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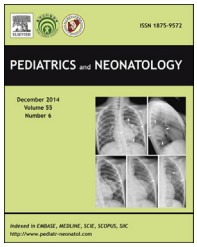

REVIEW ARTICLE

Nebulized Hypertonic Saline Treatment Reduces Both Rate and Duration of Hospitalization for Acute Bronchiolitis in Infants: An Updated Meta-analysis

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Nebulized hypertonic saline (HS) treatment reduced the length of hospitalization in infants with acute bronchiolitis in a previous meta-analysis. However, there was no reduction in the admission rate. We hypothesized that nebulized HS treatment might significantly decrease both the duration and the rate of hospitalization if more randomized controlled trials (RCTs) were included. We searched MEDLINE, PubMed, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) without a language restriction. A meta-analysis was performed based on the efficacy of nebulized HS treatment in infants with acute bronchiolitis. We used weighted mean difference (WMD) and risk ratio as effect size metrics. Eleven studies were identified that enrolled 1070 infants. Nebulized HS treatment significantly decreased the duration and rate of hospitalization compared with nebulized normal saline (NS) [duration of hospitalization: WMD = −0.96, 95% confidence interval (CI) = −1.38 to −0.54, $p < 0.001$; rate of hospitalization: risk ratio = 0.59, 95% CI = 0.37–0.93, $p = 0.02$]. Furthermore, nebulized HS treatment had a beneficial effect in reducing the clinical severity (CS) score of acute bronchiolitis infants post-treatment (Day 1: WMD = −0.77, 95% CI = −1.30 to −0.24, $p = 0.005$; Day 2: WMD = −0.85, 95% CI = −1.30 to −0.39, $p < 0.001$; Day 3: WMD = −1.14, 95% CI = −1.69 to −0.58, $p < 0.001$). There was no decrease in the rate of readmission (risk ratio = 1.08, 95% CI = 0.68–1.73, $p = 0.74$).

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Nebulized HS treatment significantly decreased both the rate and the duration of hospitalization. Due to the efficacy and cost-effectiveness, HS should be considered for the treatment of acute bronchiolitis in infants.
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1. Introduction

Acute bronchiolitis is a viral infection that occurs in children most commonly in the first 2 years of life and is characterized by respiratory symptoms, resulting in wheezing and/or crackles upon auscultation. It is usually a self-limiting illness. However, this condition may be associated with several severe complications, such as apnea, respiratory failure, or secondary bacterial infection.[1,2] The mainstay of treatment in bronchiolitis includes supportive care such as oxygenation and maintenance of hydration.[3]

Theoretically, by absorbing water from the mucosa and sub-mucosa through hyperosmolarity, hypertonic saline (HS) solution has the potential to reduce airway edema and improve the clearance of mucus plugging and thus increase mucociliary transit time inside the bronchiolar lumen.[4,5] A Cochrane review with a meta-analysis of seven trials revealed that nebulized 3% HS significantly reduced the length of hospital stay and improved the clinical severity (CS) score among infants.[6] Nevertheless, there was no significant reduction in the rate of hospitalization. The sample size assessed for admission rate in the Cochrane review was relatively small, including only three trials. We hypothesized that nebulized HS treatment might significantly decrease both the duration and the rate of hospitalization if more randomized controlled trials (RCTs) were included in the published Cochrane review. Therefore, we performed an updated meta-analysis of currently available RCTs and quasi-RCTs to assess the effectiveness and safety of the nebulized HS treatment for acute bronchiolitis in infants.

2. Methods

2.1. Inclusion criteria

RCTs or quasi-RCTs (i.e., those trials with inadequate allocation concealment) that recruited infants younger than 24 months with a diagnosis of acute bronchiolitis were included in this meta-analysis. Acute bronchiolitis was defined as the first episode of wheezing and/or crackles upon auscultation, with clinical symptoms of a viral respiratory infection. Both inpatients and outpatients were included.

2.2. Search strategy

MEDLINE (from 1966 to January 2013), PubMed (from 1966 to January 2013), and CINAHL (from 1982 to January 2013) databases were searched to identify RCTs. The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. The following medical subject heading terms and text words were used: (bronchiolitis OR acute wheezing OR respiratory syncytial virus OR RSV) AND (HS OR 3% saline OR 5% saline) AND (nebulized OR inhaled OR aerosol). We restricted the search to human studies and no language restrictions were applied. Additional information was retrieved via a manual search of references from recent reviews and relevant published original studies.

