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

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ABBREVIATIONS

AEs, Adverse events

BSS, Brochiolitis Severity Score

CIs, Confidence intervals

CSS, Clinical severity scores

HS, Hypertonic saline

LOS, Length of stay

MD, Mean difference

RACS/RDAI, Respiratory Assessment Change Score/Respiratory Distress Assessment Instrument

SaO_2, Oxygen saturation

RCTs, Randomized controlled trials

SD, Standard deviation

SMD, Standard mean difference

WDF, Wood-Downes Clinical Scoring System Modified by Ferres.

ABSTRACT

Management of acute bronchiolitis remains controversial due to lack of strong evidence-based data. Nebulized epinephrine and hypertonic saline have been studied in infants with bronchiolitis, with conflicting results. This systematic review and meta-analysis aimed 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. Outcomes were represented by mean differences (MD) or standard mean differences (SMD) and 95% confidence intervals (CIs) were utilized. 18 trials were systematically selected and 16 of them contributed for the meta-analysis (1,756 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 hours and 72 hours 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. In conclusion, nebulized epinephrine plus HS may be considered as a safe, cheap and efficient alternative for decreasing LOS and CSS in infants with acute bronchiolitis, especially on those who require more than 48 hours of hospitalization.

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 clinical practice guidelines recommend supportive care, with no specific effective therapies due to 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 70's[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 2000's 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.

MATERIALS AND METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 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).

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 were used as search strategy: [("epinephrine" OR "adrenaline") OR ("saline solution, hypertonic")] AND ("bronchiolitis"). For detailed search strategy please see **E-Box 01**.

All databases were searched from their inception until February 2021. No restriction on language or date of publication was settle d. 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 aged less than or equal to 2 years old 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, 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, 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).

Assessment of Risk of Bias

The risk of bias of RCTs was examined by two independent authors (RP, 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 judgement (VA).

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 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” vs “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, standard mean difference was chosen as effect of measure. In two trials[22,30], data was extracted from graphs using the program WebPlotDigitizer[31]. Standard deviation (SD) numerical values were missing for CSS and could not be obtained from the authors in three studies[22,28,32]. In order 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.

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 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 evidence for each outcome using the GRADE approach, classifying 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).

RESULTS

Literature Search and Study Selection

Figure 1 shows the flow diagram of study selection. 1,900 articles were identified by the search strategy described previously. After duplicates were removed, 1,450 articles were screened on basis of titles and abstracts. Of these, more 14 duplicates were found, and 1,058 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 2 studies[34,35] (11,1%) contributed to the meta-analysis, totalizing 1,756 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, 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 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 **Figure 2A**, **Figure 2B** and **Figure 2C**. Most of studies had minor

issues in one or two domains, so they were classified as “Some Concerns” in overall bias. High risk of bias was identified in three studies[29,36,37]. These studies contributed for 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** and **Figure 3B**, 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 6 studies, thus publication bias was not assessed through funnel plots.

Effects of Interventions

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 1,547 patients. Among them, 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 to 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 overall LOS forest plot.

Subgroup analysis was performed based on solution used as comparison (Epinephrine, HS or 0.9% saline), patient setting (inpatients or outpatients) and age of participants. All subgroup data showed no statistical difference between the combined therapy versus control nebulization, except when analyzing pooled data from studies which included infants up to 24 months. This subgroup involved 697 patients and had low heterogeneity (I^2 statistic = 19%) and showed

a MD of -0.59 days, 95% CI -0.78 to -0.41, $p < 0.00001$. **Table 2** shows subgroup analyses for LOS outcome.

Clinical Severity Scores

Data from fourteen 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[20-22,24,28,29,30,32,37-40]), Respiratory Assessment Change Score/Respiratory Distress Assessment Instrument (RACS/RDAI)[42] (1 trial[36]) and Wood-Downes Clinical Scoring System Modified by Ferres (WDF)[43] (1 trial[26]). Stratification by time of CSS assessment (30 minutes, 60 minutes, 120 minutes, 24 hours, 48 hours, 72 hours and 120 hours after admission) unveiled positive results in favor of the combination therapy in CSS assessed 48 hours 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 hours 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).

SaO_2

Six trials were used to analyze this outcome[22,24,29,36,37,39]; 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** represent 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.

Safety Profile

All but 3 trials[22,34,38] presented safety data, totalizing 1,576 patients assessed for AEs. We decided not to carry out a meta-analysis of safety data due to small number of events and 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.*[36] reported 4 mild events (4%) in the 0.9% saline plus Epinephrine group (3 vomiting and 1 diarrhea). Grewal and colleagues[35] reported 4 infants (8%) with adverse effects (3 vomiting and 1 diarrhea), all included in the epinephrine plus HS group.

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 (about 15 hours of reduction in LOS). Subgroup analyses showed that studies including older patients (up to 24 months of age) had better response to the combination therapy than other age groups.

We also observed a significant benefit in CSS at 48 hours and 72 hours 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 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 hours 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-analysis demonstrate a mild but statistically significant reduction of hospitalization rate, LOS and CSS compared with those receiving 0.9% saline or standard care[13,17,16,47]. Zhang and colleagues published an updated meta-analysis in 2017[17] which revealed a statistically significant shorter mean length of hospital stay compared to those treated with nebulized 0.9% saline. Infants who received HS also had statistically significant lower post-inhalation clinical scores than those who received 0.9% saline in the first three 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, 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 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 5 trials, in which pooled data from 1,157 patients showed no benefit of using epinephrine plus dexamethasone regarding CSS, respiratory rate, heart rate or hospital

admissions. Some significantly benefit was obtained in SaO_2, but authors conclude 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 7 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 were not assessed.

Safety profile is also a concern when analyzing any proposed drug intervention. This meta-analysis reinforces the overall safety and tolerability of nebulized epinephrine and hypertonic saline verified in previous data[7,16-17], evidencing a very low rate of adverse effects (1%), and all of them are mild and transitory. 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 seem to be safe as well; studies from Zhang *et al.*[16,17] show a good tolerability and very low rate of serious adverse events, reporting only one case of transient bradycardia and desaturation possibly related to nebulized HS.

There are some limitations in this study. First, lack of standardization of nebulization therapies (different concentrations, different schemes of administration and add-on therapies used in some patients) caused significant heterogeneity between studies. That, alongside with a high rate of studies with moderate and high risk of bias, was responsible for a relatively low quality of evidence. Also, we did not obtain data from authors of included studies, which might have influenced negatively in some data extraction and risk of bias analysis. To solve that, standardized imputation methods were used eventually, always chosen by the most conservative way. Finally, although safety and tolerability of HS plus epinephrine has been addressed, the power to detect important differences between groups is limited due to the infrequent occurrence of events.

In conclusion, we believe that nebulized epinephrine plus HS may be considered as a safe, cheap and efficient alternative for decreasing length of stay and clinical severity scores in infants with acute bronchiolitis, especially on those who require more than 48 hours of hospitalization. No effect on oxygen saturation was observed. However, some concerns about quality of evidence and safety of combined therapy with epinephrine and HS still need to be clarified by further studies before any definitive recommendation for their use in clinical practice.

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AUTHOR CONTRIBUTIONS

Renan Pereira: Project administration (lead); Data curation (lead); Methodology (equal); Writing original draft; Formal 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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