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PROGRAMA DE PÓS-GRADUAÇÃO *STRICTO SENSU* EM PEDIATRIA: ATENÇÃO À SAÚDE DA CRIANÇA E DO ADOLESCENTE

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Efeitos da epinefrina nebulizada em associação com solução salina hipertônica em crianças com bronquiolite aguda.

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1. Bronquiolite. 2. Epinefrina. 3. Solução Salina Hipertônica. I. Título.

Dedico este trabalho a todos os pesquisadores brasileiros. Foi a pesquisa que moveu o mundo nestes últimos, difíceis, tempos. É somente através do cientificismo que a humanidade não perecerá frente ao obscurismo da ignorância e má-fé.

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RESUMO

A bronquiolite aguda é uma doença caracterizada por sibilância torácica e sinais de infecção viral no trato respiratório que ocorre em lactentes. O tratamento da bronquiolite aguda permanece controverso devido à falta de evidências científicas robustas. A epinefrina nebulizada e a solução salina hipertônica são exemplos de intervenções estudadas em crianças com bronquiolite, com resultados conflitantes entre os trabalhos. Esta revisão sistemática e metanálise objetiva avaliar a eficácia no tempo de permanência hospitalar, escores de gravidade clínica, saturação de oxigênio e perfil de segurança da nebulização de epinefrina associada a SSH em crianças com bronquiolite aguda. Os desfechos foram representados por diferença de médias (DM) ou diferença de médias padronizadas (DMP), e foram utilizados intervalos de confiança (IC) 95%. 18 estudos foram sistematicamente selecionados e 16 deles contribuíram para a metanálise (1.756 pacientes). De maneira geral, um impacto discreto, mas significativo, foi observado no tempo de permanência hospitalar no grupo que utilizou a terapia combinada (DM de -0,35 dias, IC 95% -0,62 a -0,08, p = 0,01, I^2 = 91%). Estratificação pelo tempo da análise do escore de gravidade clínica revelou resultados positivos a favor da terapia combinada, quando avaliado 48 horas e 72 horas após a admissão (DMP de -0,35, IC 95% -0,62 a -0,09, p = 0.008, I^2 = 41% e DMP de -0.27, IC 95% -0.50 a -0.04, p = 0.02, I^2 = 0%, respectivamente). Não foi observada diferença na saturação de oxigênio entre os grupos. Dados adicionais mostraram um bom perfil de segurança, com uma baixa taxa de eventos adversos (1%), a maioria destes leves e transitórios. Em conclusão, evidências de baixa qualidade sugerem que a epinefrina nebulizada associada a SSH pode ser considerada uma alternativa segura e potencialmente eficaz para reduzir o tempo de permanência hospitalar e o escore de gravidade clínica na bronquiolite aguda.

Palavras-chave: Epinefrina; Solução Salina Hipertônica; Bronquiolite.

ABSTRACT

Acute Bronchiolitis is described as an illness in infants characterized by acute wheezing with concomitant signs of respiratory viral infection. 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, clinical severity scores, oxygen saturation and safety profile of nebulized epinephrine plus hypertonic saline 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 length of stay (MD of – 0.35 days, 95% CI -0.62 to -0.08, p = 0.01, I^2 = 91%). Stratification by time of clinical severity scores assessment unveiled positive results in favor of the combination therapy in clinical severity scores 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 oxygen saturation 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, low-quality evidence suggests that nebulized epinephrine plus HS may be considered as a potentially safe and effective therapy for decreasing LOS and CSS in acute bronchiolitis.

Keywords: Epinephrine; Saline Solution, Hypertonic; Bronchiolitis.

SUMÁRIO

1 INTRODUÇÃO

A bronquiolite aguda é classicamente definida como uma doença caracterizada por sibilância aguda e sinais de infecção viral no trato respiratório que ocorre em lactentes[1]. Ainda há algumas controvérsias em relação à sua definição: a Academia Americana de Pediatria define a bronquiolite aguda como “um conjunto de sintomas e sinais clínicos que incluem um quadro prodrômico viral do trato respiratório superior, seguido por esforço respiratório e sibilância torácica em crianças menores de 2 anos de idade”[2]. Já na Europa, o termo bronquiolite é geralmente definido como “o primeiro episódio de uma infecção aguda da via aérea inferior em lactentes abaixo de um ano de idade”[3].

Independentemente da classificação utilizada, dados populacionais mostram um impacto significativo da doença em termos de saúde pública, sendo uma importante causa de consultas médicas (tanto na atenção primária quanto em pronto-atendimentos), e responsável por altas taxas de hospitalização e mortes, especialmente na população abaixo de um ano de idade. Durante o primeiro ano de vida, a incidência da doença é calculada em aproximadamente 11-15%. Dependendo da gravidade da doença, estimativas apontam que ao menos 5 hospitalizações a cada 1000 crianças abaixo de 2 anos de idade têm como causa a bronquiolite aguda[4-8].

O uso de técnicas de detecção molecular possibilitou a identificação de diversos agentes etiológicos virais que são capazes de causar bronquiolite aguda. Dentre eles, o vírus sincicial respiratório representa 50 a 80% de todas as hospitalizações pela doença. Após um período de incubação de 4-6 dias, a replicação viral no epitélio nasal leva a congestão nasal, rinorreia, irritabilidade e hiporexia. Febre ocorre em aproximadamente 50% dos casos. Uma vez no trato respiratório inferior, o vírus infecta as células epiteliais ciliares da mucosa bronquiolar e os pneumócitos alveolares, levando a um influxo de células *natural killers*, linfócitos T CD4+, CD8+, além de granulócitos ativados. Esta resposta imunológica gera um aumento da secreção de muco, edema da via aérea, inibição do batimento ciliar e morte das células epiteliais infectadas, gerando uma obstrução ao fluxo aéreo. Além disso, durante a expiração, a pressão positiva intrapleural obstrui ainda mais as vias respiratórias, gerando a característica sibilância observada ao exame físico[9]. Combinadas, estas alterações fisiopatológicas podem levar a níveis variados de esforço respiratório nas crianças infectadas.

Apesar do vírus sincicial respiratório ser o agente etiológico mais comum, outros vírus também podem invadir as células epiteliais das pequenas vias aéreas e causar os sintomas e sinas da bronquiolite aguda, como o rinovírus, parainfluenza, metapneumovírus humano, influenza, adenovírus, coronavírus e bocavírus. Apesar disso, não foram observadas diferenças nas respostas terapêuticas entre crianças com bronquiolite causada por diferentes agentes etiológicos[10,11, 12].

Atualmente, o manejo da bronquiolite mantém-se controverso. A maioria dos protocolos clínicos recomendam um tratamento de suporte, devido ao fato de não haver evidências científicas fortes o suficiente para indicar qualquer tratamento mais específico. Este manejo basicamente inclui oxigênio suplementar caso necessário, hidratação adequada, e suporte mecânico quando há falha ventilatória[13].

Apesar de frequentemente prescritos, revisões sistemáticas e meta-análises mostram que antibióticos, drogas beta-adrenérgicas e corticosteroides apresentam mínimo ou nenhum benefício[14-17]. Outras intervenções farmacológicas e não farmacológicas foram propostas, como oxigênio nasal de alto fluxo, fisioterapia respiratória e sulfato de magnésio. Entretanto, não foi houve superioridade destes tratamentos em relação ao tratamento suportivo habitual[18-20].