2.3. Data extraction

Two reviewers (Y.-J. Chen and W.-L. Lee) independently reviewed each reference which was identified through the search, scanned the full texts of relevant studies, applied the inclusion criteria, and extracted data separately on a data abstraction form. The reviewers extracted data on the baseline characteristics of the included trials, the studied drugs and their doses, the use of placebo or no treatment, follow-up and loss of follow-up. The primary outcomes of interest were the rate of hospitalization, the duration of hospital stay, the rate of readmission, and the CS score.[7] This scoring system assesses respiratory rate, wheezing, retraction, and general condition by assigning a number from 0 to 3 to each variable, with increased severity receiving a higher score. One review author (H.-H. Chou) entered data into Review Manager (RevMan) version 5.0 statistical software (Cochrane Collaboration, Oxford, UK; RevMan 2009) and the other two authors (Y.-J. Chen and W.-L. Lee) cross-checked the printout against their own data abstraction forms.

2.4. Subgroup analysis

We performed exploratory subgroup analyses according to the source of recruitment of participants (outpatient or inpatient). The treatment regimen, including the concentration, volume, and frequency of administered saline, concomitantly inhaled medication and the duration of treatment, which may contribute to heterogeneity in the meta-analysis, were analyzed.

2.5. Quality assessment of included studies

The quality of reporting of all included RCTs was determined according to the Cochrane Collaboration Risk of Bias instrument.[8] We assessed the risk of bias using a domain-based evaluation, classifying studies primarily according to their risk of non-random allocation of patients in the intervention arm (sequence generation) and the concealment of this process (allocation concealment). Additionally, blinding, incomplete outcome data, and intention-to-treat analysis were assessed. Disagreements were resolved via discussions among the authors.

Table 1 Characteristics of the included studies.

Study/year	No. of patients	Setting	Inclusion criteria	Intervention	Primary outcome
Sarrell et al 2002[10]	65	Outpatient	Age ≤ 24 mo; mild-to-moderate viral bronchiolitis	Terbutaline 5 mg + 3% HS 2 mL Q8h for 5 days	CSS, RA score, AR
Mandelberg et al 2003[11]	52	Inpatient	Age ≤ 12 mo; viral bronchiolitis that leads to hospitalization	Epinephrine 1.5 mg + 3% HS 4 mL Q8h until discharge	LOS, change in CSS, RA score, number of add-on treatments
Tal et al 2006[12]	41	Inpatient	Age ≤ 12 mo; viral bronchiolitis that leads to hospitalization	Epinephrine 1.5 mg + 3% HS 4 mL Q8h until discharge	CSS, LOS
Kuzik et al 2007[13]	96	Inpatient	Age ≤ 18 mo; moderately severe viral bronchiolitis + RDAI score ≥ 4	3% HS 4 mL Q2h for 3 doses, Q4h for 5 doses, Q6h until discharge	LOS, treatment received during study
Grewal et al 2009[14]	46	ED	Age 6 wk—12 mo; mild-to-moderate bronchiolitis with SpO2 85—96% + RDAI score ≥ 4	2.25% epinephrine 0.5 mL + 3% HS 2.5 mL at 0 and 120 min (if needed)	Change in RDAI score, SpO2, AR, readmission rate
Anil et al 2010[16]	186	ED	Age 6 wk—24 mo; mild bronchiolitis with CSS 1—9	- epinephrine 1.5 mg + HS 4 mL at 0, 30 min - salbutamol 2.5 mg + HS 4 mL at 0, 30 min	CSS, SpO2, HR, AR, readmission rate
Al-Ansari et al 2010[15]	171	Short stay unit of ED	Age ≤ 18 mo; moderately severe viral bronchiolitis with CSS ≥ 4	- epinephrine 1.5 mL + 3% HS 3.5 mL Q4h until discharge - epinephrine 1.5 mL + 5% HS 3.5 mL Q4h until discharge	CSS, SaO2, HR
Kuzik et al 2010[17]	88	4 hospitals (3 in ED, 1 in outpatient center)	Age ≤ 24 mo; moderately severe viral bronchiolitis with SaO2 ≤ 94% + RDAI score ≥ 4	Salbutamol 1 mg + HS 4 mL every 20 min for 3 doses	Change in RDAI score, AR, AR within 7 days, unscheduled physician visits within 7 days
Luo et al 2010[18]	93	Inpatient	Age ≤ 24 mo; hospitalized with mild to moderate bronchiolitis (CSS < 9)	Salbutamol 2.5 mg + HS 4 mL Q8h until discharge	Duration of wheezing and cough, LOS, CSS
Ipek et al 2011[19]	120	ED	Age 1 mo—2 y, viral bronchiolitis with CSS 4—8	- Salbutamol 0.15 mg/kg + HS 4 mL every 20 min for 3 doses - HS 4 mL every 20 min for 3 doses	Change in CSS, corticosteroid need, AR, CSS
Luo et al 2011[20]	112	Inpatient	Age ≤ 24 mo; hospitalized with moderate to severe bronchiolitis (CSS > 5)	3% HS 4 mL Q2h for 3 doses, Q4h for 5 doses, Q6h until discharge	Time for relief of wheezing, cough, LOS, CSS

