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REVIEW

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Effects of nebulized epinephrine in association with hypertonic saline for infants with acute bronchiolitis: A systematic review and meta-analysis

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Abstract

Background: Nebulized epinephrine and hypertonic saline have been extensively studied in infants with acute bronchiolitis, with conflicting results.

Aims: To evaluate the efficacy on length of stay (LOS), clinical severity scores (CSS), oxygen saturation (SaO_2), and safety profile of nebulized epinephrine plus hypertonic saline (HS) in infants with acute bronchiolitis.

Materials & Methods: This is a systematic review and meta-analysis. Outcomes were represented by mean differences (MD) or standard mean differences (SMD) and 95% confidence intervals (CIs) were utilized.

Results: Eighteen trials were systematically selected and 16 of them contributed to the meta-analysis (1756 patients). Overall, a modest but significant positive impact was observed of the combination therapy on LOS (MD of −0.35 days, 95% CI −0.62 to −0.08, $p = 0.01$, $I^2 = 91\%$). Stratification by time of CSS assessment unveiled positive results in favor of the combination therapy in CSS assessed 48 and 72 h after the admission (SMD of −0.35, 95% CI −0.62 to −0.09, $p = 0.008$, $I^2 = 41\%$ and SMD of −0.27, 95% CI −0.50 to −0.04, $p = 0.02$, $I^2 = 0\%$, respectively). No difference in SaO_2 was observed. Additional data showed a consistent safety profile, with a low rate of adverse events (1%), most of them mild and transient.

Conclusion: Low-quality evidence from this systematic review suggests that nebulized epinephrine plus HS may be considered as a safe and efficient therapy for decreasing LOS and CSS in infants with acute bronchiolitis, especially in those who require hospitalization for more than 48 h.

KEYWORDS

adrenaline, child, hypertonic, saline solution

1 | INTRODUCTION

Acute bronchiolitis is described as an illness in infants characterized by acute wheezing with concomitant signs of respiratory viral infection.[1] Population-based data show the significant burden of the disease, as acute bronchiolitis accounts for an important cause of visits to primary care offices, emergency departments, rates of hospitalization, and deaths.[2] Respiratory syncytial virus is the most common etiologic agent of acute bronchiolitis, and the disease manifests clinically as coryza, cough, fever, tachypnoea, wheezing, and signs of respiratory distress.[3]

Currently, the treatment of bronchiolitis remains to be controversial. Most of the clinical practice guidelines recommend supportive care, with no specific effective therapies due to a lack of strong evidence-based data.[4] Management includes supplemental oxygen if required, adequate hydration, and mechanical ventilatory support when needed.[4]

Although commonly prescribed, antibiotics, beta-adrenergic drugs and corticosteroids have minimal or no clinical benefit as shown by systematic reviews.[5–8] Other pharmacological and non-pharmacological interventions have been proposed, such as high-flow oxygen nasal cannula therapy, chest physiotherapy, and magnesium sulfate. However, no substantial improvement has been demonstrated with such treatments.[9–11]

Nebulized epinephrine has been studied in acute bronchiolitis patients since 70s.[12] In theory, epinephrine may cause vasoconstriction and reduction of airway edema, due to its alpha and beta-adrenergic properties.[13] Nebulized hypertonic saline (HS) has also been used for infants with acute bronchiolitis for decades. Data from early 2000s suggested that HS nebulization may induce an osmotic flow of water into the mucus layer, thus rehydrating the airway surface liquid and improving mucociliary clearance, as well as reducing airway edema by absorbing water from the mucosa and submucosa.[14]

Both therapies have been assessed independently by meta-analyses.[7,15–17] However, so far, no meta-analysis investigated the combined strategy. Epinephrine and HS may act synergically on bronchodilatation, vasoconstriction, and reduction of bronchial edema which could result in clinical improvement. Epinephrine plus HS may offer a low-cost and widely feasible therapy for patients with bronchiolitis.

This systematic review and meta-analysis aimed to evaluate the efficacy of nebulized epinephrine plus HS on length of hospital stay (LOS), clinical severity score (CSS), and oxygen saturation (SaO_2) in infants with acute bronchiolitis.

2 | MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct and report this review. The review protocol was registered in PROSPERO (International prospective register of systematic reviews) in November 2020. (PROSPERO 2020 CRD42020211518, Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020211518. There are two major differences between the review protocol and the final review: (1) We replaced regional databases (SciELO and LILACS) with international databases (EMBASE, Cochrane Central Register of Controlled Trials and Google Scholar) for search and (2) added SaO_2 as an outcome, but excluded rate of hospitalization and (due to lack of data in the majority of studies).

2.1 | Search strategy and study selection

We searched PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Google Scholar. Ongoing trials were searched on ClinicalTrials.gov. Basically, the following combination of keywords was used as a search strategy: [("epinephrine" OR "adrenaline") OR ("saline solution, hypertonic")] AND ("bronchiolitis"). For a detailed search strategy please see Box S01.

All databases were searched from their inception until February 2021. No restriction on language or date of publication was settled. We checked reference lists of all primary studies and review articles for additional relevant trials.

Inclusion and exclusion criteria were defined a priori. Studies were included if they met the flowing PICOS criteria: (1) Population: Children up to 24 months of age clinically diagnosed with acute bronchiolitis (with or without viral confirmation of Respiratory Syncytial Virus); (2) Intervention: Nebulization of HS (defined as a concentration of saline greater than or equal to 3%) plus epinephrine (in any concentration); (3) Comparison: 0.9% normal saline or monotherapy with HS or epinephrine; (4) Outcomes: LOS, CSS, or SaO_2 (primary or secondary); and (5) randomized controlled trials (RCTs).

Two authors (RP and MZ) independently screened the titles and abstracts identified by the searches, and those which met the eligible criteria were selected for the full-text review. Any differences between the two reviewers were resolved through a third independent author (VA). The selected full-text articles were further evaluated by two independent authors (RP and MZ), and the studies were definitively included in the review when they met all the inclusion criteria. Any disagreement was resolved by a third independent author (VA).

2.2 | Assessment of risk of bias

The risk of bias of RCTs was examined by two independent authors (RP and MZ) using the Cochrane Risk-of-Bias Tool for randomized trials 2.0.[18] Each outcome of the studies was evaluated independently on five key domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. At the end, the

outcome overall bias was achieved, being graded as "low risk of bias," "some concerns," or "high risk of bias." Disagreements were resolved by a third author judgment (VA).

2.3 | Extraction and management of data

Outcome data were extracted from included trials by one review author (RP) and entered into the Review Manager 5.4.[19] A second review author (MZ) double-checked the extracted data. We resolved disagreements by reaching a consensus.

Management of data and meta-analysis was performed using Review Manager 5.4.[19] In five trials,[20–24] multiple groups were recruited, so we pooled data to create two groups: "Hypertonic saline plus epinephrine group" versus "Control group." In three studies,[23,25,26] standard deviation (SD) and mean were calculated from values of interquartile range and median respectively, using methods described elsewhere.[27] We transformed the unit of measure hours into days in three studies[22,28,29] to standardize variables. Three different scores were used to assess clinical severity among trials; therefore, the standard mean difference was chosen as an effect of the measure. In two trials,[22,30] data was extracted from graphs using the program WebPlotDigitizer.[31] SD numerical values were missing for CSS and could not be obtained from the authors in three studies.[22,28,32] To include these trials, the most conservative statistical method was chosen for imputation, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[33] Special care was taken for reporting findings from outcome data collected at more than one point to avoid participant double-counting.