A epinefrina e a solução salina hipertônica, administradas através de nebulização, têm sido estudadas em pacientes com bronquiolite aguda há algumas décadas. Em teoria, estas terapias atuariam reduzindo o edema da via aérea, diminuindo os sintomas clínicos da doença[21-23]. Ambas as terapias foram analisadas independentemente por vários estudos clínicos e metanálises[16,24-26]. Entretanto, nenhuma metanálise até o momento investigou especificamente as duas terapias em conjunto.

2 REVISÃO DA LITERATURA

Epinefrina

Diversos estudos objetivaram encontrar possíveis intervenções terapêuticas efetivas em crianças com bronquiolite aguda. Agentes como o salbutamol e o albuterol, comumente utilizados na asma, são agentes que atuam seletivamente nos receptores β_2 da musculatura lisa brônquica, levando a uma broncodilatação. Entretanto, estas propriedades seletivas beta-adrenérgicas não seriam suficientes para corrigir o edema da via aérea e a obstrução por muco, que são as principais características patológicas encontradas na doença[15].

A epinefrina tem um benefício teórico em relação a estes agentes devido a suas propriedades alfa-adrenérgicas em adição aos seu efeito beta-adrenérgico[16]. Em teoria, a epinefrina poderia levar à vasoconstrição e redução do edema na via aérea[22], melhorando assim os sintomas clínicos.

Diversos estudos investigaram este possível benefício clínico em crianças com bronquiolite aguda, com resultados controversos. Uma metanálise conduzida por Hartling[15] concluiu que a epinefrina é eficaz em pacientes na emergência, reduzindo readmissões dentro de 24 horas após a alta, além de melhoras no escore de gravidade clínica. Entretanto, apesar destes resultados positivos, houve um grau significativo de inconsistência entre os estudos analisados. Por isso, a maioria dos protocolos de tratamento da doença não recomendam o uso de epinefrina nebulizada de rotina[13].

Solução Salina Hipertônica

A nebulização com solução salina hipertônica também tem sido usada em crianças com bronquiolite aguda por décadas. Dados da década de 2000 sugerem que a nebulização com solução salina hipertônica pode induzir um fluxo osmótico direcionado para a camada de muco, hidratando esta superfície líquida no interior da via aérea e melhorando o *clearence* mucociliar. Além disso, ela pode induzir a uma redução do edema da via aérea por absorver água da mucosa e submucosa[23].

A maioria dos estudos intervencionistas, revisões sistemáticas e meta-análises demonstram uma discreta, porém significativa, redução na taxa de hospitalização, tempo de permanência hospitalar e escore de gravidade clínica de crianças com bronquiolite aguda tratadas com solução salina hipertônica em relação àquelas tratadas com salina a 0,9% ou tratamento suportivo isolado[25-27]. Apesar disto, existe uma elevada heterogeneidade entre os estudos analisados, além da existência de

fatores de confusão, diferentes concentrações e métodos de administração. Devido à baixa qualidade da evidência, o uso de salina hipertônica em crianças com bronquiolite aguda ainda não é mundialmente aceito.

Terapia Combinada

Considerando a eficácia limitada das terapias constatada nos estudos, estratégias que combinam duas ou mais terapias diferentes poderiam teoricamente melhorar a resposta clínica. A epinefrina e a solução salina hipertônica poderiam agir sinergicamente na broncodilatação, vasonconstrição e redução do edema brônquico.

Duas metanálises em rede recentemente publicadas objetivaram determinar um tratamento eficaz para crianças com bronquiolite aguda[28,29]. A revisão de Guo[28] mostrou que a combinação de epinefrina e corticosteroides e epinefrina e solução salina hipertônica tiveram resultados clínicos favoráveis em relação às outras terapias e deveriam ser considerados como primeira escolha para o tratamento da doença em crianças. Outro trabalho liderado por Elliott[29] mostrou uma redução no tempo de permanência hospitalar nos grupos que foram tratados com solução salina hipertônica isolada e com epinefrina mais solução salina hipertônica. Entretanto, questões em relação ao tamanho das amostras nestes estudos ainda levam à necessidade de mais estudos a respeito de terapias combinadas.

Efeitos Adversos

O perfil de segurança também é um ponto importante a ser considerado ao analisar uma intervenção terapêutica. A epinefrina, como um agente adrenérgico, pode, teoricamente, causar taquicardia, palidez, tremores e até mesmo complicações mais graves, como arritmias. Entretanto, estudos prévios[15] sugerem uma baixa taxa de efeitos adversos com a droga em crianças sem comorbidades prévias, com nenhum relato de efeitos graves dentre os casos analisados.

A solução salina hipertônica nebulizada também parece ser uma opção segura. Estudos de Zhang e colaboradores[25-27] demonstraram uma boa tolerabilidade e uma frequência de eventos adversos muito baixa.

Caso se mostre eficaz e segura, esta combinação pode ser uma opção barata e acessível para pacientes com bronquiolite.

3 OBJETIVOS

Esta revisão sistemática e metanálise tem como objetivos avaliar a eficácia da nebulização com epinefrina adicionada à solução salina hipertônica em relação ao tempo de permanência hospitalar, escores de gravidade clínica e saturação de oxigênio em crianças com bronquiolite aguda, bem como avaliar seu perfil de segurança nesta população.

4 HIPÓTESES

Hipótese nula

A combinação com epinefrina nebulizada associada à solução salina hipertônica não é suficientemente segura e não é capaz de reduzir o tempo de permanência hospitalar, o escore de gravidade clínica ou a saturação de oxigênio em crianças com bronquiolite aguda.

Hipótese alternativa

A combinação com epinefrina nebulizada associada à solução salina hipertônica é suficientemente segura e é capaz de reduzir o tempo de permanência hospitalar, o escore de gravidade clínica ou a saturação de oxigênio em crianças com bronquiolite aguda.

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6 ARTIGO CIENTÍFICO

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, Low-quality evidence suggests that nebulized epinephrine plus HS may be considered as a potentially safe and effective therapy for decreasing LOS and CSS in acute bronchiolitis.

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 Box 01.

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 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).