The data are presented as mean ± standard deviation, unless stated otherwise.
AR = admission rate; CSS = clinical severity score; ED = emergency department; HR = heart rate; HS = hypertonic saline; LOS = length of hospital stay; NS = normal saline; Q2/4/8h = every 2/4/8 hours; RA = radiograph assessment; RDAI = respiratory distress assessment instrument; SpO2 = oxygen saturation.

Table 2 Summary of risk bias assessment.

Study/year	Adequate sequence generation	Allocation concealment	Blinding of outcome measurement	Baseline comparability	Intention-to-treat analysis
Sarrell et al 2002[10]	Yes	Yes	Yes	Yes	Yes
Mandelberg et al 2003[11]	Yes	Yes	Yes	Yes	No
Tal et al 2006[12]	Yes	Yes	Yes	Yes	No
Kuzik et al 2007[13]	Yes	Yes	Yes	Yes	No
Grewal et al 2009[14]	Yes	Yes	Yes	Yes	Yes
Anil et al 2010[16]	Yes	Yes	Yes	Yes	No
Al-Ansari et al 2010[15]	Yes	Yes	Yes	Yes	Yes
Kuzik et al 2010[17]	Yes	Yes	Yes	Yes	Yes
Luo et al 2010[18]	Yes	Yes	Yes	Yes	No
Ipek et al 2011[19]	Yes	No	Yes	Yes	Yes
Luo et al 2011[20]	Yes	Yes	Yes	Yes	No

2.6. Statistical analyses

The primary outcomes of interest were the duration and the rate of hospitalization. Continuous outcomes were pooled as a weighted mean difference (WMD), which we expressed as a standardized mean difference due to the variations in measurements. The differences in means and their 95% confidence intervals (CIs) at the end of treatment were calculated for each trial, and the WMD was used as a summary estimator. Dichotomous outcome data from individual trials were analyzed using the relative risk measure. A random-effects model was used, followed by a test for homogeneity. The p values were two-sided, with significance set at $p < 0.05$. We assessed the p value of the χ^2 test to determine heterogeneity and I^2 to measure inconsistency. We regarded heterogeneity as "not important" when the I^2 value was $< 40\%$ and as "considerable" when the I^2 value was $> 75\%$.[8] All statistical analyses for the meta-analysis were performed using RevMan 5.0 (Cochrane Collaboration). The potential for publication bias was examined using the funnel plot method.