2.4 | Data synthesis and statistical analysis

We conducted meta-analysis using random-effects models, and mean differences or standard mean differences were calculated between groups with corresponding 95% confidence intervals (CIs). Heterogeneity was tested using the I^2 statistic, which ranges from 0% to 100%. Values greater than 50% indicate substantial heterogeneity.

Subgroup analyses were performed to determine whether the observed associations were modified by intrinsic factors. Subgroup analyses were considered according to a type of comparison (isolated HS/Epinephrine or 0.9% saline), patient's upper age limit, study setting, and points of outcome measurements.

At last, one review author (RP) performed an assessment of the certainty of the evidence for each outcome using the GRADE approach, classifying it as high certainty (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low certainty (we are very uncertain about the estimate).

3 | RESULTS

3.1 | Literature search and study selection

Figure 1 shows the flow diagram of study selection. 1900 articles were identified by the search strategy described previously. After duplicates were removed, 1450 articles were screened on basis of titles and abstracts. Of these, more 14 duplicates were found, and 1058 articles were excluded, then 378 articles were fully assessed for eligibility. After that, 315 articles did not meet inclusion criteria, 30 were duplicates and full texts were not available in 15 studies. Thus, a total of 18 studies were included in the systematic review, and all but two studies[34,35] (11,1%) contributed to the meta-analysis, totalizing 1756 patients in the quantitative synthesis. Both excluded trials lacked outcome data.

Among all 18 trials, 10 (55.5%) evaluated outpatients and 8 (44.5%) inpatients. Dates of publication varied from 2003 to 2020, being 5 of them (27%) published between 2016 and 2020. Nebulizations were administered in several regimens, and concentrations and compared with different control groups; most of them used 0.9% saline or monotherapy with HS or epinephrine. All selected studies excluded patients that required intensive care measures or had prior chronic comorbidities (including a history of prior wheezing episodes) on enrollment. Table 1 summarizes the characteristics of included studies, including information about adverse events.

Risk of bias was assessed by analyzing each outcome individually, as shown in Figures 2A–C. Most of the studies had minor issues in one or two domains, so they were classified as "Some Concerns" in overall bias. A high risk of bias was identified in three studies.[29,38,39] These studies contributed to 12.8% of the total data analyzed for LOS outcome, 20.8% for CSS outcome, and 45.3% for SaO_2 outcome.

Also, in Figure 3A,B, WE can see the funnel plots of LOS and CSS outcomes, indicating no significant publication bias in both outcomes, confirmed by Egger's test ($p = 0.25$ and $p = 0.33$ for LOS and CSS, respectively). SaO_2 analysis included six studies, thus publication bias was not assessed through funnel plots.

3.2 | Effects of interventions

3.2.1 | Length of stay in hospital/ED

Thirteen trials[20–23,25,26,28–30,32,36,38,40] were included in the meta-analysis to evaluate LOS, totalizing 1547 patients. Trials that included outpatients in LOS analysis[20,23,28,29,38] assessed this outcome as: (1) Time between admission and discharge in the emergency department or (2) time between admission in the emergency department and discharge after subsequent hospitalization. LOS was defined as a primary outcome in eight studies. Pooled results indicate an overall positive effect of the combination of nebulized epinephrine and HS compared with the control group (MD of −0.35 days, 95% CI −0.62 to −0.08, $p = 0.01$). There was significant heterogeneity among studies (I^2 statistic = 91%). Figure 4 represents the overall LOS forest plot.

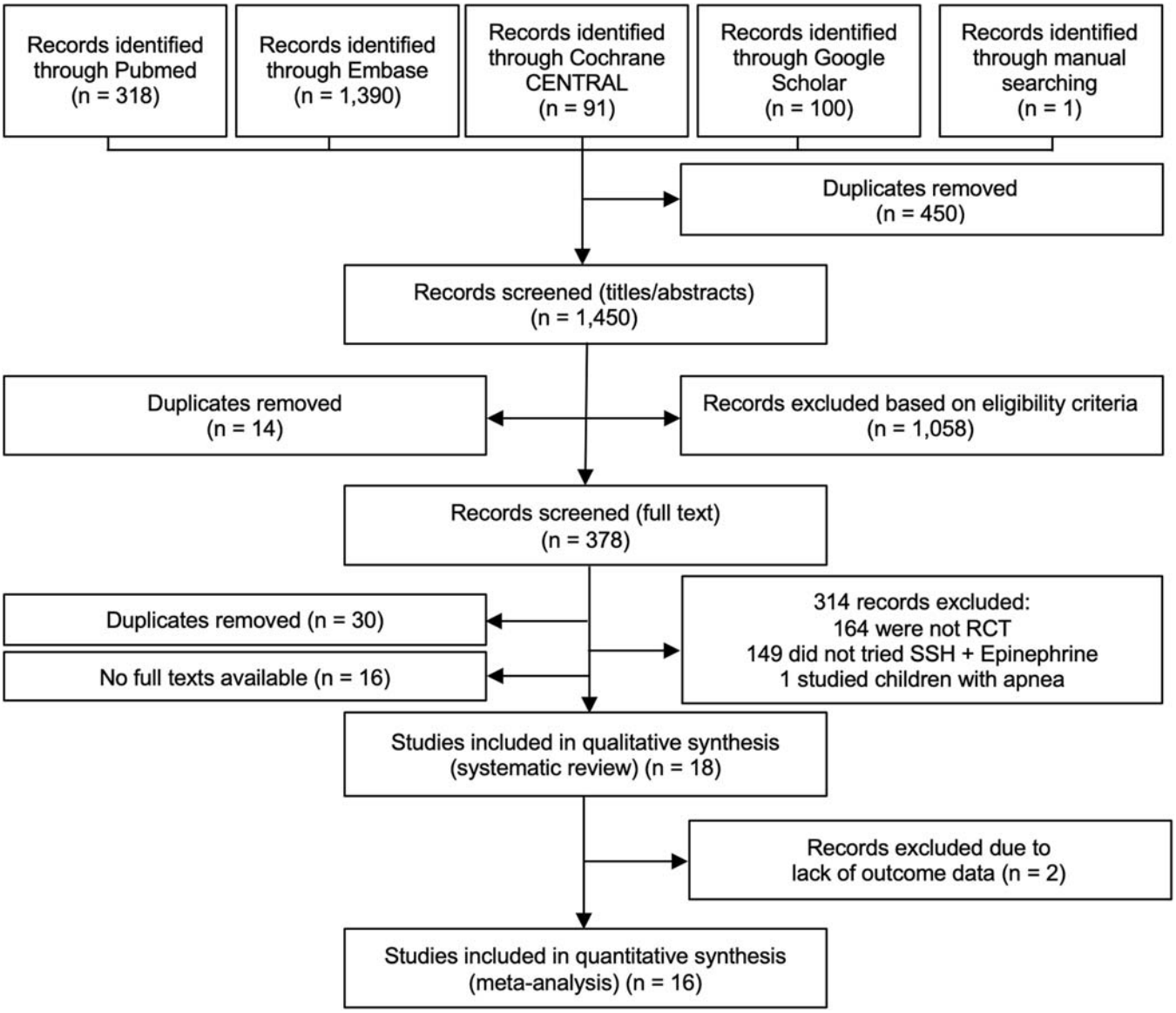

FIGURE 1 Flow diagram of study selection.