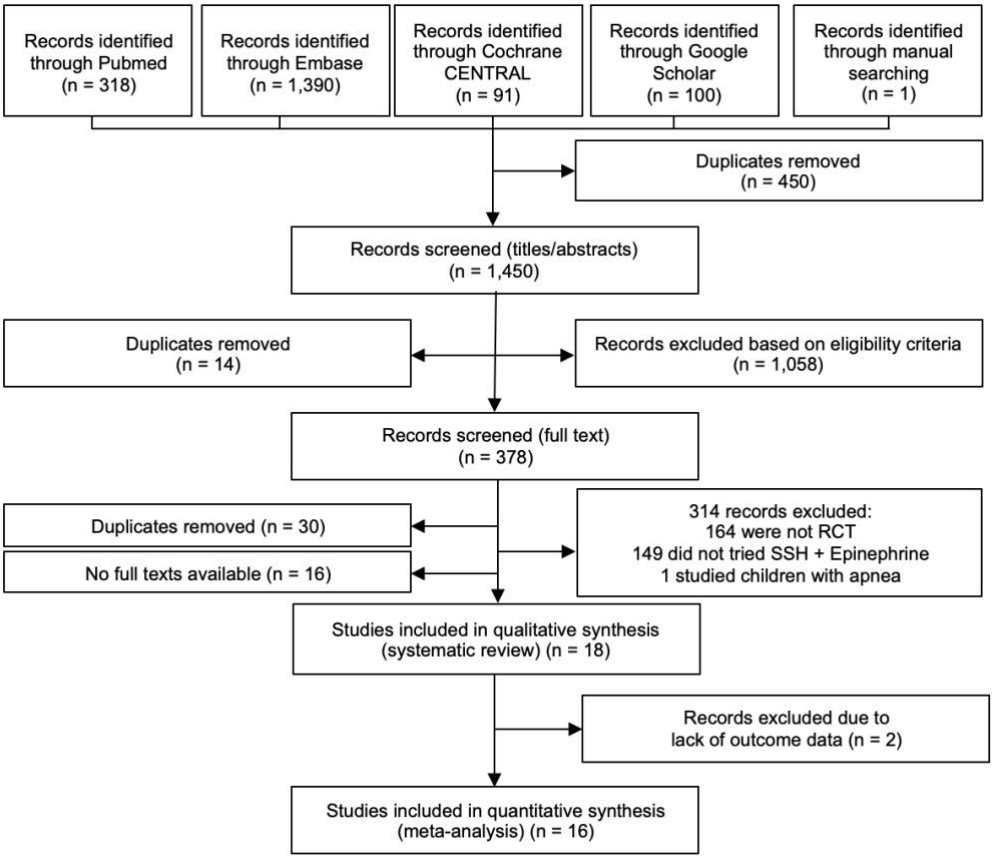
RESULTS

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.

FIGURE 1 Flow diagram of study selection



Risk of bias was assessed by analyzing each outcome individually, as shown in **Figure 2**. 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 3**, 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.

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+Ep1.5mg - HS3%+Ep1.5mg - HS5%Ep1.5mg	Nebulization given on enrollment and every 4 hours thereafter until discharge	- Primary: Wang CSS at 48 hours - Secondary: LOS, Wang CSS at 24 hours and 72 hours, 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+Ep1.5mg - HS3%+Ep1.5mg - 0,9% saline+Salbutamol - HS3%+Salbutamol - 0.9% saline	Nebulization given at 0 and 30 min	- Primary: Wang CSS - Secondary: SaO_2, heart rate, AEs Outcomes were assessed at 0, 30, 60 and 120 minutes	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%+Ep0.5mL/Kg (max 3mL) - 0,9% saline+Ep0.5mL/Kg (max 3mL) via high flow therapy	Nebulization given every 4 hours until discharge	- Primary: difference in mean RACS at 30min before nebulization and 60-90 minutes 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[38]	Inpatient	< 24 mo Children with significant respiratory distress and $SatO_2$ < 94%	- HS3%+Ep1.5mg - 0,9% saline	Nebulization given every 6 hours until discharge	- Primary: LOS - Secondary: Wang CSS Outcomes were assessed before and 30 minutes after nebulization	Significant difference favoring HS3% in LOS and CSS, seen already after the first 24 hours of therapy and was sustained through the third day of treatment

Faten, 2015, Tunisia[21]	Inpatient	1 mo – 12 mo Moderate Bronchiolitis (Wang classification)	- HS5%+Ep2mg - HS5% - 0.9% saline	Nebulization given every 4 hours until discharge	- Primary: Wang CSS - Secondary: respiratory rate, heart rate, SaO_2, AEs Outcomes were assessed at 0, 30, 60, 120 minutes	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 Mild/Moderate Bronchiolitis (WDF classification)	- HS3%+Ep3mg - HS3%	Nebulization given every 4 hours until discharge	- Primary: LOS - Secondary: respiratory rate, heart rate, oxygen saturation, inhaled FIO_2, WDF score, AEs Outcomes were assessed daily until discharge.	The addition of epinephrine significantly shortens LOS 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+Ep1.125mg - HS3%+Ep1.125mg	Nebulization given once on enrollment. A second dose could be administered within 120 minutes if needed	- Primary: RACS 0-120 minutes, change in SaO_2 0-120 minutes - Secondary: rate of admission to hospital, rate of readmission to ED Outcomes were assessed at 0, 30, 60,90 e 120 minutes	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%+Ep1.125mg - 0.9% saline+Ep1.125mg	Nebulization given once on ED and every 4 hours thereafter until discharge	- Primary: change in modified Wang BSS, assessed before, immediately after, and 4 hours after nebulization, or at disposition - Secondary: hospitalization rate, discharge rate at 23 hours, 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[39]	Outpatient (ED)	6 wk – 24 mo Mild/Moderate Bronchiolitis (Wang classification)	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given at 0 and 30 min	- Primary: mean change in Wang CSS - Secondary: SaO2, respiratory rate, heart rate, discharge readiness at 2h, readmission rates 24h after discharge Outcomes were assessed at 30, 60 and 120 minutes after the first nebulization	Significant difference in the mean change in CSS, heart rate, respiratory rate and SaO2 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 hours 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%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given every 8 hours until discharge	- Primary: LOS, change in Wang CSS each day - Secondary: heart rate, SaO_2, radiograph assessment score, number of add-on treatments, AEs Outcomes were assessed before and 30 minutes after nebulization	Significant statistical reduction of LOS in the experimental group, compared to control No difference when compared post nebulization CSS between the two groups No adverse effects were observed.
Pandit, 2013, India[36]	Outpatient (ED)	2 – 12 mo Severity not specified	- HS3%+Ep1mg - 0.9% saline+Ep1mg	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, AEs Outcomes were assessed before and 30 minutes 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

