendations (Higgins 2009). Assessment results are summarized in the 'Risk of bias' tables.

Measures of treatment effect

We synthesized dichotomous data using risk ratios (RR) and 95% confidence intervals (CI) as the effect measures. We used the mean difference (MD) and 95% CI as the metrics of effect size for continuous outcomes.

Dealing with missing data

We contacted three principal investigators (Kuzik 2007; Luo 2010; Mandelberg 2003) for additional data on clinical score and methodological aspects. All three trial authors responded and provided the requested data.

Assessment of heterogeneity

We assessed heterogeneity in results between studies using the Cochrane Q test ($P < 0.1$ considered significant) and the I^2 statistic. The I^2 statistic ranges from 0% to 100% and measures the degree of inconsistency across studies, with values of 25%, 50% and 75% corresponding to low, moderate and high heterogeneity, respectively (Higgins 2003).

Assessment of reporting biases

Reporting biases, especially publication bias, may be expected to occur in the majority of systematic reviews. Unfortunately there is no reliable method to detect publication bias. To minimize the potential reporting biases, we used no language restrictions for the literature searches. We contacted experts and searched the currently available trial registration databases for additional published or unpublished trials.

Data synthesis

We performed the meta-analyses using the Cochrane statistical package RevMan 5 (RevMan 2008). We used the random-effects model for meta-analyses. We conducted meta-regression using Stata version 11.0 (Stata-Corp, College Station, TX, USA). Whenever possible, we used intention-to-treat (ITT) analysis data.

Subgroup analysis and investigation of heterogeneity

We performed pre-planned subgroup analysis according to patient status (outpatient versus inpatient). The severity of disease and treatment regime (concentration of saline, volume, interval of inhalation, drug delivery and duration of treatment) may also contribute to heterogeneity in effect sizes across studies. We conducted post hoc meta-regression to explore these possible causes of heterogeneity between studies.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The initial 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 we reviewed in full text. Four trials met all the criteria for study selection and were included in the initial review. The update search retrieved 39 citations; from them we identified three new trials and included them in this updated review. See the Characteristics of included studies table.

Included studies

All seven 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). Three trials were conducted by the same group of investigators in Israel (Mandelberg 2003; Sarrell 2002; Tal 2006). The remaining three studies were conducted in Turkey (Anil 2010), Canada (Grewal 2009) and China (Luo 2010).

Participants

One trial recruited outpatient participants (Sarrell 2002), two trials recruited emergency department participants (Anil 2010; Grewal 2009) and four trials recruited inpatients (Kuzik 2007; Luo 2010; 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 by three trials (Anil 2010; Grewal 2009; Kuzik 2007). Virological investigation was available in all trials except one (Anil 2010) and the positive rate for respiratory syncytial virus (RSV) varied from 69% to 87%. Patients with a previous wheezing episode were excluded in all seven trials. Patients hospitalized with severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation < 85% on room air) were also excluded in all inpatient trials.

Interventions

The concentration of hypertonic saline was defined at 3% in all seven trials. The volume of saline for each inhalation was 4 ml in five trials (Anil 2010; Kuzik 2007; Luo 2010; Mandelberg 2003; Tal 2006) and 2 ml to 2.5 ml in two trials (Grewal 2009; Sarrell 2002). Bronchodilators were added to the study solution per protocol in six trials; two used 1.5 mg of epinephrine (Mandelberg 2003; Tal 2006), one used 5 mg of terbutaline (Sarrell 2002), one used 22.5 mg of racemic epinephrine (Grewal 2009), one used 2.5 mg of salbutamol (Luo 2010), and one used 1.5 mg of epinephrine or 2.5 mg of salbutamol (Anil 2010). The study protocol for one trial (Kuzik 2007) 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 or compressed air-driven jet 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 four trials (Luo 2010; 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. Two emergency department-based trials used up to two doses of inhalation solution (Anil 2010; Grewal 2009). The duration of the treatment varied from 30 minutes (Anil 2010) to five days (Sarrell 2002) among outpatients or emergency department participants. For inpatients, the treatment was delivered until discharge.

Outcome measures

All four inpatient trials (Kuzik 2007; Luo 2010; Mandelberg 2003; Tal 2006) used length of hospital stay as the primary outcome measure. The same clinical severity score was used by three trials (Luo 2010; Mandelberg 2003; Tal 2006) 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 or emergency department participants (Anil 2010; Grewal 2009; Sarrell 2002), rate of hospitalization, rate of readmission and/or clinical severity score were used as the outcome measures. Side effects associated with inhaled therapies were reported in all seven trials.

Excluded studies

We excluded three studies from the review. The reasons for exclusion are summarized in the Characteristics of excluded studies table.

Risk of bias in included studies

All seven included trials were of high methodological quality with low risk of bias. Summary assessment of six key domains is presented below.

Allocation

Four trials (Grewal 2009; Mandelberg 2003; Tal 2006; Sarrell 2002) used an online randomizer and the remaining three (Anil 2010; Kuzik 2007; Luo 2010) used a computer-based random number program to generate the random sequence. All seven included studies used the sequentially numbered drug containers of identical appearance for allocation concealment.

Blinding

In all seven studies, participants, care providers and investigators were blinded to group assignment.

Incomplete outcome data

The number of participants with missing data was small in all seven trials. Thus, incomplete outcome data may not be a source of bias in this review. Intention-to-treat (ITT) analysis was used by three trials (Grewal 2009; Kuzik 2007; Sarrell 2002).

Selective reporting

There was no evidence of selective reporting of outcomes in the included studies.

Other potential sources of bias

No other potential sources of bias were observed in the included trials.

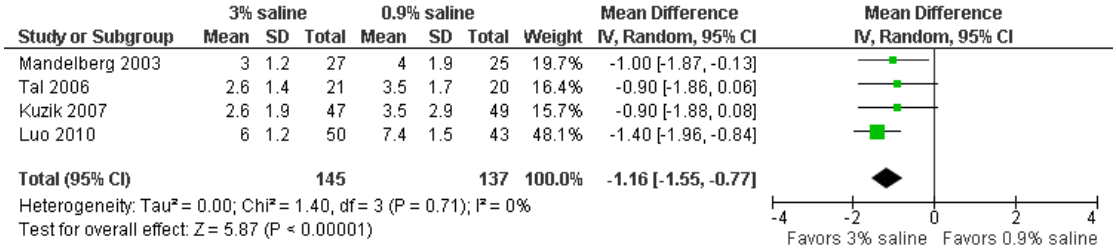
Effects of interventions

Seven RCTs involving 581 infants with mild to moderate acute viral bronchiolitis (282 inpatients, 65 outpatients and 234 emergency department patients) compared nebulized 3% saline to nebulized 0.9% saline.