Table 2 shows subgroup analyses of LOS outcomes, based on type of control solution (epinephrine, HS, or 0.9% saline), type of patients (inpatients or outpatients), and upper age limits of patients (6, 12, 18, or 24 months). Only the subgroup analysis of four trials involving 697 patients with the upper age limit of 24 months showed a significant reduction of LOS in favor of the combined therapy (MD of −0.59 days, 95% CI −0.78 to −0.41, $p < 0.00001$; I^2 statistic = 19%).

3.2.2 | Clinical severity scores

Data from 14 trials were used to assess this outcome.[20–22,24,26,28–30,32,36–40] Of those, nine used CSS for bronchiolitis as a primary outcome. Three different scores were used on selected studies: Brochiolitis Severity Score (BSS) by Wang[41] (12 trials[20–22,24,28–30,32,36,37,39,40]), Respiratory Assessment Change Score/Respiratory Distress Assessment Instrument (RACS/RDAI)[42] (1 trial[38]), and Wood-Downes Clinical Scoring System Modified by Ferres (WDF)[43] (1 trial[26]). We used standard mean difference (SMD) to assess CSS, which is the preferred statistical method to represent continuous data if the studies measured the same outcome but used different measurement instruments. Stratification by time of CSS assessment (30 min, 60 min, 120 min, 24 h, 48 h, 72 h, and 120 h after admission) unveiled positive results in favor of the combination therapy in CSS assessed 48 h after the admission (4 trials, $n = 429$, SMD of −0.35, 95% CI −0.62 to −0.09, $p = 0.008$, $I^2 = 41\%$) and also 72 h after admission (2 trials, $n = 285$, SMD of −0.27, 95% CI −0.50 to −0.04, $p = 0.02$, $I^2 = 0\%$). Figure 5 illustrates CSS forest plot. Totals are not represented in this graph (subgroups cannot be pooled together due to different times of CSS assessment).

TABLE 1 Characteristics of included studies

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
Al-Ansari, 2010, Qatar[20]	Outpatient (ED)	<18 mo Moderate/Severe Bronchiolitis (Wang classification)	– 0.9% saline + Ep1.5 mg – HS3% + Ep1.5 mg – HS5% Ep1.5 mg	Nebulization given on enrollment and every 4 h thereafter until discharge	– Primary: Wang CSS at 48 h – Secondary: LOS, Wang CSS at 24 h and 72 h, rate of admission to ICU, rate of ER readmissions after 1 week, AEs.	Consistent trend (but no statistical difference) favoring HS5% Intermediate results for HS3% No difference in LOS between groups No patient was withdrawn because of apnea, cyanosis or decreased SaO_2, no evidence of toxicity among groups
Anil, 2010, Turkey[24]	Outpatient (ED)	6–24 mo Mild/Moderate Bronchiolitis (Wang classification)	– 0.9% saline + Ep1.5 mg – HS3% + Ep1.5 mg – 0.9% saline + Salbutamol – HS3% + Salbutamol – 0.9% saline	Nebulization given at 0 and 30 min	– Primary: Wang CSS – Secondary: SaO_2, heart rate, AEsOutcomes were assessed at 0, 30, 60, and 120 min	No clinically significant difference in CSS score, SaO_2, and heart rate among groups No adverse events occurred in treatment groups, no children were withdrawn due to side-effects or clinical deterioration
Campaña, 2014, Spain[25]	Inpatient	<6 mo Moderate Bronchiolitis (McConnochie classification)	– HS3% + Ep0.5 ml/kg (max 3 ml) – 0.9% saline + Ep0.5 ml/kg (max 3 ml) via high flow therapy	Nebulization given every 4 h until discharge	– Primary: difference in mean RACS at 30 min before nebulization and 60–90 min after – Secondary: difference – in mean comfort score over the monitoring period (Comfort1–Comfort6), LOS and rate of admission to ICU	No difference in RACS, comfort evaluation, LOS, or rate of admission to ICU between groups No adverse events were observed
Del Giudice, 2012, Italy[36]	Inpatient	<24 mo Children with significant respiratory distress and $SatO_2 < 94\%$	– HS3% + Ep1.5 mg – 0.9% saline	Nebulization given every 6 h until discharge	– Primary: LOS – Secondary: Wang CSSOutcomes were assessed before and 30 min after nebulization	Significant difference favoring HS3% in LOS and CSS, seen already after the first 24 h of therapy and was sustained through the third day of treatment
Faten, 2015, Tunisia[21]	Inpatient	1–12 mo Moderate Bronchiolitis (Wang classification)	– HS5% + Ep2 mg – HS5% – 0.9% saline	Nebulization given every 4 h until discharge	– Primary: Wang CSS – Secondary: respiratory rate, heart rate, SaO_2, AEsOutcomes were assessed at 0, 30, 60, and 120 min	No benefit of HS5% plus epinephrine on CSS, respiratory rate, or SaO_2 at any time point or duration of hospital stay No significant adverse side effects (tachycardia, flushing, tremor, or bronchospasm)
Flores-Gonzales, 2015, Spain[26]	Inpatient	<24 mo	– HS3% + Ep3 mg – HS3%	Nebulization given every 4 h until discharge	– Primary: LOS – Secondary: respiratory rate, heart rate, oxygen saturation, inhaled FIO_2, WDF	The addition of epinephrine significantly shortens LOS

(Continues)

TABLE 1 (Continued)