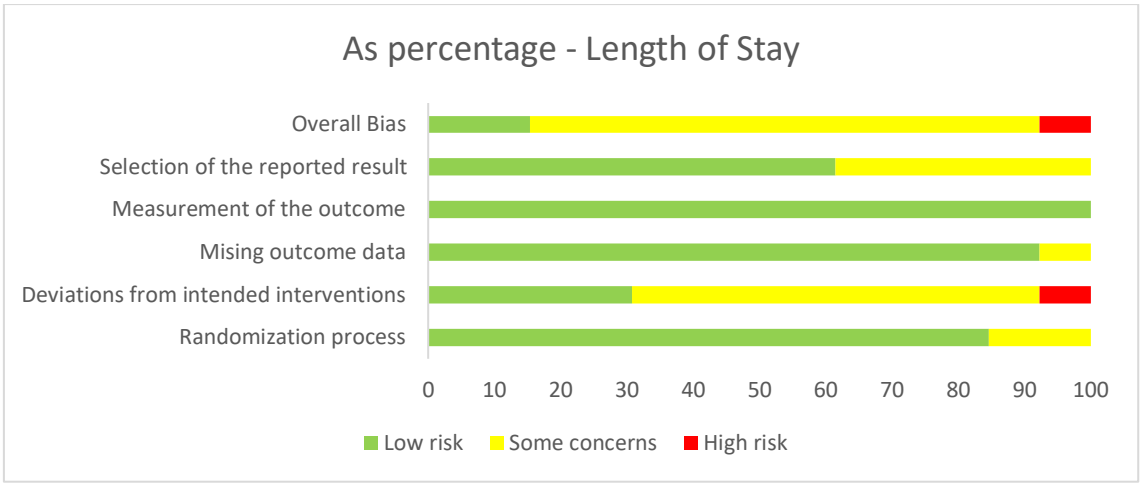
Reisi, 2018, Iran[22]	Inpatient	Age and severity not specified	- HS7%+Ep1mg - HS5%+Ep1mg - HS3%+Ep1mg - 0.9% saline+Ep1mg	Nebulization given on enrollment and every 4 hours until discharge	- Primary: Wang CSS - Secondary: LOS, SaO_2 and oxygen therapy duration Outcomes were assessed at 0, 1 hour, 5 hours, 12 hours and 24 hours 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%+Ep 2mg - 0.9% saline+Ep 2mg	Nebulization given on enrollment twice with 30 min intervals and thereafter every 6 hours until discharge	- Primary: LOS - Secondary: Wang CSS, respiratory rate, SaO_2, AEs Outcomes were assessed at 0, 15 minutes after each nebulization and then every 1-4 hours	Improvement of CSS was significantly more pronounced in HS3% group at 24 hours 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
Sharmin, 2014, India[37]	Outpatient (ED)	2 – 24 mo Moderate/Severe Bronchiolitis (Wang classification)	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Single dose on enrollment	Respiratory rate, Wang CSS, SaO_2, heart rate, AEs Outcomes were assessed at 0 and 30 minutes 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%+Ep1mg - 0.9% saline+Ep1mg	Nebulization given every 4 hours until discharge	- Primary: LOS - Secondary: Wang CSS, SaO_2, heart rate, number of add-on treatment, AEs Outcomes were assessed at 12-hour 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

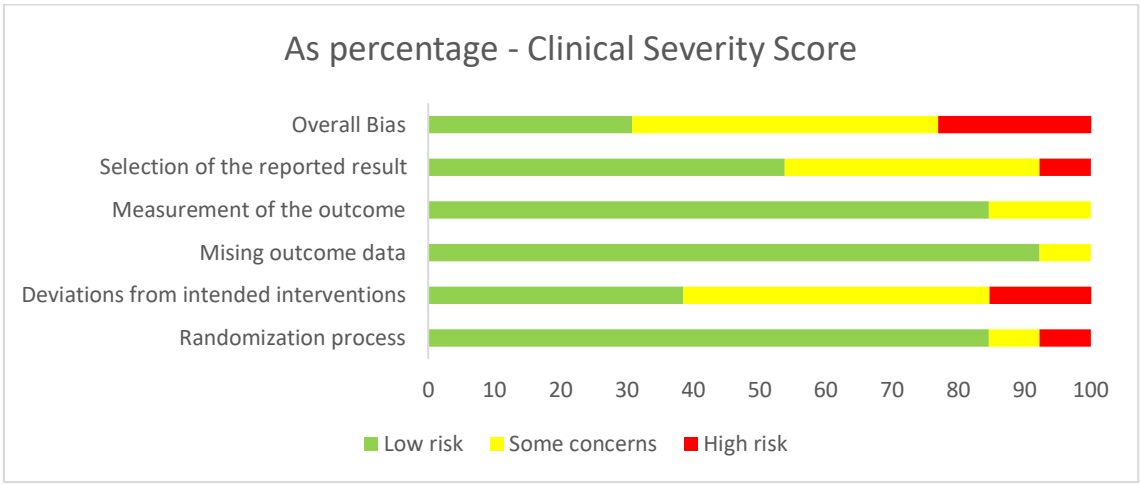
						rate at any time between two groups.
Tal, 2006, Israel[40]	Inpatient	< 12 mo SaO_2 > 85%	- HS3%+Ep1.5mg - 0.9% saline+Ep1.5mg	Nebulization given every 8 hours until discharge	- Primary: LOS, Wang CSS - Secondary: radiographic score, AEs Outcomes were assessed at admission and daily, before and 30 minutes 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% - Ep0.1mg/Kg - Salbutamol - HS3%+Ep0.1mg/Kg - 0.9% saline	Nebulization given at 0, 30, and 60 minutes, and every 4 hours thereafter if needed to a maximum of 24 hours	- Primary: LOS, discharge rates at 4 / 24 hours, 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 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%+Ep1mg - HS3% - 0.9% saline+Ep 1mg	Nebulization given every 30 minutes 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)

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 Risk of bias of selected studies





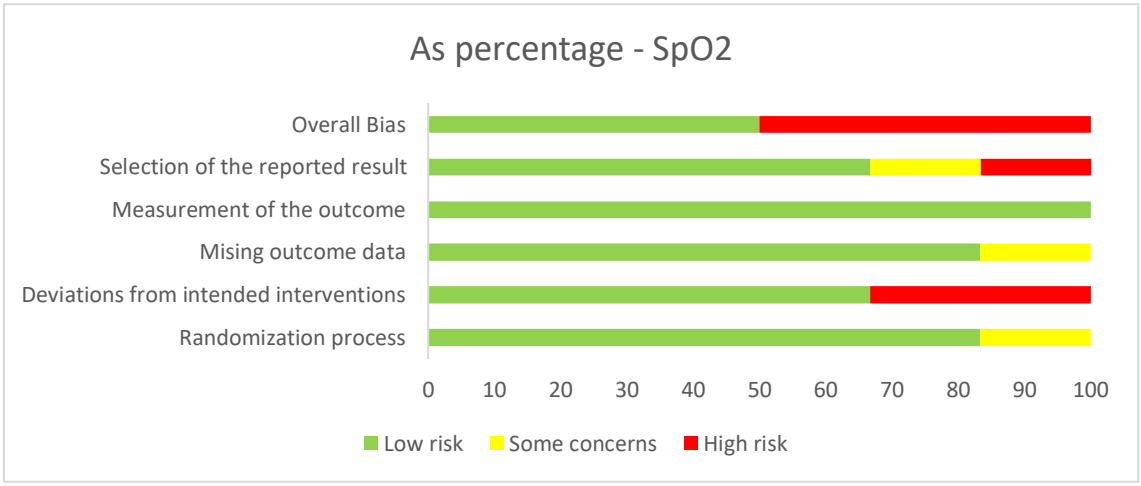
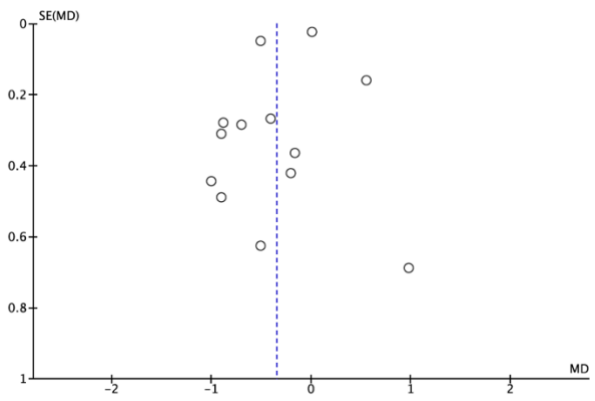
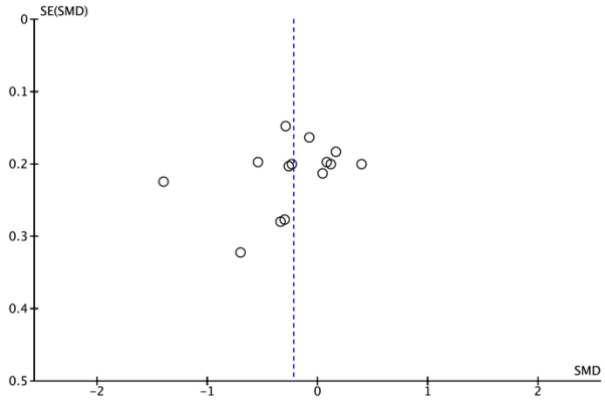


FIGURE 3 Funnel plots



LOS



CSS

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.