1. Length of hospital stay

All four inpatient trials (Kuzik 2007; Luo 2010; Mandelberg 2003; Tal 2006) 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 pooled MD of -1.16 days (95% CI -1.55 to -0.77, P < 0.00001) (Figure 1). This represents a 24.1% reduction from the mean length of hospital stay in the 0.9% saline group. There was no significant heterogeneity in results between studies (I^2 statistic = 0%).

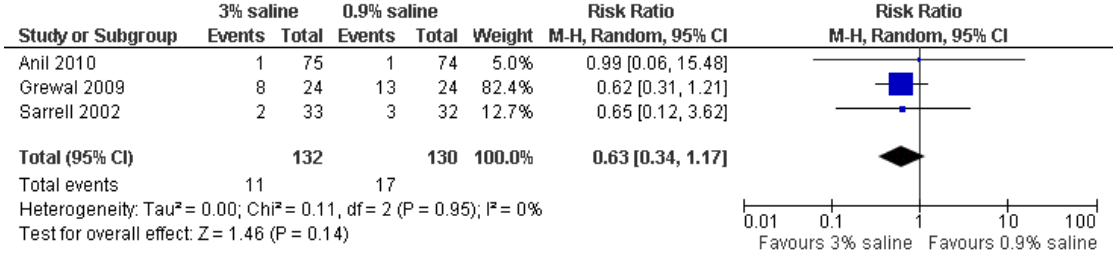
Figure 1. 3% saline versus 0.9% saline: Length of hospital stay (days)



2. Rate of hospitalization

One outpatient trial (Sarrell 2002) and two emergency department trials (Anil 2010; Grewal 2009) with a combined total of 262 participants assessed the efficacy of nebulized 3% saline in reducing the risk of hospitalization. There was no significant reduction in rate of hospitalization. The pooled RR was 0.63 (95% CI 0.34 to 1.17, P = 0.14) (Figure 2). There was no significant heterogeneity between studies (I^2 statistic = 0%).

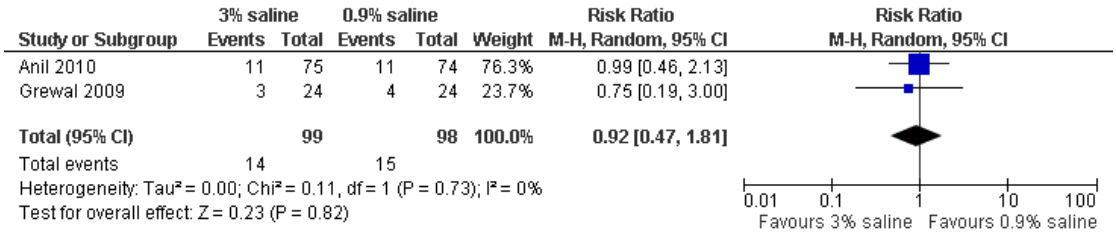
Figure 2. 3% saline versus 0.9% saline: Rate of hospitalization.



3. Rate of readmission

Two emergency department trials with a total of 234 participants (Anil 2010; Grewal 2009) used rate of readmission as an outcome. The pooled results of these trials did not demonstrate significant benefits of nebulized 3% saline in reducing the risk of readmission (pooled RR 0.92, 95% CI 0.47 to 1.81, P = 0.82) (Figure 3). There was no significant heterogeneity between studies (I^2 statistic = 0%).

Figure 3. 3% saline versus 0.9% saline: Rate of readmission.

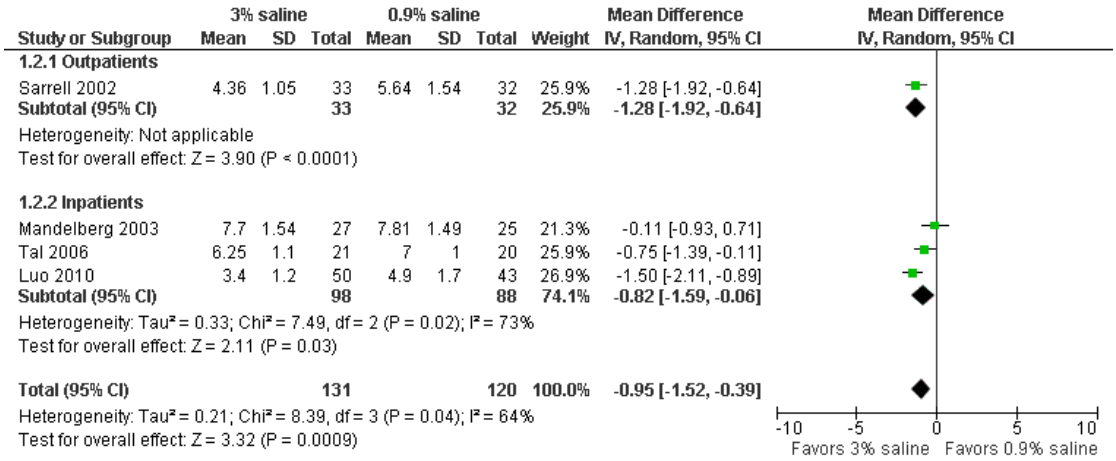


4. Clinical severity score

One outpatient (Sarrell 2002) and three inpatient trials (Luo 2010; Mandelberg 2003; Tal 2006) used the Wang 1992 clinical severity score as an outcome. All four 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. The baseline clinical scores were comparable between the two groups in all four trials.