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
		Mild/Moderate Bronchiolitis (WDF classification)			score, AEsOutcomes were assessed daily until discharge.	WDF score improved more rapidly in HS3% plus epinephrine group observed already at Day 3 and sustained by Day 5 No adverse events (i.e., tachycardia, sweating, pallor, trembling, or hypertension) during hospitalization
Grewal, 2009, Canada[35]	Outpatient (ED)	6 wk–12 mo Mild/Moderate Bronchiolitis (RDAI classification) and SaO_2 between 85 e 96%	– 0.9% saline + Ep1.125 mg – HS3% + Ep1.125 mg	Nebulization given once on enrollment. A second dose could be administered within 120 min if needed	– Primary: RACS 0–120 min, change in SaO_2 0–120 min – Secondary: rate of admission to hospital, rate of readmission to EDOutcomes were assessed at 0, 30, 60,90, e 120 min	No significant difference between groups in RACS, admission rates and readmission to ED Adverse effects were noted in 4 infants (vomiting:3; diarrhea:1); all were enrolled in the HS group
Jacobs, 2014, USA[28]	Outpatient (ED)	6 wk–18 mo Moderate/Severe Bronchiolitis (Wang classification) and SaO_2 > 85%	– HS7% + Ep1.125 mg – 0.9% saline + Ep1.125 mg	Nebulization given once on ED and every 4 h thereafter until discharge	– Primary: change in modified Wang BSS, assessed before, immediately after, and 4 h after nebulization, or at disposition – Secondary: hospitalization rate, discharge rate at 23 h, LOS, AEs	HS7% plus epinephrine was no better than normal saline with epinephrine in improvement of CSS, or decreasing admission rate, discharge rate, or LOS Neither group had any adverse effects.
Khanal, 2015, Nepal[37]	Outpatient (ED)	6 wk–24 mo Mild/Moderate Bronchiolitis (Wang classification)	– HS3% + Ep1.5 mg – 0.9% saline + Ep1.5 mg	Nebulization given at 0 and 30 min	– Primary: mean change in Wang CSS – Secondary: SaO_2, respiratory rate, heart rate, discharge readiness at 2 h, readmission rates 24 h after dischargeOutcomes were assessed at 30, 60, and 120 min after the first nebulization	Significant difference in the mean change in CSS, heart rate, respiratory rate and SaO_2 between the two groups, favoring the combination therapy More infants were eligible for early discharge and less likely to need hospital re-visit within the next 24 h in the combination therapy group No adverse events occurred in either treatment groups, no children were withdrawn from the trial due to side effects
Mandelberg, 2003, Israel[30]	Inpatient	<12 mo SaO_2 > 85%	– HS3% + Ep1.5 mg – – 0.9% saline + Ep1.5 mg	Nebulization given every 8 h until discharge	– Primary: LOS, change in Wang CSS each day	Significant statistical reduction of LOS in the experimental group, compared to control

TABLE 1 (Continued)

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
					– Secondary: heart rate, SaO_2, radiograph assessment score, number of add-on treatments, AEsOutcomes were assessed before and 30 min after nebulization	No difference when compared post nebulization CSS between the two groups No adverse effects were observed
Pandit, 2013, India[38]	Outpatient (ED)	2–12 mo Severity not specified	– HS3% + Ep1 mg – 0.9% saline + Ep1 mg	Nebulization given three times with an interval of one hour between two nebulizations	– Primary: LOS – Secondary: improvement in RDAI score, respiratory rate, SaO_2, heart rate, number of add-on treatment, AEsOutcomes were assessed before and 30 min after the third nebulization	No significant improvement in LOS or clinical parameters (RDAI, respiratory rate, and SaO_2) pre to post nebulization between groups recorded on Days 1 and 2 4 infants had side effects (4%) (vomiting:3; diarrhea:1), all were enrolled in 0.9% saline + epinephrine group No adverse effects as tremors or paleness reported
Reisi, 2018, Iran[22]	Inpatient	Age and severity not specified	– HS7% + Ep1 mg – HS5% + Ep1 mg – HS3% + Ep1 mg – 0.9% saline + Ep1 mg	Nebulization given on enrollment and every 4 h until discharge	– Primary: Wang CSS – Secondary: LOS, SaO_2 and oxygen therapy durationOutcomes were assessed at 0, 1, 5, 12, and 24 h after enrollment	Nebulization with HS (3%, 5%, 7%) had not significant superiority to 0.9% saline to reduce LOS, duration of oxygen supplementation use, or BSS
Sharma, 2020, India[29]	Outpatient (ED)	6–12 mo Moderate/Severe Bronchiolitis (Wang classification)	– HS3% + Ep2 mg – 0.9% saline + Ep2 mg	Nebulization given on enrollment twice with 30 min intervals and thereafter every 6 h until discharge	– Primary: LOS – Secondary: Wang CSS, respiratory rate, SaO_2, AEsOutcomes were assessed at 0, 15 min after each nebulization and then every 1–4 h	Improvement of CSS was significantly more pronounced in HS3% group at 24 h than in control group, but this improvement didn't translate into early discharge or decrease in length of hospital stay No significant adverse events occurred in either of the treatment groups, no children were withdrawn from the trial due to side effects

(Continues)

TABLE 1 (Continued)

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
Sharmin, 2014, India[39]	Outpatient (ED)	2–24 mo Moderate/Severe Bronchiolitis (Wang classification)	– HS3% + Ep1.5 mg – 0.9% saline + Ep1.5 mg	Single-dose on enrollment	Respiratory rate, Wang CSS, SaO_2, heart rate, AEs Outcomes were assessed at 0 and 30 min after nebulization	Nebulized adrenaline plus HS3% is more effective than nebulized epinephrine diluted with 0.9% saline in improving CSS, but no difference on respiratory rate or SaO2 No adverse effects were noticed, no significant change in heart rate after nebulization
Sreenivasa, 2015, India[32]	Inpatient	1–24 mo Severity not specified	– HS3% + Ep1 mg – 0.9% saline + Ep1 mg	Nebulization given every 4 h until discharge	– Primary: LOS – Secondary: Wang CSS, SaO_2, heart rate, number of add-on treatment, AEsOutcomes were assessed at 12-h intervals until discharge	Significantly shorter LOS and better improvement in CSS after combination therapy as compared to 0.9% saline plus epinephrine No adverse effects were observed in patients in either of the groups and no significant difference was seen in pulse rate at any time between two groups.
Tal, 2006, Israel[40]	Inpatient	<12 mo SaO_2 > 85%	– HS3% + Ep1.5 mg – 0.9% saline + Ep1.5 mg	Nebulization given every 8 h until discharge	– Primary: LOS, Wang CSS – Secondary: radiographic score, AEsOutcomes were assessed at admission and daily, before and 30 min after nebulization	Significant reduction in LOS following treatment with combination therapy. Fall in values of CSS and radiographic score differed significantly between the two groups during the first 2 days after treatment, favoring the experimental group No adverse effects were observed in either of the groups.
Uysalol, 2017, Turkey[23]	Outpatient (ED)	2–24 mo Moderate Bronchiolitis (Wang classification)	– HS3% – Ep0.1 mg/Kg – Salbutamol – HS3% + Ep0.1 mg/Kg – 0.9% saline	Nebulization given at 0, 30, and 60 min, and every 4 h thereafter if needed to a maximum of 24 h	– Primary: LOS, discharge rates at 4/24 h, readmission rate within 15 days – Secondary: AEs, number of add-on treatment	The mean LOS was significantly shorter for children in the group receiving HS3% plus epinephrine than in other groups and had the highest dismission rate at 4th hour of all five groups

TABLE 1 (Continued)

Study ID, date and country	Setting	Age and severity of participants	Intervention and Control groups	Treatment Regimen	Outcomes	Main Conclusions
						Within the treatment options, there was no statistically significant difference in terms of dismission rates at 24th hour The total frequency of adverse events was 5.5%; frequencies were not different when compared between groups
Zayed, 2018, Egypt[34]	Outpatient (ED)	<24 mo Mild/Moderate Bronchiolitis SaO_2 < 95%	– HS3% + Ep1 mg – HS3% – 0.9% saline + Ep1 mg	Nebulization given every 30 min to a maximum of 4 doses	– Primary: Heart rate on admission and before discharge – Secondary: SaO_2 on admission and before discharge, Wang CSS after each dose until discharge upon improvement or inpatient admission	No significant difference between change of heart rate before and after treatment in the three study groups. No significant differences in the change of clinical score after treatment between the first group (HS3%) and the second group (HS3% plus epinephrine), but there were significant differences between both those groups and the third group (normal saline 0.9% plus epinephrine)

Abbreviations: AEs, adverse events; BSS, bronchiolitis severity score; CSS, Clinical Severity Score; ED, Emergency Department; Ep, epinephrine; RACS, Respiratory Assessment Change Score; SaO2, Saturation of oxygen in room air; WDF Score, Wood–Downes Clinical Scoring System Modified by Ferres.