FIGURE 4 Overall LOS forest plot

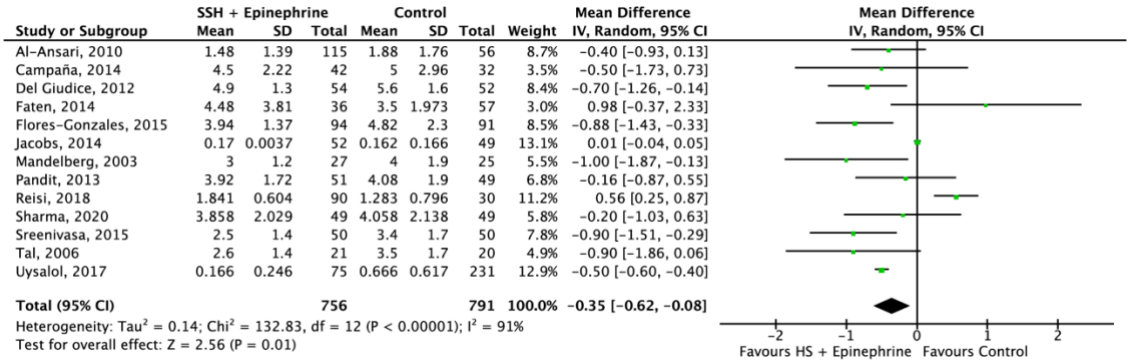


TABLE 2 LOS subgroup analysis

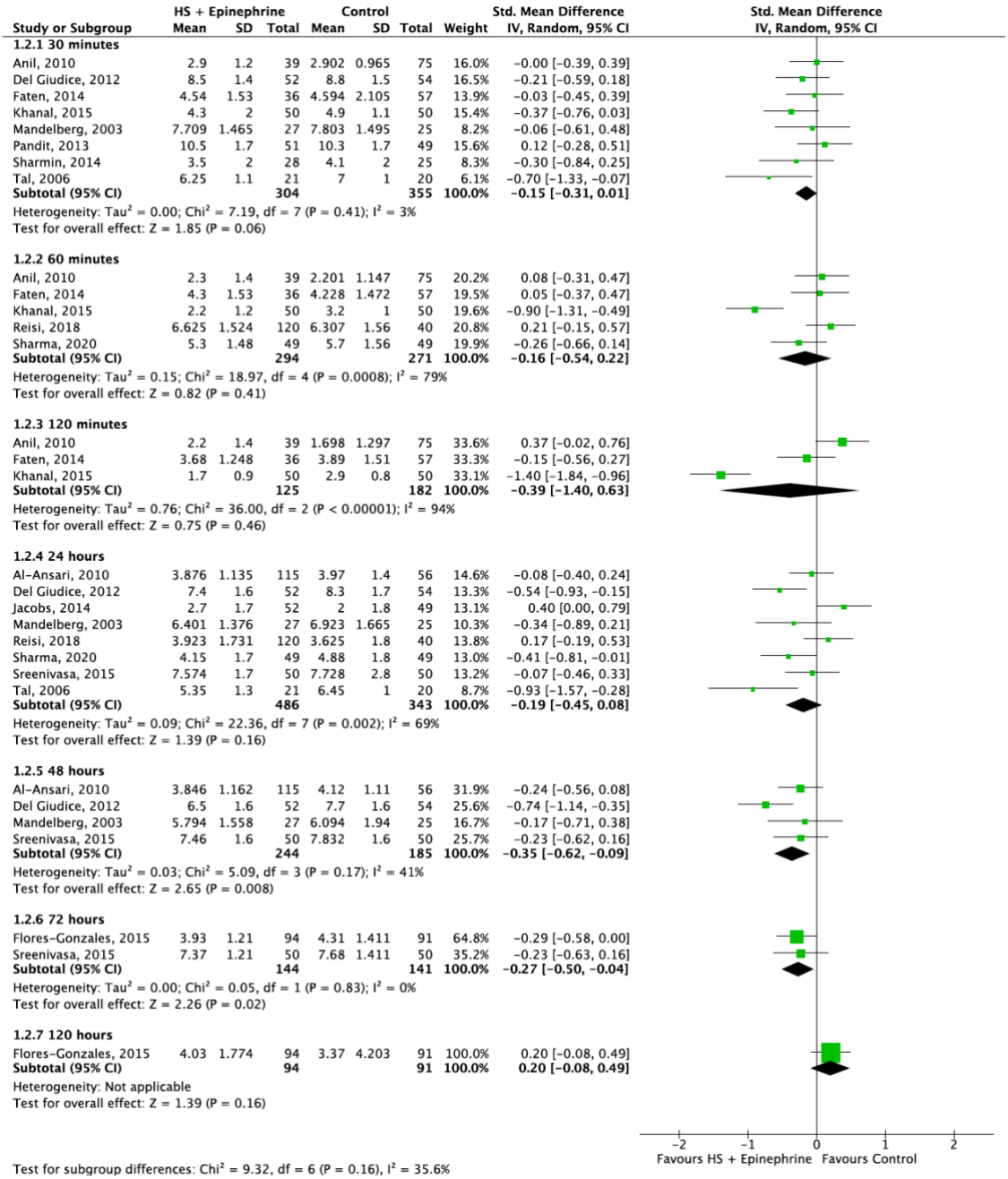
Subgroups	Trials (n)	Patients (n)	Effect size (MD, 95%CI)	*p*-value	I^2 (%)
Comparison					
Epinephrine	10	1007	-0.10 (-0.28, 0.08)	0.29	72
Hypertonic Saline	3	404	-0.26 (-0.92, 0.39)	0.43	77
0.9% Saline	3	322	-0.44 (-0.90, 0.03)	0.07	55
Patient setting					
Outpatients	5	776	-0.26 (-0.62, 0.11)	0.16	95
Inpatients	8	771	-0.45 (-1.05, 0.15)	0.14	85
Upper age limits					
Not specified	1	120	0.56 (0.25, 0.87)	0.0004	-
6 mo	1	74	-0.50 (-1.73, 0.73)	0.42	-
12 mo	5	384	-0.35 (-0.90, 0.21)	0.22	47
18 mo	2	272	-0.11 (-0.47, 0.25)	0.56	56
24 mo	4	697	-0.59 (-0.78, -0.41)	<0.00001	19

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).