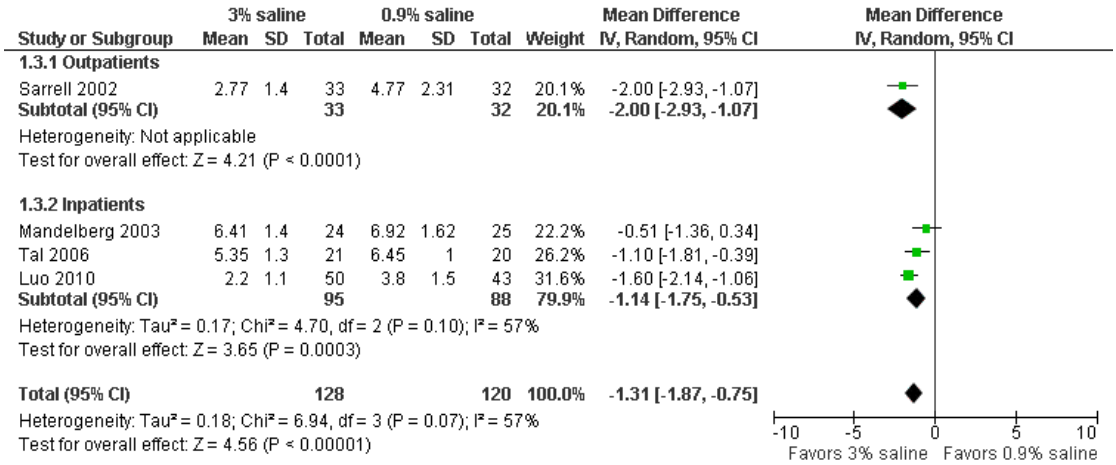
On the first day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed that the 3% saline group had a statistically significant lower post-inhalation clinical score compared to the 0.9% saline group, with a MD of -1.28 (95% CI -1.92 to -0.64, P < 0.0001). Three inpatient trials with a total of 186 patients (Luo 2010; Mandelberg 2003; Tal 2006) also demonstrated significant benefits of hypertonic saline in reducing clinical score (pooled MD -0.82, 95% CI -1.59 to -0.06, P = 0.02), in spite of significant heterogeneity between studies (I^2 statistic = 73%). The pooled results from the four trials showed 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 pooled MD of -0.95 (95% CI -1.52 to -0.39, P = 0.0009) (Figure 4). This difference represents a 15.7% reduction from the mean clinical score in the 0.9% saline group on the first day of treatment. There was significant heterogeneity in results between studies (I^2 statistic = 64%).

Figure 4. 3% saline versus 0.9% saline: Clinical severity score (post-treatment) at day 1



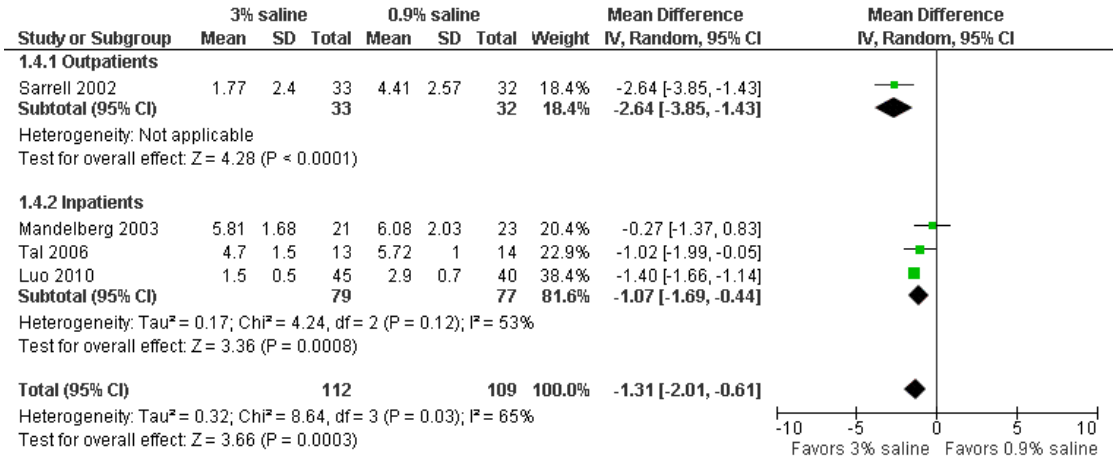
On the second day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed a lower post-inhalation clinical score in the 3% saline group compared to the 0.9% saline group, with a MD of -2.0 (95% CI -2.93 to -1.07, P < 0.0001). A significant difference between the treatment and control groups was also observed among 183 inpatients (Luo 2010; Mandelberg 2003; Tal 2006), with a pooled MD of -1.14 favoring 3% saline group (95% CI -1.75 to -0.53, P = 0.0003). There was significant heterogeneity between inpatient trials (I^2 statistic = 57%). The meta-analysis of four trials demonstrated the superiority of nebulized 3% saline over 0.9% saline in reducing the post-inhalation clinical score on the second day of treatment, with a pooled MD of -1.31 (95% CI -1.87 to -0.75, P < 0.00001) (Figure 5). This difference represents a 25.4% reduction from the mean clinical score in the 0.9% saline group for the second day of treatment. Significant heterogeneity was found between studies (I^2 statistic = 57%).

Figure 5. 3% saline versus 0.9% saline: Clinical severity score (post-treatment) at day 2



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 compared to the 0.9% saline group, with a MD of -2.64 (95% CI -3.85 to -1.43, P < 0.0001). The three inpatient trials (n = 156) (Luo 2010; Mandelberg 2003; Tal 2006) also showed a lower post-inhalation clinical score in the 3% saline group (pooled MD -1.07, 95% CI -1.69 to -0.44, P = 0.0008). Significant heterogeneity was observed between inpatient trials (I^2 statistic = 53%). The pooled results from these four trials demonstrated the superiority of nebulized 3% saline over 0.9% saline in reducing the post-inhalation clinical score on the third day of treatment (pooled MD -1.31, 95% CI -2.01 to -0.61, P = 0.0003) (Figure 6). This difference represents a 29.9% reduction from the mean clinical score in the 0.9% saline group. There was significant heterogeneity between studies (I^2 statistic = 65%).

Figure 6. 3% saline versus 0.9% saline: Clinical severity score (post-treatment) at day 3.



To explore the possible causes of heterogeneity in effect sizes across studies, we performed post hoc meta-regression. The small number of studies allowed us to include only one predicator in the model which was the severity of bronchiolitis assessed by clinical score in the 0.9% saline group. The meta-regression yielded a regression coefficient of 0.10 (95% CI -0.08 to 0.28), indicating a trend toward an inverse relationship between the severity of disease and effect size of hypertonic saline, that is, each 1 point increasing in baseline clinical score may yield a reduction of 0.10 point in effect size of hypertonic saline in improving clinical severity score. However, the results were not statistically significant (P = 0.22).

Two emergency department-based trials (Anil 2010; Grewal 2009) assessed short-term effects (30 to 120 minutes) of up to two doses of nebulized 3% saline in improving clinical score among infants with acute bronchiolitis. No significant benefits were observed. There were also no significant effects on oxygen saturation.

5. Adverse events

No significant adverse events related to 3% saline inhalation were reported in six trials. In one trial (Grewal 2009), three participants presented with vomiting and one presented with diarrhea during the study period. All four participants were enrolled in the 3% saline group. Three trials (Anil 2010; Mandelberg 2003; Sarrell 2002) reported no difference in pulse rate on any day of the treatment, between the 3% saline group and the 0.9% saline group. Three trials (Anil 2010; Grewal 2009; 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, we defined the length of hospital stay 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 four independent studies (Kuzik 2007; Luo 2010; 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 four trials demonstrate that nebulized 3% saline could produce a reduction of 1.16 days in the mean length of hospital stay. This represents a 24.1% 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 for both the health system and the individual families.