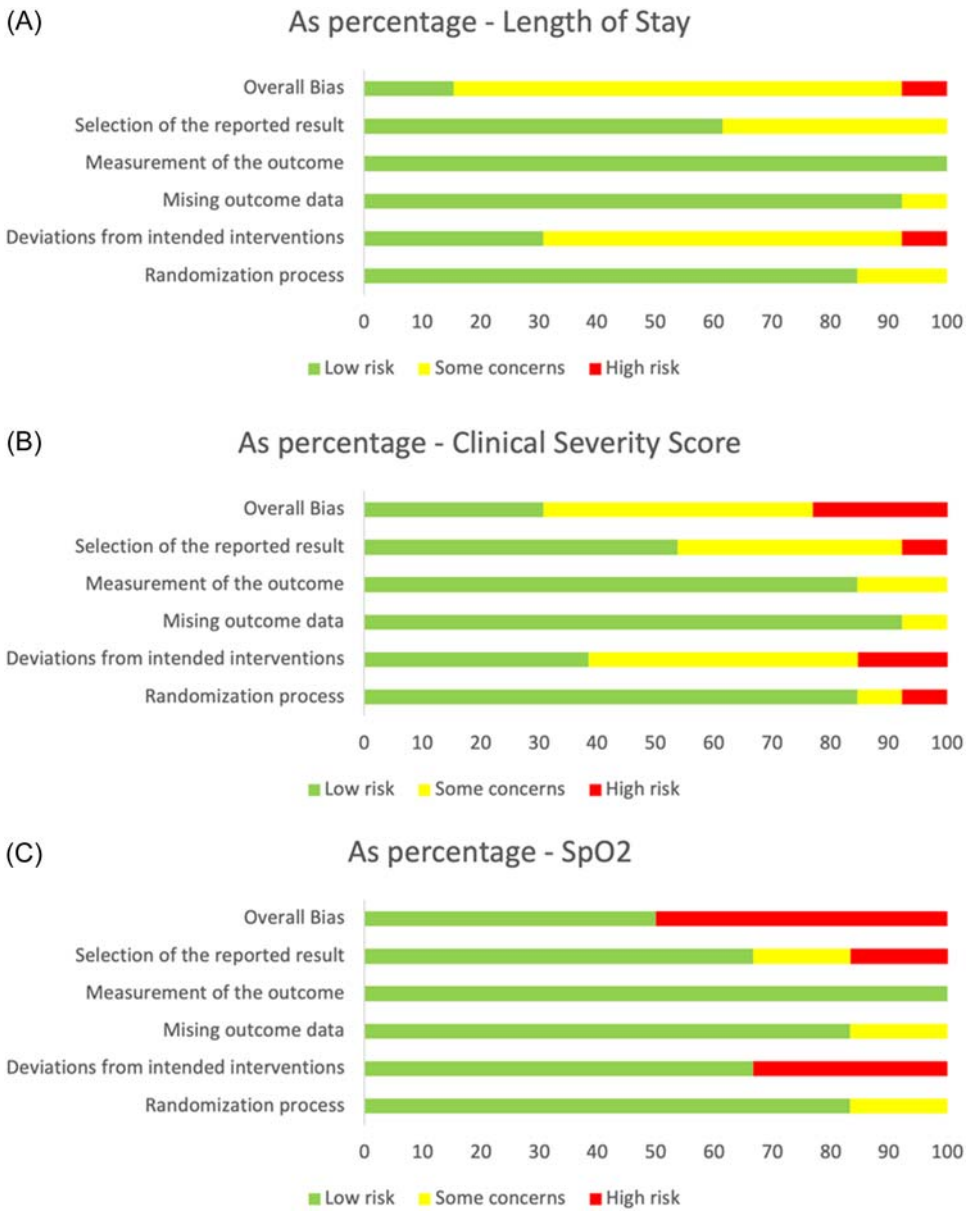

FIGURE 2 (A) Risk of bias of selected studies—Length of stay. (B) Risk of bias of selected studies—Clinical Severity Scores. (C) Risk of bias of selected studies—Saturation of oxygen.

3.2.3 | SaO_2

Six trials were used to analyze this outcome[22,24,29,37–39]; all of them used SaO_2 as a secondary outcome. Pooled data reviewed a total of 622 patients (334 in the intervention arm and 288 in the control arm) and showed no benefit of nebulized HS plus epinephrine in patients with acute bronchiolitis versus other therapies (MD of 0.07, 95% CI −0.80 to 0.94, $p = 0.88$). Significant heterogeneity was observed among studies (I^2 statistic = 87%). Even when stratified in subgroups (time of SaO_2 assessment, upper age limits, or patient setting), there was no difference between treatments. Figure 6 represents SaO_2 forest plot. Totals are also not represented in this graph (subgroups cannot be pooled together due to different times of SaO_2 assessment).

Certainty of evidence for each outcome was assessed using the GRADE approach, being classified as moderate for LOS, low for CSS, and very low for SaO_2.

3.3 | Safety profile

All but three trials[22,34,36] presented safety data, totalizing 1576 patients assessed for AEs. We decided not to carry out a meta-analysis of safety data due to a small number of events and