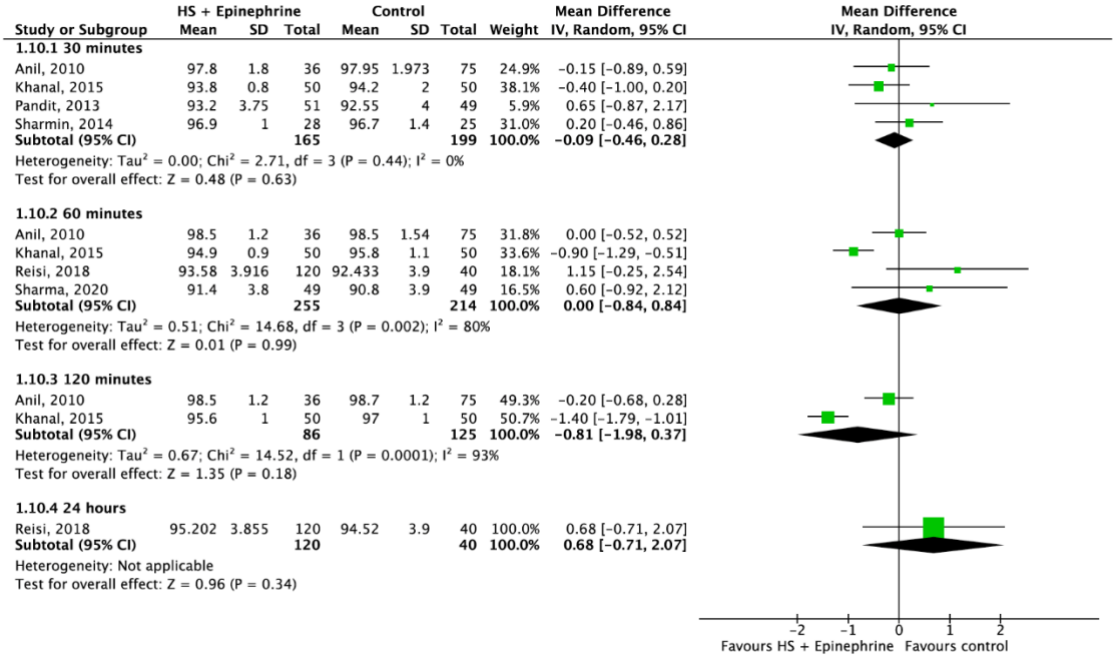
FIGURE 5 CSS forest plot



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).

FIGURE 6 SaO_2 forest plot



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 (**Figure 7**).

FIGURE 7 GRADE Certainty Assessment

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HS + Epinephrine	other therapies	Relative (95% CI)	Absolute (95% CI)	
Length of Stay											
13	randomized trials	not serious	serious [a]	not serious	not serious	none	756	791	-	MD **0.35 days fewer** (0.63 fewer to 0.08 fewer)	⨁⨁⨁◯ MODERATE
Clinical Severity Score											
14	randomized trials	serious [b]	serious [a]	not serious	not serious	none	784	690	-	MD **0.22 SD lower** (0.44 lower to 0)	⨁⨁◯◯ LOW
SaO2											
6	randomized trials	serious [b]	serious [a]	not serious	very serious [c]	none	334	288	-	MD **0.07 % higher** (0.8 lower to 0.94 higher)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Different point estimatives, high heterogeneity between studies
b. Three studies with high risk of bias
c. Low number of events, large 95% CI

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[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 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, the heterogeneity of the results among studies is clear, probably generated by lack of standardization of several factors: nebulization therapies (different concentrations, different schemes of administration and add-on therapies used in some patients), control groups, severity of participants and outcomes measures. That heterogeneity, alongside with a high rate of studies with moderate and high risk of bias, was responsible for a 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 – i.e. 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 risk of bias analysis. To solve that, standardized imputation methods were used eventually, always chosen by the most conservative way. It is also worth mentioning that, 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. Finally, the moderate reduction rates found in LOS and CSS may have limited practical implications in a real-life setting.

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. When no specific therapy is currently available for infants with acute bronchiolitis, any potentially effective treatment for symptom alleviation and clinical improvement is worthy for further research. Several challenges in conducting new trials have been pointed out by Zhang et al.[16], such as development of valid diagnostic criteria for acute bronchiolitis, selection of reliable and clinically meaningful outcomes, selection of the appropriate control group, and adequacy of delivery system and inhalation technique.

In conclusion, this meta-analysis suggests that nebulized epinephrine plus HS may be considered as a potentially safe and efficient alternative therapy for decreasing

length of stay and clinical severity scores in infants with acute bronchiolitis. Although the results are encouraging, further trials are still needed before any definitive recommendation for their use in clinical practice.

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AUTHOR CONTRIBUTIONS

Renan Pereira: Conceptualization/design, Methodology, Supervision/oversight, Data curation, Formal analysis, Writing (drafting the inciial manuscript and review or editing of the manuscript). **Versiéri de Almeida:** Data curation, Writing (review or editing of the manuscript)**. Mariana Zambrano**: Data curation, Writing (review or editing of the manuscript)**. Linjie Zhang:** Conceptualization/design, Methodology, Investigation, Supervision/oversight, Formal analysis, Resources, Writing (review or editing of the manuscript). **Sérgio Luís Amantéa:** Conceptualization/design, Methodology, Supervision/oversight, Funding acquisition, Resources, Writing (review or editing of the manuscript).

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BOX 01 – FULL SEARCH STRATEGY

PubMed:

#1: "Epinephrine"[Mesh] OR "Epinephrine" OR "4-(1-Hydroxy-2-(methylamino)ethyl)-1,2-benzenediol" OR "Adrenaline" OR "Epinephrine Acetate" OR "Medihaler-Epi" OR "Epinephrine Hydrochloride" OR "Adrenaline Hydrochloride" OR "Epitrate" OR "Lyophrin" OR "Epifrin" OR "Epinephrine Bitartrate" OR "Adrenaline Acid Tartrate" OR "Epinephrine Hydrogen Tartrate" OR "Adrenaline Bitartrate"

#2: "Saline Solution, Hypertonic"[Mesh] OR "Saline Solution, Hypertonic" OR "Hypertonic Solutions, Saline" OR "Saline Hypertonic Solutions" OR "Solutions, Saline Hypertonic" OR "Saline Solutions, Hypertonic" OR "Sodium Chloride Solution, Hypertonic" OR "Hypertonic Solution, Saline" OR "Saline Hypertonic Solution" OR "Solution, Saline Hypertonic" OR "Sodium Chloride Solutions, Hypertonic" OR "Hypertonic Saline Solutions" OR "Solutions, Hypertonic Saline" OR "Hypertonic Saline Solution" OR "Solution, Hypertonic Saline"

#3: #1 OR #2

#4: "Bronchiolitis"[Mesh] OR "Bronchiolitis" OR "Bronchiolitides"