The benefit of nebulized hypertonic saline in reducing the rate of hospitalization was assessed by three trials, one in outpatients (Sarrell 2002) and two in emergency departments (Grewal 2009; Anil 2010). The pooled results of these two trials showed a 37% reduction in the risk of hospitalization among participants 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 small sample sizes may have contributed to this negative result. Further large RCTs are required to evaluate the efficacy of nebulized 3% saline in preventing hospitalization among infants with acute viral bronchiolitis seen at outpatient setting or emergency department. The effects of hypertonic saline in reducing the rate of readmission were also assessed by two emergency department trials (Anil 2010; Grewal 2009). The meta-analysis of two trials showed a 8% reduction in the risk of readmission, however the results were not statistically significant. Caution should be taken when interpreting the results for two emergency department-based trials, given the small number of participants, the small number of inhalations (up to two doses) and short monitoring time (up to 120 minutes post inhalation). Moreover, the change in airway surface liquid depth after saline inhalation is not only a function of the saline concentration but rather a direct result of the total mass of sodium chloride added to the airway surface (Mandelberg 2010). High volume of normal saline used as the "placebo" control in the trial of Anil 2010 could be sufficient to cause a significant improvement and this might lead to a sub-estimation of true effect of hypertonic saline in reducing the risk of hospitalization or readmission among infants with non-severe acute bronchiolitis.

Clinical score is generally considered a relatively objective measure to assess the severity of illness. There are two clinical severity scoring systems more commonly used by randomized trials involv-

ing 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, retraction and general condition, providing a score ranging from 0 to 12, with increased severity receiving a higher score (Wang 1992). In this review, four trials utilized the clinical severity score system proposed by Wang 1992. The pooled results from these four trials (one outpatient and three 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 three 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 30% from the mean clinical score in the 0.9% saline group. The benefits of nebulized 3% saline in improving clinical score are observed in both outpatients and inpatients, however there is significant heterogeneity in effect sizes across studies, especially between inpatient trials. Post hoc meta-regression suggests a trend toward an inverse relationship between the severity of disease and effect size of hypertonic saline, but the results are not statistically significant. Low statistical power due to the small number of studies may have contributed to this negative finding. A less favorable treatment response among participants with more severe bronchiolitis than among those with less severe disease was also observed in another Cochrane Review which evaluated the efficacy of nebulized epinephrine in infants with viral bronchiolitis (Hartling 2006).

The potential side effects, principally acute bronchospasm, remain a concern with nebulized hypertonic saline. This review included 276 infants receiving 3% saline in repeated doses and no significant adverse events were reported. In six trials (Anil 2010; Grewal 2009; Luo 2010; Mandelberg 2003; Sarrell 2002), the participants 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 broncho constrictive effect. Moreover, the potential benefits of bronchodilators in acute bronchiolitis may also provide the rationale for the combined treatment. 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 participants (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 optimal treatment regime of nebulized hypertonic saline in acute bronchiolitis remains unclear. One outpatient (Sarrell 2002) and four inpatient trials (Kuzik 2007; Luo 2010; Mandelberg 2003; Tal 2006) used multiple daily doses during several days. All five trials demonstrated significant effects of hypertonic saline in reducing length of hospital stay and improving clinical severity score. The most commonly used delivery regime was three times daily at intervals of eight hours (Luo 2010; Mandelberg 2003; Sarrell 2002; Tal 2006), and more frequent deliveries may not yield an additional benefit (Kuzik 2007). In contrast, two emergency department-based trials (Anil 2010; Grewal 2009) used small numbers of inhalations during a short period (up to two inhalations within 120 minutes) and both trials failed to show significant effects of hypertonic saline in improving clinical score/oxygen saturation or in reducing the risk of hospitalization/readmission. These results may suggest that nebulized hypertonic saline is effective for acute bronchiolitis only when the treatment is given at multiple daily doses during a reasonable period of time. However, the optimal treatment regime of nebulized hypertonic saline in infants with viral bronchiolitis still need to be established by further studies.

Overall completeness and applicability of evidence

This review included trials conducted in both high-income and low-income countries and in different settings (inpatient, outpatient and emergency department). Thus evidence derived from this review may have a wide applicability. However, all seven trials included in this review recruited only infants with mild to moderate bronchiolitis, so caution should be taken when extrapolating the findings of this review to patients with more severe bronchiolitis, such as those requiring mechanical ventilation, intensive care

or having an oxygen saturation reading below 85% on room air. The underlying airway pathological changes may differ between severe and mild to moderate bronchiolitis, so different responses to treatments with hypertonic saline may be expected in more severe cases. Further trials are needed to assess the potential effects of nebulized hypertonic saline in infants hospitalized with severe acute bronchiolitis.

Quality of the evidence

All seven included trials are of high methodological quality with low risk of bias. However, some methodological considerations should be mentioned. Firstly, four trials (Anil 2010; Luo 2010; Mandelberg 2003; Tal 2006) did not use an intention-to-treat analysis. 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 participants withdrawn after randomization was small in all these 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 not sufficient for some outcome measures, such as rate of hospitalization and rate of readmission among outpatients or emergency department patients. The small number of studies included in the review also precludes an analytic approach to heterogeneity across studies.

Potential biases in the review process

The strength of this review is that all included trials have high quality and low risk of bias. The main concern regarding potential biases of this review is publication bias. We did not use funnel plots or other analytic approaches to deal with the potential publication bias, given lack of reliable methods and small number of included studies.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there is no other systematic review or traditional narrative review which assesses the efficacy and safety of nebulized hypertonic saline in infants with acute bronchiolitis. We also failed to find observational studies that address this question. This precludes a comparison of findings between this review and other studies.

AUTHORS' CONCLUSIONS

Implications for practice

Nebulized 3% saline produces a 1.2 day reduction in the mean length of hospital stay, compared to nebulized normal saline, among infants hospitalized with non-severe acute bronchiolitis. This therapy also significantly reduces clinical severity score among outpatients and inpatients with mild to moderate 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 mild to moderate acute viral bronchiolitis.

Implications for research

Further large randomized controlled trials, preferably multi-centered, are still required to evaluate the effectiveness of nebulized hypertonic saline in infants with acute viral bronchiolitis, principally in infants who attend the emergency department and infants hospitalized with severe acute bronchiolitis. The optimal delivery intervals, duration of treatment 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 in future studies.

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REFERENCES

References to studies included in this review

Anil 2010 *{published data only}*
Anil AB, Anil M, Saglam AB, Cetin N, Bal A, Aksu N. High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. *Pediatric Pulmonology* 2010;**45**(1):41–7.