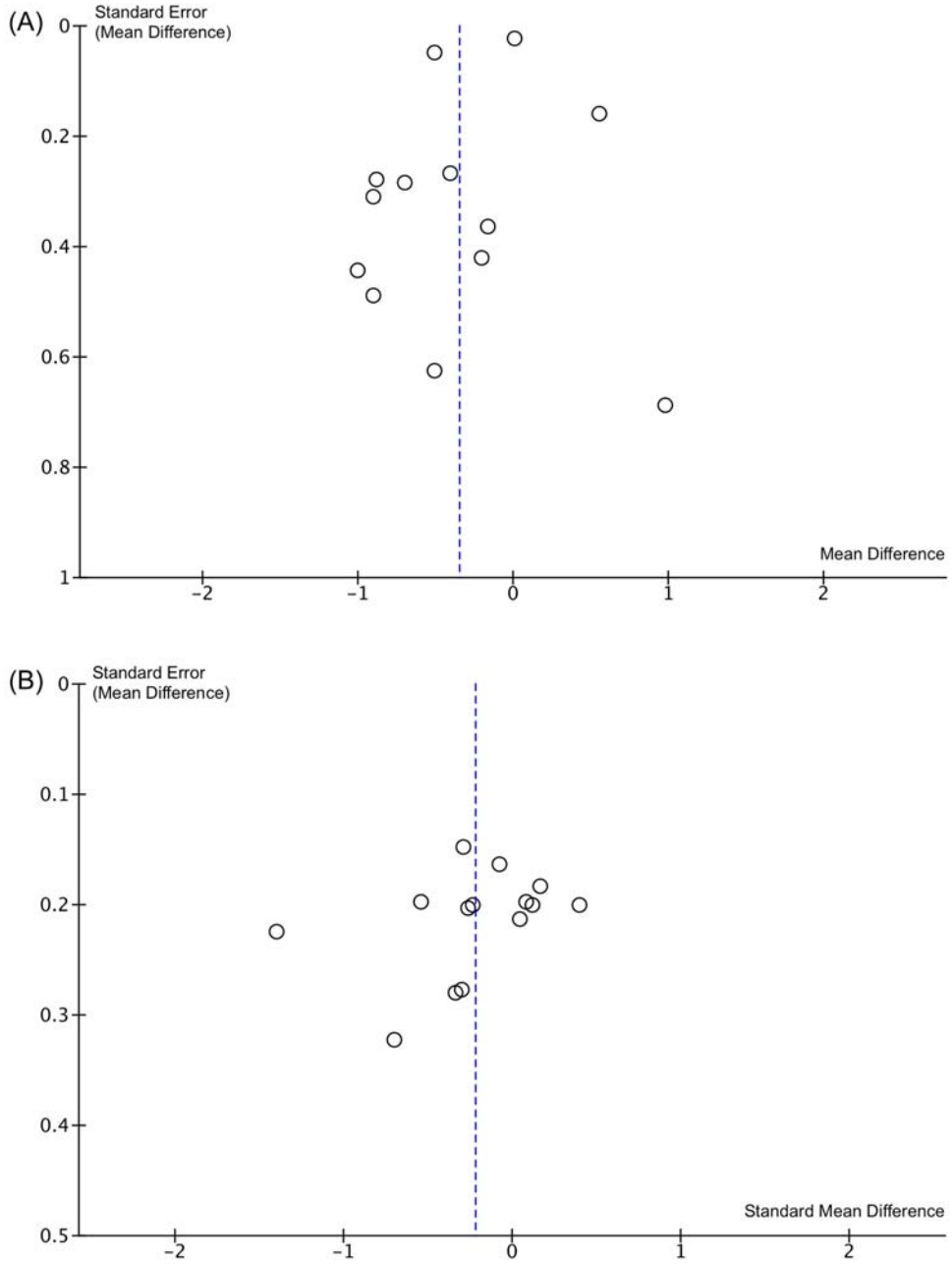

FIGURE 3 (A) Length of stay funnel plot. No publication bias was observed. ($p = 0.25$). (B) Clinical Severity Scores funnel plot. No publication bias was observed. ($p = 0.33$).

insufficient information in most of the included trials. Pooled data show a very low rate of mild adverse events during or post nebulization (1%) and no patient was withdrawn from the study due to side effects. One trial[23] reported a total frequency of 5.5% of adverse events (including tachycardia, pallor, tremor, nausea, and vomiting), but rates were not significantly different when comparing intervention and control groups. Pandit et al.[38] reported four mild events (4%) in the 0.9% saline plus epinephrine group (three vomiting and one diarrhea). Grewal and colleagues[35] reported four infants (8%) with adverse effects (three vomiting and one diarrhea), all included in the epinephrine plus HS group.

4 | DISCUSSION

Overall, this systematic review and meta-analysis evidenced a modest but significant positive impact of nebulized epinephrine plus HS on the LOS of infants with acute bronchiolitis (MD of −0.35 days, i.e., 8.4 h of reduction in LOS). Subgroup analyses showed that studies

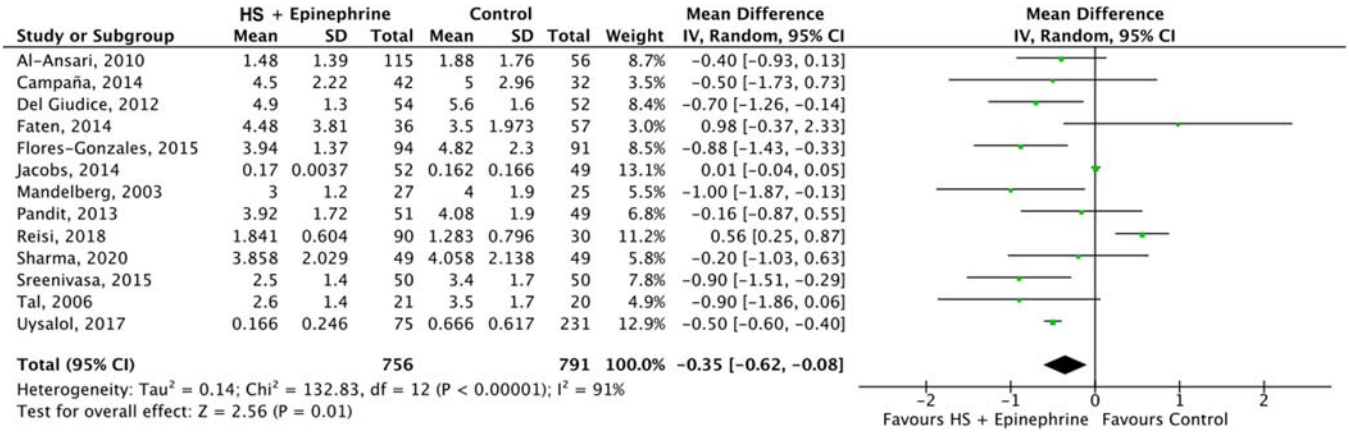

FIGURE 4 Overall LOS forest plot. CI, confidence intervals; HS, hypertonic saline; IV, interval variable; LOS, length of stay; SD, standard deviation

TABLE 2 LOS subgroup analysis.

Subgroups	Trials (*n*)	Patients (*n*)	Effect size (MD, 95% CI)	*p* value	I^2 (%)
Comparison					
Epinephrine	10	1007	−0.10 (−0.28 to 0.08	0.29	72
Hypertonic saline	3	4004	−0.26 (−0.92 to 0.39)	0.43	77
0.9% saline	3	322	−0.44 (−0.90 to 0.03)	0.07	55
Patient setting					
Outpatients	5	776	−0.26 (0.62–0.11)	0.16	95
Inpatients	8	771	−0.45 (−1.05 to 0.15)	0.14	85
Upper age limits					
Not specified	1	120	0.56 (0.25–0.87)	0.0004	–
6 months	1	74	−0.50 (−1.73 to 0.73)	0.42	–
12 months	5	384	−0.35 (−0.90 to 0.21)	0.22	47
18 months	2	272	−0.11 (−0.47 to 0.25)	0.56	56
24 months	4	697	−0.59 (−0.78 to −0.41)	<0.00001	19

Abbreviations: CI, confidence interval; LOS, length of stay; MD, mean differences.

including older patients (up to 24 months of age) had a better response to the combination therapy than other age groups.