3. Results

We identified 66 citations in MEDLINE, PubMed, CINAHL, and CENTRAL databases, and by manual searches of relevant journals. Of these, 15 were review articles, case series, or basic science papers. In total, 39 dealt with non-relevant outcomes. One trial was excluded for including preschool children with or without a previous wheezing history.[9] Eleven RCTs, with a total of 1070 patients meeting the inclusion criteria were included in this analysis.[10–20] Of the 1070 patients, 552 patients who received nebulized HS (either 3% or 5% saline) were assigned to the treatment group and 518 patients who received nebulized NS were assigned to the control group. Details regarding the interventions, the baseline characteristics of the populations, age and birth body weight, the HS dosage and duration, the use of additional medication or not, and the primary outcome of each RCT are summarized in Table 1. All 11 studies were double-blind RCTs. Six trials recruited outpatient or emergency department participants, and five trials recruited inpatients. Patients with previous wheezing episodes were excluded in all trials, except one study reported viral bronchiolitis patients either with or without wheezing history.[17] Patients with severe bronchiolitis, oxygen saturation $< 85\%$ on room air, or respiratory failure requiring mechanical ventilation were also excluded from all trials. The concentration of HS was 3% in all trials except for one trial that used both nebulized 5% HS and 3% NS as the treatment group in comparison with NS as the control group.[15] Bronchodilators (terbutaline, salbutamol, or albuterol) were added to the inhalation solution in six studies, five used epinephrine, and no additional medication was used in two studies. The duration of treatment varied from 30 minutes to 5 days among outpatients and emergency department participants. For inpatients, the treatment was delivered until discharge. Virological identification was reported in nine trials and the positive respiratory syncytial virus (RSV) rate varied from 42% to 87%. The risk of bias assessments is described in Table 2. All included trials had high methodological quality and a low risk of bias. Blinding of the intervention was found in all trials. The methods of randomization were adequate in all trials except one, in which all patients were randomly assigned to one of four groups according to the consecutive order of their admission to the short stay unit of the emergency department,[19] rather than by random number sequence generation. Blinding of the caregivers and investigators and allocation concealment might not have been adequate in this trial.

3.1. Effects on duration of hospitalization

Six RCTs provided data regarding the duration of hospitalization in both the treatment and the control groups.[11–13,15,20] The pooling of all data revealed that infants treated with nebulized HS had a statistically significantly shorter duration of hospitalization compared with infants treated with nebulized NS (WMD $= -0.96$; 95% CI $= -1.38$ to -0.54; $p < 0.001$; 6 studies, 565 infants, heterogeneity $\chi^2 = 16.19$; $p = 0.01$; $I^2 = 63\%$, Figure 1).

3.2. Effects on rate of hospitalization

Five RCTs assessed the efficacy of nebulized HS in reducing the risk of hospitalization in a total of 430 patients.[10,14,16,17,19] Overall, nebulized HS treatment

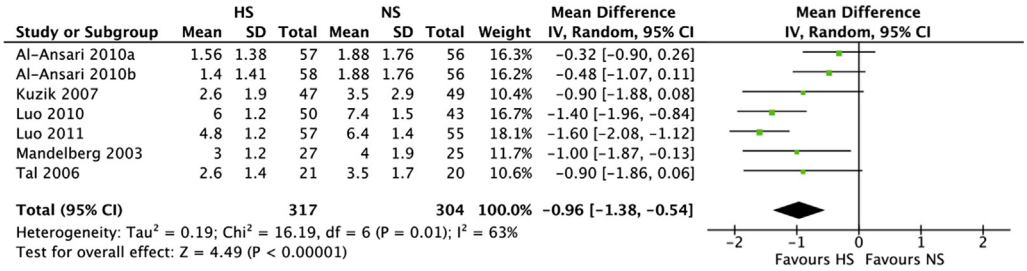

Figure 1 The effects of nebulized hypertonic saline treatment compared with normal saline on the duration of hospitalization (days).

demonstrated a beneficial effect on reducing the rate of hospitalization compared with the control (risk ratio = 0.59; 95% CI = 0.37–0.93; $p = 0.02$; 5 studies; heterogeneity $\chi^2 = 0.46$; $p = 0.98$; $I^2 = 0\%$, Figure 2).

3.3. Effects on rate of readmission

Three emergency department trials provided data regarding the rate of readmission as an outcome.[14–16] The pooling of all data did not demonstrate any significant difference in the rate of readmission among infants treated with nebulized HS compared to those treated with nebulized NS (risk ratio = 1.08; 95% CI = 0.68–1.73; $p = 0.74$; 3 studies, 366 infants, heterogeneity $p = 0.88$; $I^2 = 0\%$, Figure 3).