Grewal 2009 *{published data only}*
Grewal S, Ali S, McConnell DW, Vandermeer B, Klassen TP. A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Archives of Pediatrics & Adolescent Medicine* 2009;**163**(11):1007–12.

Kuzik 2007 *{published data only}*
Kuzik BA, Al Qaghi SA, Kent S, Flavin MP, Hopman W, Hotte S, et al.Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *Journal of Pediatrics* 2007;**151**:266–70.

Luo 2010 *{published data only}*
Luo Z, Liu E, Luo J, Li S, Zeng F, Yang X, et al.Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. *Pediatrics International* 2010;**52**:199–202.

Mandelberg 2003 *{published data only}*
Mandelberg A, Tal G, Witzling M, Someck E, Houri S, Balin A, et al.Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest* 2003;**123**:481–7.

Sarrell 2002 *{published data only}*
Sarrell EM, Tal G, Witzling M, Someck E, Houri S, Cohen HA, et al.Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. *Chest* 2002;**122**:2015–20.

Tal 2006 *{published data only}*
Tal G, Cesar K, Oron A, Houri S, Ballin A, Mandelberg A. Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. *Israel Medical Association Journal* 2006;**8**:169–73.

References to studies excluded from this review

Amirav 2005 *{published data only}*
Amirav I, Oron A, Tal G, Cesar K, Ballin A, Houri S, et al.Aerosol delivery in RSV bronchiolitis: hood or face-mask?. *Journal of Pediatrics* 2005;**147**(5):627–31.

Guomo 2007 *{published data only}*
Guomo R, Cossettini M, Saretta F, Fasoli L, Guerrera T, Canciani M. Efficacy of hypertonic saline solution in infants with acute bronchiolitis. European Respiratory Journal 2007; Vol. 30, issue Suppl:51, E3016.

Tribastone 2003 *{published data only}*
Tribastone AD. Nebulized 3% saline effective for viral bronchiolitis. *Journal of Family Practice* 2003;**52**(5):359–60.

Additional references

Assouline 1977
Assouline G, Leibson V, Danon A. Stimulation of prostaglandin output from rat stomach by hypertonic solution. *European Journal of Pharmacology* 1977;**44**:271–3.

Bertrand 2001
Bertrand P, Aranibar H, Castro E, Sanchez I. Efficacy of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis. *Pediatric Pulmonology* 2001;**31**(4):284–8.

Daviskas 1996
Daviskas E, Anderson SD, Gonda I, Eberl S, Meikle S, Seale JP, et al.Inhalation of hypertonic saline aerosol enhances mucociliary clearance in asthmatic and healthy subjects. *European Respiratory Journal* 1996;**9**(4):725–32.

Dickersin 1994
Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

Garcia-Garcia 2006
Garcia-Garcia ML, Calvo C, Perez-Brena P, De Cea JM, Acosta B, Casas I. Prevalence and clinical characteristics of human metapneumovirus infections in hospitalized infants in Spain. *Pediatric Pulmonology* 2006;**41**(9):863–71.

Hartling 2006
Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. Epinephrine for bronchiolitis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD003123.pub2]

Henderson 1979
Henderson FW, Clyde WA Jr, Collier AM, Denny FW, Senior RJ, Sheaffer CI, et al.The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *Journal of Pediatrics* 1979;**95**: 183–90.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557–60.

Higgins 2009
Higgins JTP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Jacques 2006
Jacques J, Bouscambert-Duchamp M, Moret H, Carquin J, Brodard V, Lina B, et al.Association of respiratory picornaviruses with acute bronchiolitis in French infants. *Journal of Clinical Virology* 2006;**25**(4):463–6.

Kellett 2005
Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respiratory Medicine* 2005;**99**(1):27–31.

Klassen 1997a
Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. *Pediatric Clinics of North America* 1997;**44**(1):249–61.

Klassen 1997b
Klassen TP, Sutcliffe T, Watters LK, Wells GA, Allen UD, Li MM. Dexamethasone in salbutamol-treated in patients with acute bronchiolitis: a randomized, controlled trial. *Journal of Pediatrics* 1997;**130**:191–6.

Langley 2003
Langley JM, LeBlanc JC, Smith B, Wang EEL. Increasing incidence of hospitalization for bronchiolitis among Canadian children, 1980-2000. *Journal of Infectious Diseases* 2003;**188**:1764–7.

Lowell 1987
Lowell DI, Lister G, Von Kloss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics* 1987;**87**:939–45.

Mandelberg 2010
Mandelberg A, Amirav I. Hypertonic saline or high volume normal saline for viral bronchiolitis: Mechanisms and rationale. *Pediatric Pulmonology* 2010;**45**:36–40.

Meissner 2003
Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. *Pediatric Infectious Disease Journal* 2003;**22**((Suppl 2)):S40–4.

Nasr 2001
Nasr SZ, Strouse PJ, Soskoline E, Maxvold NJ, Garver KA, Rubin BK, et al.Efficacy of recombinant human deoxyribonuclease I in the hospital management of respiratory syncytial virus bronchiolitis. *Chest* 2001;**120**(1):203–8.

Njoo 2001
Njoo H, Pelletier L, Spika L. Respiratory disease in Canada. Ottawa: Canadian Institute for Health Information, Health Canada and Statistics Canada 2001:65–87.

Panitch 1993
Panitch HB, Callahan CW, Schidlow DV. Bronchiolitis in children. *Clinics in Chest Medicine* 1993;**14**(4):715–31.

Panitch 2003
Panitch HB. Respiratory syncytial virus bronchiolitis: supportive care and therapies designed to overcome airway obstruction. *Pediatric Infectious Disease Journal* 2003;**22**(Suppl):83–8.

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
Rakshi K, Couriel JM. Management of acute bronchiolitis. *Archives of Disease in Childhood* 1994;**71**(5):463–9.

RevMan 2008
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Robinson 1997
Robinson M, Hemming A, Regnis J, Wong A, Bailey D, Bautotvich GJ, et al.Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. *Thorax* 1997; **52**(10):900–3.

Rose 1987
Rose RM, Pinkston P, O'Donnell C, Jensen WA. Viral infection of the lower respiratory tract. *Clinical Chest Medicine* 1987;**8**:405–18.

Schuh 1992
Schuh S, Johnson D, Canny G, Reisman J, Shields M, Kovesi T, et al.Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis. *Pediatrics* 1992;**90**:920–3.

Shay 1999
Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis hospitalizations. *JAMA* 1999;**282**(15):1440–6.

Shay 2001
Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis-associated mortality and estimates of respiratory syncitial virus-associated deaths among US children 1979-1997. *Journal of Infectious Diseases* 2001;**183**:16–22.