We also observed a significant benefit in CSS at 48 and 72 h when infants were given nebulized epinephrine plus HS in comparison with other therapies ($p = 0.008$ and 0.02, respectively), but no effects in SaO_2. These data may be useful in clinical practice since acute bronchiolitis is a worldwide health problem in children below 2 years of age and no pharmacological treatment has been proven effective for the disease.

Several studies attempted to find possible effective interventions in infants with acute bronchiolitis. Results are very heterogenous and pooling data using meta-analysis is possibly the best way to assess the clinical benefit of these therapies. Nebulized epinephrine has been studied for several years. Several trials[44–46] investigated its possible clinical benefit in children with acute bronchiolitis, with controversial results. A meta-analysis conducted by Hartling[7] analyzed 19 studies involving 2256 children that used this drug for infants with acute bronchiolitis, and found evidence that epinephrine is effective for outpatients in terms of reducing admissions within 24 h and short-term decreases in CSS; however, there was insufficient evidence to support its use among inpatients. Despite these significantly positive results, there are substantial inconsistencies and heterogeneity among studies. Thus, the majority of Clinical Practice Guidelines for Bronchiolitis do not recommend the routine use of nebulized epinephrine.[4]

HS has also been studied in infants with acute bronchiolitis, mainly in the last 15 years. Most randomized controlled trials and meta-analyses demonstrate a mild but statistically significant reduction of hospitalization rate, LOS, and CSS compared with those receiving 0.9% saline or standard care.[13,16,17,47] Zhang and colleagues published an updated meta-analysis in 2017[17] which revealed a statistically significant shorter mean length of hospital stay compared

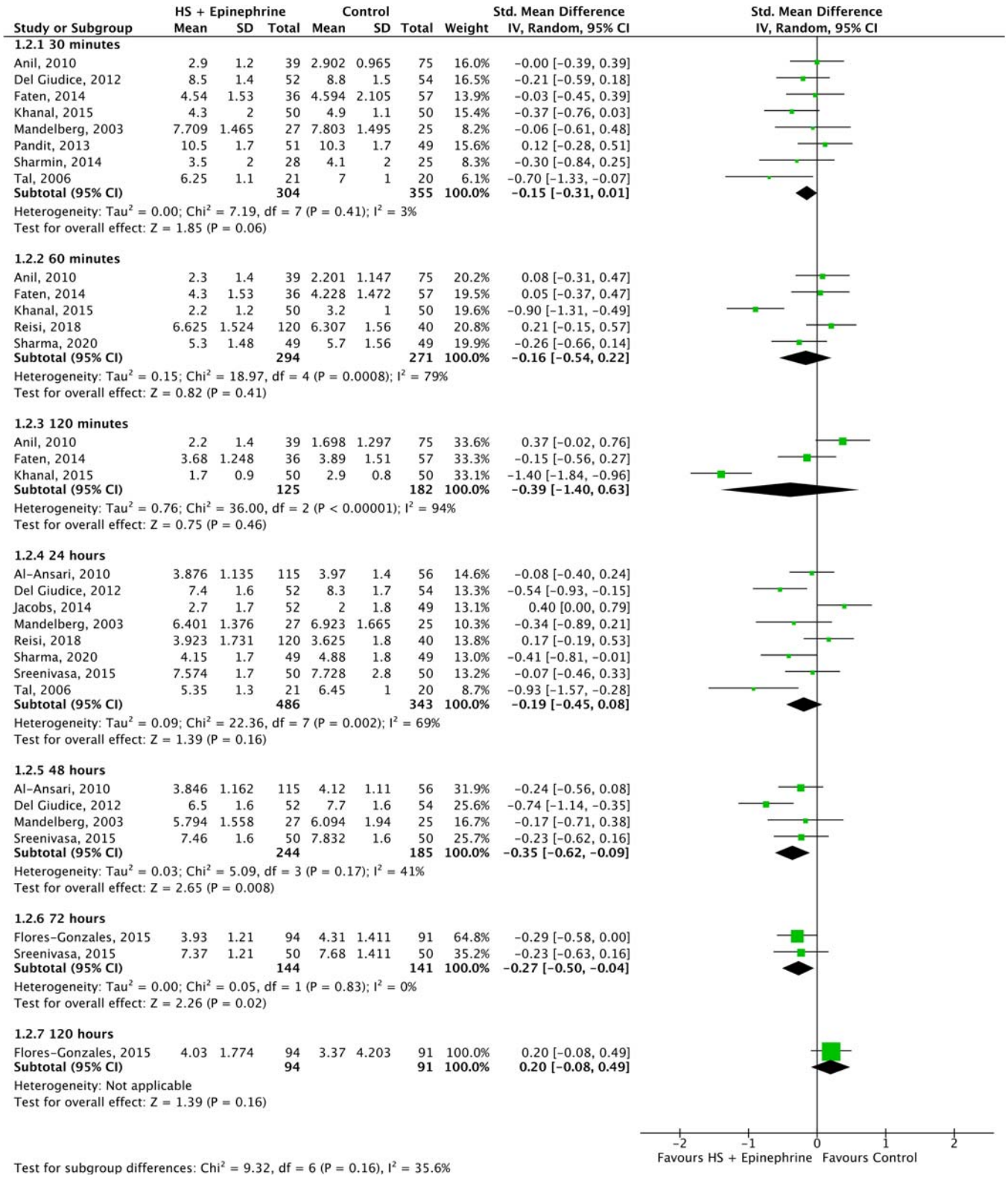

FIGURE 5 CSS forest plot. CI, confidence intervals; CSS, clinical severity scores; HS, hypertonic saline; IV, interval variable; SD, standard deviation.