#5: #3 AND #4

EMBASE

#1: ('epinephrine'/exp OR '1 (3, 4 dihydroxyphenyl) 2 (methylamino) ethanol' OR '3, 4 dihydroxy 1 [1 hydroxy 2 (methylamino) ethyl] benzene' OR '3, 4 dihydroxy alpha [(methylamino) methyl] benzyl alcohol' OR 'adnephrin' OR 'adnephrine' OR 'adrenal hydrochloride' OR 'adrenalin' OR 'adrenalin chloride' OR 'adrenalin hydrochloride' OR 'adrenalin in oil' OR 'adrenalin, topical' OR 'adrenalina' OR 'adrenalina sintetica' OR 'adrenaline' OR 'adrenaline aguettant' OR 'adrenaline chloride' OR 'adrenaline hydrochloride' OR 'adrenaline injection' OR 'adrenaline
tartrate' OR 'adrenamine' OR 'adrenapax' OR 'adrenazin' OR 'adrenine' OR 'adrin' OR 'adrine' OR 'advaradin' OR 'asthmahaler' OR 'balmadren' OR 'biorenine' OR 'bosmin' OR 'bronitin mist' OR 'bronkaid mist' OR 'chelafrin' OR 'd adrenalin' OR 'dextro

adrenalin' OR 'dl adrenalin' OR 'drenamist' OR 'dylephrin' OR 'dyspne inhal' OR 'epiglaufrin' OR 'epimephrine' OR 'epinefrina' OR 'epinephran' OR 'epinep hrin' OR 'epinephrine' OR 'epinephrine chloride' OR 'epinephrine hydrochloride' OR 'epirenamine'OR 'epirenan' OR 'exadrin' OR 'glaucon' OR 'glauco san' OR 'glaufrin' OR 'glin
epin' OR 'glycirenan' OR 'haemostatin' OR 'hemisine' OR 'hemostasin' OR 'hemosta tin' OR 'hypernephrin' OR 'isopto epinal' OR 'l adrenalin' OR 'l adrenaline' OR 'l epinephrine' OR 'l-adrenalin' OR 'levo adrenalin' OR 'levo adrenalin hydrochloride' OR 'levo adrenaline' OR 'levo epinephrine' OR 'levoadrenalin' OR 'levoadrenaline' OR 'levoepinephrine' OR 'levor enin' OR 'levorenine' OR 'methylaminoethanolcatechol' OR 'methylarterenol' OR 'm ucidrina' OR 'myosthenine'OR 'n
methylnoradrenalin' OR 'nephridine' OR 'nieraline' OR 'paranephrin' OR 'posumin' O R 'primatene mist' OR 'racemic
adrenalin' OR 'renaglandin' OR 'renaglandulin' OR 'renaleptine' OR 'renalina' OR 're naline' OR 'renoform' OR 'renostypticin' OR 'renostyptin' OR 'scurenaline' OR 'simpl ene' OR 'soladren' OR 'sphygmogenin' OR 'styptirenal' OR 'supracapsulin' OR 'supr anephrane' OR 'supranephrin'OR 'supranol' OR 'suprarenaline' OR 'suprarenin' OR 'suprarenine' OR 'suprel' OR 'surenine' OR 'surrenine' OR 'sus phrine injection' OR 'sus-phrine injection' OR 'sus-phrine sulfite-free' OR 'susphrine' OR 'symjepi' OR 'sympathin
i' OR 'takamina' OR 'tonogen' OR 'trenamist'OR 'vasoconstrictine' OR 'vasodrine' O R 'vasotonin' OR 'vasotonin forte seron' OR 'weimer adrenaline' OR ‘weradren’)

#2: ('sodium chloride'/exp OR 'alcathion' OR 'broncho saline' OR 'hypertonic lactated saline solution' OR 'hypertonic saline' OR 'hypertonic saline bath'OR 'hypertonic sodium chloride' OR 'hypertonic sodium chloride solution' OR 'natrium chloride' OR 'saline' OR 'saline solution' OR 'saline solution, hypertonic' OR 'salt' OR 'sodium chloride' OR 'sodium chloride 23.4%' OR 'sodium chloride 3%' OR 'sodium chloride 5%' OR 'sodium chloride solution' OR ‘sodium chloride')

#3: #1 OR #2

#4: ('bronchiolitis'/exp OR 'bronchiolitis' OR bronchiolitides OR 'viral bronchiolitis'/exp OR 'bronchiolitis, viral' OR 'viral bronchiolitis' OR 'virus bronchiolitis')

#5: #3 AND 4

Cochrane CENTRAL

#1: MeSH descriptor: [Epinephrine] explode all trees

#2: "Lyophrin" OR "Epifrin" OR "Epinephrine Acetate" OR "Acetate, Epinephrine" OR "Medihaler-Epi" OR "4-(1-Hydroxy-2-(methylamino)ethyl)-1,2-benzenediol" OR "Adrenaline" OR "Adrenaline Acid Tartrate" OR "Epinephrine Hydrogen Tartrate" OR "Adrenaline Bitartrate" OR "Epinephrine Bitartrate" OR "Epitrate" OR "Epinephrine Hydrochloride" OR "Adrenaline Hydrochloride"

#3: #1 OR #2

#4: MeSH descriptor: [Saline Solution, Hypertonic] explode all trees

#5: "Sodium Chloride Solution, Hypertonic" OR "Solution, Hypertonic Saline" OR "Solutions, Saline Hypertonic" OR "Hypertonic Solutions, Saline" OR "Solution, Saline Hypertonic" OR "Hypertonic Saline Solution" OR "Saline Hypertonic Solution" OR "Sodium Chloride Solutions, Hypertonic" OR "Solutions, Hypertonic Saline" OR "Saline Solutions, Hypertonic" OR "Saline Hypertonic Solutions" OR "Hypertonic Saline Solutions" OR "Hypertonic Solution, Saline"

#6: #4 OR #5

#7: MeSH descriptor: [Bronchiolitis] explode all trees

#8: "Bronchiolitides"

#9: #7 OR #8

#10: #3 OR #6

#11: #10 AND #9

Google Scholar:

“Bronchiolitis” AND “Epinephrine” AND “Hypertonic Solution”

Note: We stipulated that the search in this database will be proceeded until page 10 (total of 100 articles).

7 CONCLUSÃO

Em crianças com bronquiolite aguda, a nebulização com epinefrina adicionada à solução salina hipertônica reduz o tempo de permanência hospitalar, além de reduzir também os escores de gravidade clínica em crianças hospitalizadas que requerem mais de 48 horas de hospitalização, mas sem mudança em relação à saturação de oxigênio. Também se mostrou uma opção segura, com baixa taxa de eventos adversos, em sua maioria leves e transitórios.

8 ANEXOS

ANEXO A – Normas da Revista: Pediatric Pulmonology

ENGLISH LANGUAGE SERVICES

Article Preparation Support

The Editors reserve the right to return any manuscript that is not in acceptable English. Translations from another language will not be provided by the Editorial Office. Authors from countries in which English is not the primary language should have their manuscript reviewed and corrected by an English language service before submission.

MANUSCRIPT GUIDELINES

Reviews/State of the Art Papers

Editors generally commission Reviews and State of the Art papers, but uninvited submissions are also welcome, particularly if the submission outlines an important and topical subject with a focus on recent advances. Reviews should be limited to 4,000 words, while State of the Art papers should be limited to 5,000 words (not including the abstract or references). We ask that the abstracts for these manuscript types do not exceed 250 words. There is no set limit on images, tables, or references for these types of manuscripts. We would encourage a PRISMA statement to be provided with these submissions.