Shoseyov 1998
Shoseyov D, Bibi H, Shai P, Ahoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. *Journal of Allergy and Clinical Immunology* 1998;**101**(5):602–5.

Wainwright 2003
Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D, et al.A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *New England Journal of Medicine* 2003;**349**:27–35.

Wang 1992
Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *American Review of Respiratory Diseases* 1992; **145**(1):106–9.

Wark 2007
Wark PAB, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD001506.pub2]

Wohl 1978
Wohl MEB, Chernick V. State of the art: bronchiolitis. *American Review of Respiratory Diseases* 1978;**118**:759–81.

Wohl 2003
Wohl ME, Chernick VC. Treatment of acute bronchiolitis. *New England Journal of Medicine* 2003;**349**:82–3.

Zhang 2003
Zhang L, Ferruzzi E, Bonfanti T, Auler MI, Davila NE, Faria CS, et al.Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis. *Journal of Paediatrics and Child Health* 2003;**39**:548–51.

Ziment 1978
Ziment I. *Respiratory pharmacology and therapeutics*. Philadelphia: WB Saunders, 1978.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anil 2010

Methods	Design: randomized, double-blind, parallel-group, controlled trial
Participants	Setting: emergency department of a teaching hospital in Turkey Eligible: 190 Randomized: 75 HS group; 111 NS group Completed: 75 HS group;111 NS group Gender (male): 64.5% Age: mean age 9.5 months, range 1.5 to 24 months Inclusion criteria: infants with diagnosis of bronchiolitis, which required a history of upper respiratory infection and the presence of bilateral wheezing and/or crackles on chest auscultation, plus clinical severity score between 1 and 9 Exclusion criteria: prematurity, any underlying disease (e.g. cystic fibrosis, bronchopulmonary dysplasia and cardiac or renal disease), prior history of wheezing, atopic dermatitis, allergic rhinitis or asthma, oxygen saturation (SaO_2) < 85% on room air, CS score > 9, obtunded consciousness, progressive respiratory failure requiring mechanical ventilation, previous treatment with bronchodilators, and any steroid therapy within 2 weeks
Interventions	Test groups: Group 1: nebulized 3% hypertonic saline (4 ml) plus 1.5 mg of epinephrine Group 2: nebulized 3% hypertonic saline (4 ml) plus 2.5 mg of salbutamol Control groups: Group 3: nebulized 0.9% normal saline (4 ml) plus 1.5 mg of epinephrine Group 4: nebulized 0.9% normal saline (4 ml) plus 2.5 mg of salbutamol Group 5: nebulized 0.9% normal saline (4 ml) alone The study drug was administered at 0 and 30 min by Medic-Aid Sidestream nebulizer (Medic-Aid Ltd., West Sussex, UK) using a face mask with continuous flow of 100% oxygen at 6 L/min
Outcomes	Clinical severity score Oxygen saturation Heart rate Rate of hospitalization Rate of readmission Adverse events
Notes	Virological identification not available

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-based randomization program

Anil 2010 (*Continued*)

Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	4 withdrawals (2 protocol deviation, 2 parents refused to participate in the study)
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Grewal 2009

Methods	Design: randomized, double-blind, parallel-group, controlled trial
Participants	Setting: emergency department of a children's hospital in Canada Eligible: 48 Randomized: 24 HS group; 24 NS group Completed: 23 HS group; 23 NS group Gender (male): 60.9% Age: mean age 5 months, range 6 weeks to 12 months Inclusion criteria: infants presenting with a first episode of wheezing and clinical symptoms of a viral respiratory infection, plus an initial oxygen saturation of 85% or more but 96% or less, and Respiratory Distress Assessment Instrument (RDAI) score >= 4 Exclusion criteria: preexisting cardiac or pulmonary disease, previous diagnosis of asthma by a physician, any previous use of bronchodilators (except for treatment of the current illness), severe disease requiring resuscitation room care, inability to take medication using a nebulizer, inability to obtain informed consent secondary to a language barrier, or no phone access for follow up
Interventions	Test group: nebulized 3% hypertonic saline (2.5 ml) plus 0.5 ml of 2.25% racemic epinephrine Control group: nebulized 0.9% normal saline (2.5 ml) plus 0.5 ml of 2.25% racemic epinephrine Both groups received inhalation solutions at 0 minutes. Each treatment was given by nebulizer with continuous flow of oxygen at 6 L/min. Two doses of the study drug were available for each patient such that, if the physician felt that a second dose of racemic epinephrine was needed during the 120-minute study period, the patient received the same drug combination again
Outcomes	Clinical severity score Oxygen saturation Rate of hospitalization Rate of readmission Adverse events

Grewal 2009 (*Continued*)

Notes	RSV positive: 82.6% in HS group; 81.8% in NS group	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Website randomization scheme
Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	1 withdrawal due to age > 12 months (HS) , 1 inadvertently discharged prior to completion of study period (NS) Intention-to-treat analysis used
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Kuzik 2007

Methods	Design: randomized, double-blind, parallel-group, controlled trial
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, 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

Kuzik 2007 (*Continued*)

	face-mask, or head box, whichever was better tolerated by the infant
Outcomes	Length of hospital stay Treatments received during the study Adverse events
Notes	RSV positive: 62% in HS group; 75% in NS group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-based randomization program
Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	2 patients from HS group and 3 from NS group were withdrawn at parental request because of perceived adverse effects of therapy Intention-to-treat analysis used
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Luo 2010

Methods	Design: randomized, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient wards of a teaching hospital for children in China Eligible: not stated Randomized: 50 HS group; 43 NS group Completed: 50 HS group; 43 NS group Gender (male): 60.2% Age: mean age 5.8 months, range 1 to 16.5 months Inclusion criteria: infants with a diagnosis of mild to moderately severe bronchiolitis Exclusion criteria: 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

Luo 2010 (*Continued*)

Interventions	Test group: nebulized 3% hypertonic saline (4 ml) plus 2.5 mg of salbutamol Control group: nebulized 0.9% normal saline (4 ml) plus 2.5 mg of salbutamol Patients in each group received 3 treatments every day, delivered at intervals of 8 h until discharge using air-compressed nebulizers
Outcomes	Length of hospital stay Duration of symptoms and signs Clinical score Adverse events
Notes	RSV positive: 70% in HS group; 69.7% in NS group

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Unclear	Double-blind
Free of selective reporting?	Yes	

Mandelberg 2003

Methods	Design: randomized, double-blind, parallel-group, controlled trial
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 > 38 °C that lead to hospitalization Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, oxygen saturation < 85% in room air, changes in 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