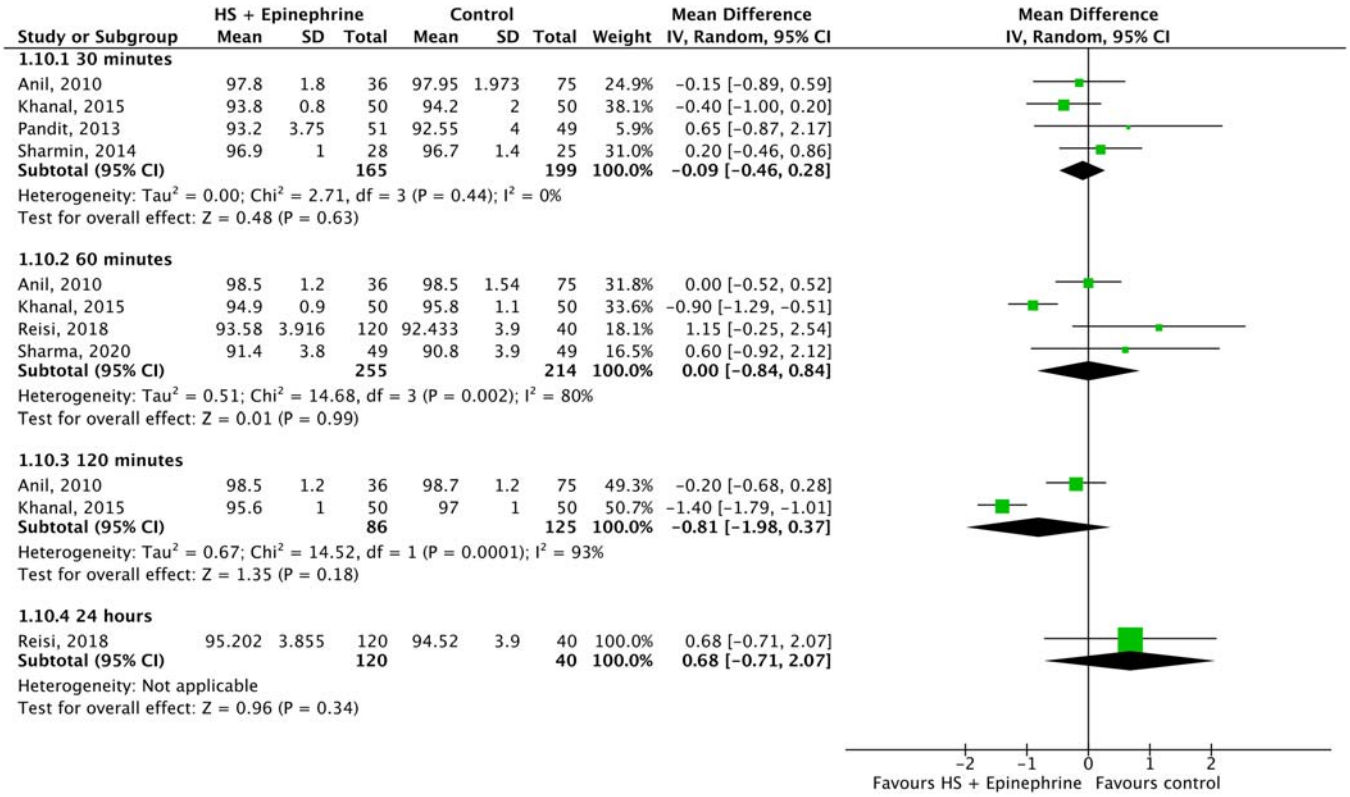

FIGURE 6 SaO_2 forest plot. CI, confidence intervals; HS, hypertonic saline; IV, interval variable; SD, standard deviation; SO_2, oxygen saturation.

to those treated with nebulized 0.9% saline. Infants who received HS also had statistically significantly lower post-inhalation clinical scores than those who received 0.9% saline in the first 3 days of treatment. More recently, another meta-analysis[16] evaluated the risk of hospitalization among patients treated with HS compared to 0.9% saline and found a significant effect in the subgroup analyses of trials in which HS was mixed with bronchodilators and multiple doses were given. However, there are some concerns about these data, mainly due to high heterogeneity among studies, the existence of effect modifiers, different concentrations, and methods of administering medications. Thus, due to relatively low quality of evidence, the use of HS in infants with bronchiolitis is not worldwide accepted.[4]

Considering the above-mentioned limited efficacy of monotherapy, strategies which combine two or more different therapies may theoretically boost positive clinical response. However, Kua[48] published a meta-analysis of five trials, in which pooled data from 1157 patients showed no benefit of using epinephrine plus dexamethasone regarding CSS, respiratory rate, heart rate or hospital admissions. Some significant benefit was obtained in SaO_2, but the authors concluded that evidence may not support its use in current practice.

Two recent network meta-analysis aimed to determine the optimal bronchiolitis treatment. The review from Guo[49] included 40 articles and synthesized seven therapeutic regimens and ranked them based on curative effect on clinical scores and length of stay. Results showed that both epinephrine plus corticosteroids and epinephrine plus hypertonic saline treatments had outstanding efficacy performance and should be the first choice for bronchiolitis treatment in children. A network meta-analysis from Elliott[50] and colleagues found a significant reduction of LOS in patients that utilized nebulized hypertonic saline and nebulized hypertonic saline plus epinephrine. Nebulized epinephrine monotherapy and nebulized hypertonic saline plus salbutamol reduced the admission rate on Day 1, but no treatment significantly reduced the admission rate on Day 7; CSS was not assessed.

The safety profile is also a concern when analyzing any proposed drug intervention. Epinephrine, as an adrenergic agent, might theoretically cause tachycardia, sweating, pallor, trembling, or even more serious events such as arrhythmias. However, previous studies[7] suggest no serious or frequent short-term harms from nebulized epinephrine in the absence of comorbidities. Nebulized HS seems to be safe as well; studies from Zhang et al.[16,17] show good tolerability and very low rate of serious AEs, reporting only one case of transient bradycardia and desaturation possibly related to nebulized HS. Although trials included in our review describe a very low rate of AEs (1%), all of them mild and transitory, it is important to notice that they have not included sufficient data to report an adequate summary of AE risk for the combination therapy.

There are some limitations to this study. First, the lack of standardization of nebulization therapies (different concentrations, different schemes of administration, and add-on therapies used in some patients) might have partially contributed to the significant

heterogeneity of the results between studies. That, alongside a high rate of studies with a moderate and high risk of bias, was responsible for relatively low quality of evidence. The umbrella term "acute bronchiolitis" may include a heterogenous group of patients with different phenotypes and endotypes as shown by Rodríguez-Martínez et al.[51,52] This might also contribute to the heterogeneity in the meta-analyses. However, the point estimates of most of the trials showed the effects on both LOS and CSS in favor of nebulized epinephrine plus HS, suggesting that the heterogeneity between studies is quantitative rather than qualitative—that is, the results differ in magnitude but not effect direction. We did not obtain data from authors of included studies, which might have influenced negatively in some data extraction and the risk of bias analysis. To solve that, standardized imputation methods were used eventually, always chosen in the most conservative way. Finally, although the safety and tolerability of HS plus epinephrine have been addressed, the power to detect important differences between groups is limited due to the infrequent occurrence of events.

Given the low quality of evidence from this systematic review, adequately powered and well-designed randomized trials are still needed to confirm the efficacy and safety of combined therapy with nebulized epinephrine plus HS in infants with acute bronchiolitis. Several challenges in conducting new trials have been pointed out by Zhang et al.,[16] such as the development of valid diagnostic criteria for acute bronchiolitis, selection of reliable and clinically meaningful outcomes, selection of the appropriate control group, and adequacy of the delivery system and inhalation technique.

In conclusion, low-quality evidence from this systematic review suggests that nebulized epinephrine plus HS may be considered a safe and efficient alternative therapy for decreasing length of stay and clinical severity scores in infants with acute bronchiolitis, especially in those who require hospitalization for more than 48 h. Although the results are encouraging, further trials are needed before any definitive recommendation for their use in clinical practice.

AUTHOR CONTRIBUTIONS

Renan Pereira: Project administration (lead); data curation (lead); methodology (equal); writing original draft; fomnal analysis (lead). **Versiéri Almeida:** Data curation (equal); review and editing (supportive). **Mariana Zambrano**: Data curation (equal); review and editing (supportive). **Linjie Zhang:** Project administration (equal); methodology (equal); formal analysis (equal); review and editing (equal). **Sérgio Luís Amantéa:** Conceptualization; project administration (equal); methodology (equal); review and editing (supportive).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

TRANSPARENCY STATEMENT

I, Renan Augusto Pereira, main author of the referred article, declare that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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