3.4. Effects on CS score

Eight trials used the CS score as an outcome. Six of these trials compared the post-inhalation CS score between infants treated with nebulized HS and infants treated with nebulized NS during the first 3 days of treatment.[10–12,15,18,20] The baseline CS scores were comparable between the two groups in all six trials. On the 1st post-treatment day, infants treated with nebulized HS had a significantly lower CS score compared with infants treated with nebulized NS in both outpatient and inpatient trials (pooled WMD = −0.77; 95% CI = −1.31 to −0.24; $p = 0.005$; 6 studies, 534 infants, heterogeneity $p < 0.001$; $I^2 = 83\%$, Figure 4A). On the 2nd day of treatment, a significant difference between the treatment and the control groups was observed (pooled WMD = −0.85; 95% CI = −1.30 to −0.39; $p < 0.001$; 6 studies, 531 infants, heterogeneity $p < 0.001$; $I^2 = 79\%$, Figure 4B). On the 3rd day of treatment, the pooled results from five trials still demonstrated a lower post-inhalation CS score in the treatment group compared to the control group, with a WMD of −1.36 (95% CI = −1.70 to −1.02; $p < 0.001$, 333 infants, heterogeneity $p = 0.07$; $I^2 = 54\%$, Figure 4C).

3.5. Sensitivity analysis and publication bias

A sensitivity analysis was used to assess whether the methodological quality of the trials may have affected the results of the meta-analysis. The substitution of the random-effects model with the fixed model did not change our initial qualitative interpretation of the pooled treatment effects on all outcomes. Furthermore, the removal of studies with small patient numbers or a short intervention period did not alter the results regarding the effects of HS compared with NS on the duration of hospitalization and the rate of readmission. There was no evidence of publication bias as the funnel plots exhibited symmetric patterns by visual inspection for all outcome measures.

4. Discussion

Our meta-analysis shows that nebulized HS significantly decreased the duration of hospital stay by approximately 1 day compared with nebulized NS in infants hospitalized with acute bronchiolitis. This treatment also significantly reduced the rate of hospitalization among outpatients and the CS score among outpatients and inpatients with mild-to-moderate acute bronchiolitis. The risk of readmission was not different between infants treated with nebulized HS and NS.

A previous meta-analysis indicated that nebulized HS might significantly reduce the length of hospital stay among infants hospitalized with non-severe acute viral bronchiolitis and improve the CS score in both outpatient and inpatient populations.[6] However, there was no significant reduction in the rate of hospitalization in the previous

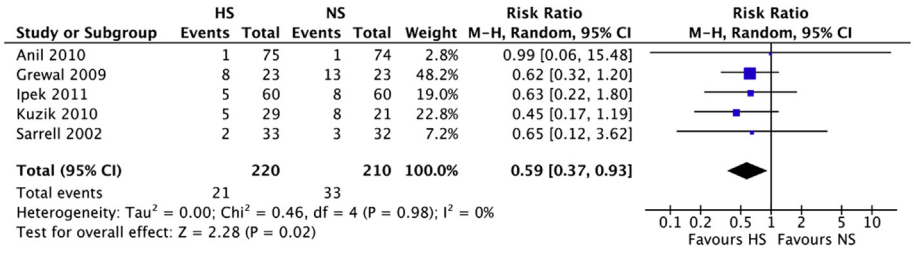

Figure 2 The effects of nebulized hypertonic saline treatment compared with normal saline on the rate of hospitalization.

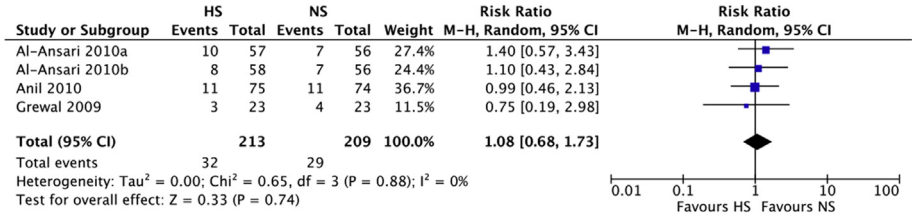

Figure 3 The effects of nebulized hypertonic saline treatment compared with normal saline on the rate of readmission.