Mandelberg 2003 (*Continued*)

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, adverse events
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization in blocks of 4, using an on-line randomizer
Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	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)
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Sarrell 2002

Methods	Design: randomized, double-blind, parallel-group, controlled trial
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

Sarrell 2002 (*Continued*)

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, adverse events
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization in blocks of 4, using an online randomizer
Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Unclear	5 patients were withdrawn, but the reasons were not stated Intention-to-treat analysis used
Free of selective reporting?	Yes	
Free of other bias?	Yes	

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
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

Tal 2006 (*Continued*)

	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization in blocks of 4, using an online randomizer
Allocation concealment?	Yes	Sequentially numbered drug containers of identical appearance
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	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
Free of selective reporting?	Yes	
Free of other bias?	Yes	

CS = clinical severity
h = hours
HS = hypertonic saline
NS = normal saline
RDAI = Respiratory Distress Assessment Instrument
RSV = respiratory syncytial virus
SaO_2 = oxygen saturation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amirav 2005	Study of drug delivery (hood versus face-mask)
Guomo 2007	Abstract only
Tribastone 2003	Summary of Sarrell 2002

DATA AND ANALYSES

Comparison 1. 3% saline versus 0.9% saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay (days)	4	282	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.55, -0.77]
2 Clinical severity score (post-treatment) at day 1	4	251	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.52, -0.39]
2.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.92, -0.64]
2.2 Inpatients	3	186	Mean Difference (IV, Random, 95% CI)	-0.82 [-1.59, -0.06]
3 Clinical severity score (post-treatment) at day 2	4	248	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.87, -0.75]
3.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	0.00 [-2.93, -1.07]
3.2 Inpatients	3	183	Mean Difference (IV, Random, 95% CI)	-1.14 [-1.75, -0.53]
4 Clinical severity score (post-treatment) at day 3	4	221	Mean Difference (IV, Random, 95% CI)	-1.31 [-2.01, -0.61]
4.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	-2.64 [-3.85, -1.43]
4.2 Inpatients	3	156	Mean Difference (IV, Random, 95% CI)	-1.07 [-1.69, -0.44]
5 Rate of hospitalization	3	262	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.34, 1.17]
6 Rate of readmission	2	197	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.47, 1.81]

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)

Study or subgroup	3% saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mandelberg 2003	27	3 (1.2)	25	4 (1.9)		19.7 %	-1.00 [-1.87, -0.13]
Tal 2006	21	2.6 (1.4)	20	3.5 (1.7)		16.4 %	-0.90 [-1.86, 0.06]
Kuzik 2007	47	2.6 (1.9)	49	3.5 (2.9)		15.7 %	-0.90 [-1.88, 0.08]
Luo 2010	50	6 (1.2)	43	7.4 (1.5)		48.1 %	-1.40 [-1.96, -0.84]
Total (95% CI)	**145**		**137**			**100.0 %**	**-1.16 [-1.55, -0.77]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.40$, df = 3 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 5.87 (P < 0.00001)

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

Study or subgroup	3% saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Outpatients							
Sarrell 2002	33	4.36 (1.05)	32	5.64 (1.54)		25.9 %	-1.28 [-1.92, -0.64]
Subtotal (95% CI)	**33**		**32**			**25.9 %**	**-1.28 [-1.92, -0.64]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.90 (P = 0.000095)							
2 Inpatients							
Mandelberg 2003	27	7.7 (1.54)	25	7.81 (1.49)		21.3 %	-0.11 [-0.93, 0.71]
Tal 2006	21	6.25 (1.1)	20	7 (1)		25.9 %	-0.75 [-1.39, -0.11]
Luo 2010	50	3.4 (1.2)	43	4.9 (1.7)		26.9 %	-1.50 [-2.11, -0.89]
Subtotal (95% CI)	**98**		**88**			**74.1 %**	**-0.82 [-1.59, -0.06]**
Heterogeneity: Tau^2 = 0.33; Chi^2 = 7.49, df = 2 (P = 0.02); I^2 =73%							
Test for overall effect: Z = 2.11 (P = 0.035)							
Total (95% CI)	**131**		**120**			**100.0 %**	**-0.95 [-1.52, -0.39]**
Heterogeneity: Tau^2 = 0.21; Chi^2 = 8.39, df = 3 (P = 0.04); I^2 =64%							
Test for overall effect: Z = 3.32 (P = 0.00090)							

Analysis 1.3. Comparison 1 3% saline versus 0.9% saline, Outcome 3 Clinical severity score (post-treatment) at day 2.

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 3% saline versus 0.9% saline

Outcome: 3 Clinical severity score (post-treatment) at day 2

Study or subgroup	3% saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Outpatients							
Sarrell 2002	33	2.77 (1.4)	32	4.77 (2.31)		20.1 %	-2.00 [-2.93, -1.07]
Subtotal (95% CI)	**33**		**32**			**20.1 %**	**-2.00 [-2.93, -1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.21 (P = 0.000026)							
2 Inpatients							
Mandelberg 2003	24	6.41 (1.4)	25	6.92 (1.62)		22.2 %	-0.51 [-1.36, 0.34]
Tal 2006	21	5.35 (1.3)	20	6.45 (1)		26.2 %	-1.10 [-1.81, -0.39]
Luo 2010	50	2.2 (1.1)	43	3.8 (1.5)		31.6 %	-1.60 [-2.14, -1.06]
Subtotal (95% CI)	**95**		**88**			**79.9 %**	**-1.14 [-1.75, -0.53]**
Heterogeneity: Tau^2 = 0.17; Chi^2 = 4.70, df = 2 (P = 0.10); I^2 =57%							
Test for overall effect: Z = 3.65 (P = 0.00026)							
Total (95% CI)	**128**		**120**			**100.0 %**	**-1.31 [-1.87, -0.75]**
Heterogeneity: Tau^2 = 0.18; Chi^2 = 6.94, df = 3 (P = 0.07); I^2 =57%							
Test for overall effect: Z = 4.56 (P < 0.00001)							

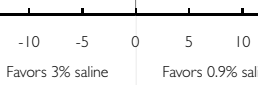
Analysis 1.4. Comparison 1 3% saline versus 0.9% saline, Outcome 4 Clinical severity score (post-treatment) at day 3.