study. Because there were only three trials included in the meta-analysis on the rate of hospitalization, low statistical power due to small sample sizes may have played a role in this negative result. By adding two more recent trials with a total of 432 patients, our updated meta-analysis showed a 41% reduction in the rate of hospitalization among patients treated with HS inhalation compared with patients treated with NS inhalation, which is consistent with the pooled

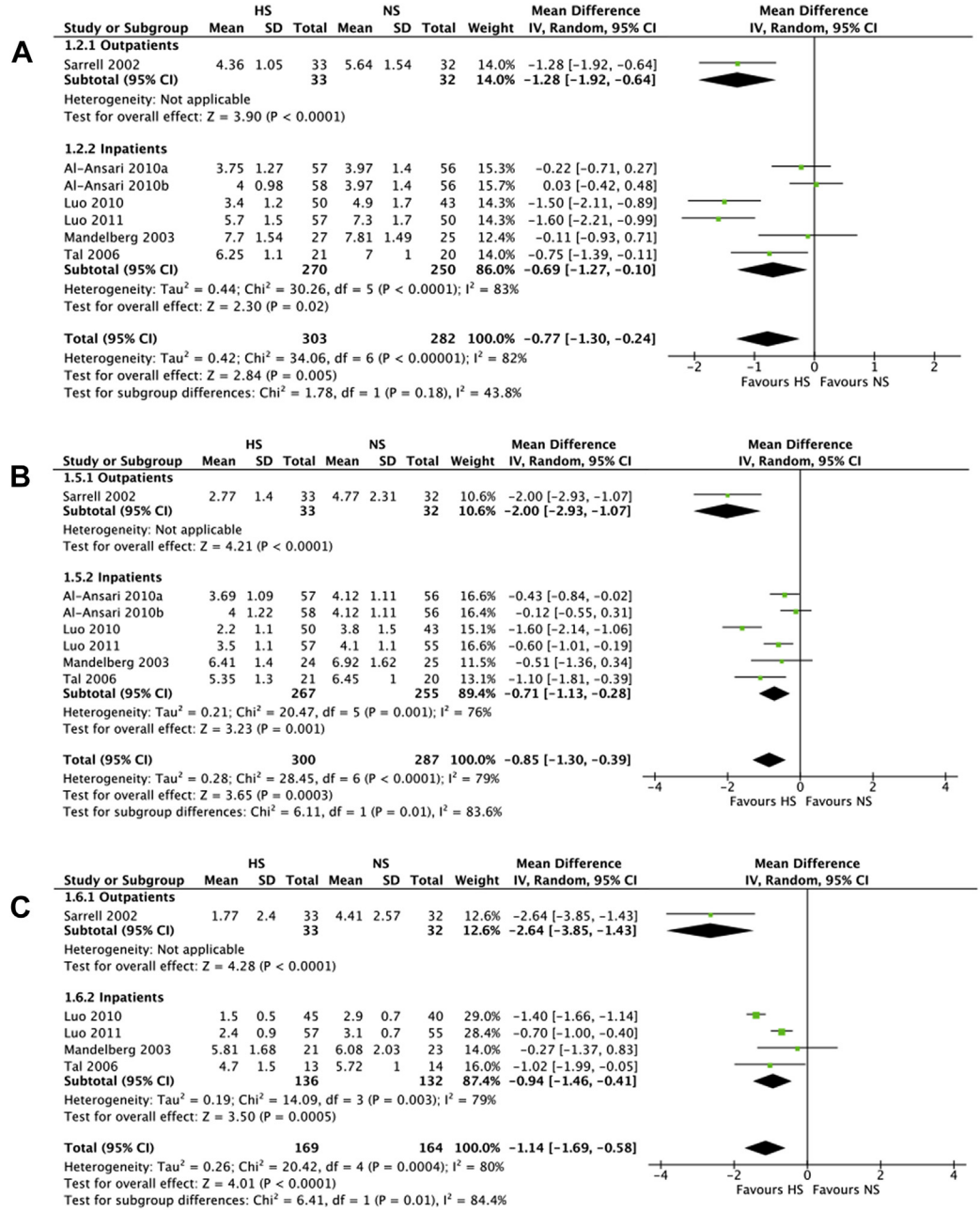

Figure 4 The effects of nebulized hypertonic saline treatment compared with normal saline on the clinical severity score on post-treatment (A) Day 1, (B) Day 2, and (C) Day 3.