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

Study or subgroup	3% saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Outpatients							
Sarrell 2002	33	1.77 (2.4)	32	4.41 (2.57)		18.4 %	-2.64 [-3.85, -1.43]
Subtotal (95% CI)	**33**		**32**			**18.4 %**	**-2.64 [-3.85, -1.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.28 (P = 0.000019)							
2 Inpatients							
Mandelberg 2003	21	5.81 (1.68)	23	6.08 (2.03)		20.4 %	-0.27 [-1.37, 0.83]
Tal 2006	13	4.7 (1.5)	14	5.72 (1)		22.9 %	-1.02 [-1.99, -0.05]
Luo 2010	45	1.5 (0.5)	40	2.9 (0.7)		38.4 %	-1.40 [-1.66, -1.14]
Subtotal (95% CI)	**79**		**77**			**81.6 %**	**-1.07 [-1.69, -0.44]**
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 4.24$, df = 2 (P = 0.12); $I^2 = 53\%$							
Test for overall effect: Z = 3.36 (P = 0.00079)							
Total (95% CI)	**112**		**109**			**100.0 %**	**-1.31 [-2.01, -0.61]**
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 8.64$, df = 3 (P = 0.03); $I^2 = 65\%$							
Test for overall effect: Z = 3.66 (P = 0.00025)							



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

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 3% saline versus 0.9% saline

Outcome: 5 Rate of hospitalization

Study or subgroup	3% saline n/N	0.9% saline n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Anil 2010	1/75	1/74		5.0 %	0.99 [0.06, 15.48]
Grewal 2009	8/24	13/24		82.4 %	0.62 [0.31, 1.21]
Sarrell 2002	2/33	3/32		12.7 %	0.65 [0.12, 3.62]
Total (95% CI)	**132**	**130**		**100.0 %**	**0.63 [0.34, 1.17]**

Total events: 11 (3% saline), 17 (0.9% saline)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Analysis 1.6. Comparison 1 3% saline versus 0.9% saline, Outcome 6 Rate of readmission.

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 3% saline versus 0.9% saline

Outcome: 6 Rate of readmission

Study or subgroup	3% saline n/N	0.9% saline n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Anil 2010	11/75	11/74		76.3 %	0.99 [0.46, 2.13]
Grewal 2009	3/24	4/24		23.7 %	0.75 [0.19, 3.00]
Total (95% CI)	**99**	**98**		**100.0 %**	**0.92 [0.47, 1.81]**

Total events: 14 (3% saline), 15 (0.9% saline)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 1 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.23 (P = 0.82)

APPENDICES

Appendix 1. Previous search

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.
6 exp Parainfluenza Virus 1, Human/
7 exp Parainfluenza Virus 2, Human/
8 exp Parainfluenza Virus 3, Human/
9 exp Respirovirus Infections/
10 exp Adenoviridae Infections/
11 exp Influenza, Human/
12 (parainfluenza or adenovirus$ or influenza).mp.
13 or/1-12
14 exp Saline Solution, Hypertonic/
15 hypertonic saline.mp.
16 exp Sodium Chloride/
17 saline.mp.
18 or/14-17
19 exp "Nebulizers and Vaporizers"/
20 (nebulis$ or nebuliz$).mp.
21 exp Administration, Inhalation/
22 inhal$.mp.
23 exp Aerosols/
24 aerosol$.mp.
25 or/19-24
26 13 and 18 and 25
27 from 26 keep 1-79

There were no language or publication restrictions.

Appendix 2. Embase.com search strategy

24. #12 AND #16 AND #23
23. #17 OR #18 OR #19 OR #20 OR #21 OR #22
22. aerosol*:ab,ti
21. 'aerosol'/de
20. inhal*:ab,ti
19. 'inhalational drug administration'/de
18. nebuli*:ab,ti OR vapour*:ab,ti OR vapour*:ab,ti OR atomi*:ab,ti
17. 'nebulizer'/exp
16. #13 OR #14 OR #15
15. 'sodium chloride':ab,ti OR saline:ab,ti
14. (hypertonic NEAR/3 (saline OR solution*)):ab,ti
13. 'hypertonic solution'/de OR 'sodium chloride'/de
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11. parainfluenza*:ab,ti OR respirovirus*:ab,ti OR adenovirus*:ab,ti OR rhinovirus*:ab,ti OR influenza*:ab,ti
10. 'influenza virus'/de OR 'influenza virus a'/exp OR 'influenza virus b'/de OR 'influenza'/exp
9. 'rhinovirus infection'/de
8. 'human adenovirus infection'/de
7. 'respirovirus infection'/de
6. 'parainfluenza virus 1'/de OR 'parainfluenza virus 2'/de OR 'parainfluenza virus 3'/de
5. 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti
4. 'respiratory syncytial virus infection'/de
3. 'respiratory syncytial pneumovirus'/de
2. bronchiolit*:ab,ti
1. 'bronchiolitis'/exp

Appendix 3. LILACS search strategy

Mh bronchiolitis or Tw bronchiolit$ or Tw bronquiolit$ or Mh respiratory syncytial viruses or Mh respiratory syncytial virus infections or Tw respiratory syncytial virus infection$ or Tw rsv or Tw virus sincitial respiratorio or Tw virus respiratorio sincicial or Mh parainfluenza virus 1, human or Mh parainfluenza virus 2, human or Mh parainfluenza virus 3, human or Tw parainfluenza$ or Mh respirovirus infections or Tw respirovirus$ or Mh adenovirus infections, human or Tw adenovirus$ or Mh rhinovirus or Tw rhinovirus$ or Mh influenza a virus or Mh influenza b virus or Mh influenza, human or Tw influenza$ or Tw gripe humana [Words] and Mh saline solution, hypertonic or Tw saline or Tw salina or Tw hypertonic or Tw hypertonic$ or Tw solution$ or Tw solucion or Tw solucao or Mh sodium chloride or Tw sodium chloride or Tw cloruro de sodio or Tw cloreto de sodio [Words] and Mh nebulizers and vaporizers or Tw nebuliz$ or Tw vapour$ or Tw vapour$ or Tw atomi$ or Mh aerosols or Tw aerosol$ or Tw aeros$ [Words]

WHAT'S NEW

Last assessed as up-to-date: 6 June 2010.

Date	Event	Description
7 June 2010	New search has been performed	Searches conducted. We included three new trials (Anil 2010; Grewal 2009; Luo 2010) and conducted new analyses. The conclusions remain unchanged.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2008

Date	Event	Description
13 May 2009	Amended	No changes - republished to fix technical problem.
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, the primary review and updated 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 updated 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 the comparison of nebulized hypertonic saline alone versus nebulized 0.9% saline. We also clarified the population according to the age and changed the title to specify infants.

NOTES

We performed post hoc meta-regression in the updated review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Bronchiolitis, Viral [*therapy]; Bronchodilator Agents [administration & dosage]; Nebulizers and Vaporizers; Randomized Controlled Trials as Topic; Saline Solution, Hypertonic [*administration & dosage]

MeSH check words

Humans; Infant