result reported by the previous meta-analysis. There was no significant heterogeneity in results between included studies (I^2 statistic = 0%). Furthermore, after the removal of one trial with inadequate randomization and allocation concealment,[19] the pooled results of the remaining four trials still demonstrated the superiority of nebulized HS in reducing the rate of hospitalization. We believe that our updated meta-analysis, with more trials and larger sample sizes with better statistical power, make the conclusion of the beneficial effect of nebulized HS treatment more sufficiently persuasive. Given the high prevalence and morbidity of acute bronchiolitis in infants and the economic burden on the health care system, the superiority of nebulized HS in reducing both the rate and the duration of hospitalization should be considered in the treatment of this commonly observed disease.

The pathophysiology of acute bronchiolitis is characterized by acute inflammation, submucosal edema and necrosis of epithelial cells lining small airways, diminished mucus clearance due to dehydration of the airway surface, increased mucus production, and bronchospasm.[3] Thus, treatments to maintain hydration of the mucosal surface and to decrease submucosal edema are crucial in acute bronchiolitis patients. Theoretically, nebulized HS may improve not only the hydration of the airway surface, but also the absorption of water from the mucosa and submucosa through hyperosmolarity,[21] which result in hydration of the mucosal surface, decreased submucosal edema, and improvement of the rheological properties of the mucus, thereby improving mucus clearance.[22]

The participants in the included trials received saline inhalation in conjunction with variable medication, including bronchodilators, epinephrine, or no medication. Inhaled bronchodilators and epinephrine are widely used and studied in the treatment of acute bronchiolitis. However, the published results are variable and the efficacy is uncertain. A Cochrane meta-analysis of RCTs provided little evidence of benefit from bronchodilator inhalation in infants with acute bronchiolitis.[23] Another meta-analysis compared nebulized epinephrine with placebo and revealed that epinephrine decreased admissions within 24 hours of administration, but it did not affect admission within 1 week or the length of hospital stay.[24] Moreover, a recent multi-center, double-blind randomized trial evaluated the efficacy of inhaled racemic adrenaline in moderate-to-severe acute bronchiolitis.[25] The length of hospital stay and improvement in the CS score were similar in the infants treated with inhaled racemic adrenaline and the infants treated with placebo. The authors concluded that inhaled racemic adrenaline was not more effective than inhaled NS. Moreover, either bronchodilators or epinephrine was used at the same dose with the same schedule in both the treatment and the control groups in the included studies. The only difference in treatment modality between each treatment group and each control group was the concentration of nebulized saline. Given all of the above reasons, we believe that nebulized HS is beneficial in decreasing both the rate and the duration of hospitalization in infants with acute bronchiolitis.

The main limitation of our study is related to the quality of the available RCTs. As previously mentioned, most of the included trials are of high methodological quality and have a low risk of bias. However, intention-to-treat analysis was not used in six trials. This analysis strategy includes every individual who is randomized according to randomized treatment assignment and maintains prognostic balance generated from the original random treatment allocation. Given the small percentage of participants withdrawn after randomization in the six trials, ranging from 4.8% to 17.3% of all participants, we believe that the lack of application of intention-to-treat analysis was unlikely to have caused significant bias. Furthermore, the sample size of the included trials was generally small. As more RCTs have been published in recent years, this updated meta-analysis should provide more solid evidence on the relevant outcome measures of acute bronchiolitis in infants.

In conclusion, our meta-analysis demonstrates that nebulized HS therapy not only reduces the duration of hospitalization for acute bronchiolitis in infants, but also is beneficial in decreasing the rate of admission. Due to the efficacy and cost-effectiveness of the treatment, nebulized HS should be considered in clinical practice for the treatment of acute bronchiolitis in infants. Further RCTs are warranted to address the optimal treatment regimen of nebulized HS in infants with acute bronchiolitis.

Conflicts of interest

All authors declare no conflicts of interest.

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