PRIOR TO SUBMITTING

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

COMPONENTS OF ARTICLE/FILE PREPARATION

Please make note of the following when preparing your submission:

Main Document

All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

Title page: The title should be brief (no more than 100 words in length including spaces) and useful for indexing. All authors' names with highest academic degree, affiliation of each, but no position or rank, should be listed. For cooperative studies, the institution where research was primarily done should be indicated. In a separate paragraph, specify grants, other financial support received, and the granting institutions (grant number(s) and contact name(s) should be indicated on the title page). If support from manufacturers of products used is listed, assurances about the absence of bias by the sponsor and principal author must be given. Identify meetings, if any, at which the paper was presented. The name, complete mailing address, telephone number, fax number, and e-mail address of the person to whom correspondence and reprint requests are to be sent must be included. Keywords should also be noted on the title page. For usage as a running head, provide an abbreviated title (maximum 50 characters) on the bottom of the title page.

Summary/Abstract: In accordance with the structure of the article, with or without separate headings, outline the objectives, working hypothesis, study design, patient-subject selection, methodology, results (including numerical findings) and conclusions. The Summary should not exceed the word counts outlined above. If abbreviations are used several times, spell out the words followed by the abbreviations in parentheses.

Acknowledgements: Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under “Acknowledgements.”

Informed Consent: Informed consent statements, if applicable, should be included in the Methods section.

References/citations: References may be included at the end of your text, or uploaded as a separate file. Ensure your references are up to date, and include a critical selection from the world literature. References should be prepared according to CSE (Council of Science Editors) citation-sequence style. Refer to the *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers*, 8th edition (University of Chicago Press). Start the listing on a new page, double-spaced throughout.

Number the references in the sequence in which they first appear in the text, listing each only once even though it may be cited repeatedly.

When citing a reference in the text, the style advocated by CSE suggests numbers appear in superscript, and appear before punctuation marks (commas or periods). In the **citation-sequence**system, sources are numbered by order of reference so that the first reference cited in the paper is [1], the second [2], and so on. If the numbers are not in a continuous sequence, use commas (with no spaces) between

numbers. If you have more than two numbers in a continuous sequence, use the first and last number of the sequence joined by a hyphen, for example [2,4,6-10].

In the references, list the first ten authors of the cited paper. If there are more than ten authors, list the first 10 authors followed by 'et al'.

Journals' names should be shown by their abbreviated title in *Index Medicus*.

Manuscripts in preparation or submitted for publication are not acceptable references. If a manuscript "in press" is used as a reference, a copy of it must be provided with your submission.

Sample references:

Standard journal article Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.

Book with authors Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.

Book with editors Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.

Chapter from a book Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.

For a book reference only include the page numbers that have direct bearing on the work described.

Keywords: On the title page, supply a minimum of 3 to 5 keywords, exclusive of words in the title of the manuscript. A guide to medical subject heading terms used by PubMed is available at **http://www.nlm.nih.gov/mesh/MBrowser.html**

Abbreviations: Define abbreviations when they first occur in the manuscript and from there on use only the abbreviation. Whenever standardized abbreviations are available use those. Use standard symbols with subscripts and superscripts in their proper place.

Drug names: Use generic names. If identification of a brand name is required, insert it in parentheses together with the manufacturer's name and address after the first mention of the generic name.

Eponyms: Eponyms (diseases or biologic entities named for persons) should not be used when standard descriptive terminology is available. Examples include club cells (formerly known as Clara cells); and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). It is permissible to use the eponym in parenthesis at the first mention of the term in cases in which the eponym is still in common use.

Formatting Specific to Original Research Articles: Divide article into: Title Page, Summary/Abstract, Introduction, Materials and Methods, Results, Discussion, and References, starting each section on a new page. All methodology and description of experimental subjects should be under Materials and Methods; results should not be included in the Introduction. Please ensure the following appears in the appropriate section of your manuscript:

- A concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- A succinct description of the working hypothesis;
- A detailed explanation of assumptions and choices made regarding study design and methodology;

- a description of the reasons for choosing the type and number of experimental subjects (patients, animals, controls) and individual measurements; if applicable, information about how and why the numbers may differ from an ideal design (e.g., the number required for achieving 90% confidence in eliminating Type II error);
- Specifics about statistical principles, techniques and calculations employed and, if applicable, methods for rejecting the null hypothesis;
- A concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- A brief summary of the limitations of the scientific methods and results; and
- A brief discussion of the implications of the findings for the field and for future studies.

Tables

Tables should not be included in the Main Document, but submitted as a separate DOC or RTF file. Number tables with Arabic numbers consecutively and in order of appearance. Type each table double-spaced on a separate page, captions typed above the tabular material. Symbols for units should be used only in column headings. Do not use internal horizontal or vertical lines; place horizontal lines between table caption and column heading, under column headings, and at the bottom of the table (above the footnotes if any). Use footnote letters (a, b, c, etc.) in consistent order in each table. All tables should be referred to in the text. Do not submit tables as photographs and do not separate legends from tables.

Images

Image files must be submitted in TIF or EPS (with preview) formats. Do not embed images in the Main Document. Number images with Arabic numbers and refer to each image in the text. The preferred form is 5 X 7 inches (12.5 X 17.5 cm). Print reproduction requires files for full color images to be in a CMYK color space.

Please note authors are encouraged to supply color images regardless of whether or not they are amenable to paying the color reproduction fees. Color images will be published online, while greyscale versions will appear in print at no charge to the author. See **Author Charges** below.

Journal quality reproduction requires grey scale and color files at resolutions yielding approximately 300 ppi. Bitmapped line art should be submitted at resolutions yielding 600-1200 ppi. These resolutions refer to the output size of the file; if you anticipate that your images will be enlarged or reduced, resolutions should be adjusted accordingly.

Lettering on images should be of a size and weight appropriate to the content and the clarity of printing must allow for legibility after reduction to final size. Labeling and arrows on images must be done professionally. Spelling, abbreviations, and symbols should precisely correspond to those used in the text. Indicate the stain and magnification of each photomicrograph. Photographs of recognizable subjects must be accompanied by signed consent of the subject of publication. Images previously published must be accompanied by the author's and publisher's permission.

Image legends should be brief, and included as a separate DOC file under the heading: "Image Legends." When borrowed material is used, the source of the image should be shown in parentheses after its legend, either by a reference number or in full if not listed under References.

Online Supporting Information

Additional non-essential material such as text, appendices, tables, images, video, and soundtrack files may be submitted for posting as supporting information to an article. The scientific value of such material should be evident. The material should be submitted simultaneously with the manuscript so that it may undergo peer review. In naming these files, please note the file names should be preceded by the letter “E.” For example “E-table 1,“E-image 1,” “E-text,” etc.

Note that supporting online material is not typeset, nor proofread following the review process, so please ensure the material is accurate and free of typographical errors. Supporting material should be prepared in the same manner as the print material.

While supporting information does not appear in the print version, a notation is made that supporting material is available online.

POLICIES/DISCLOSURE STATEMENTS

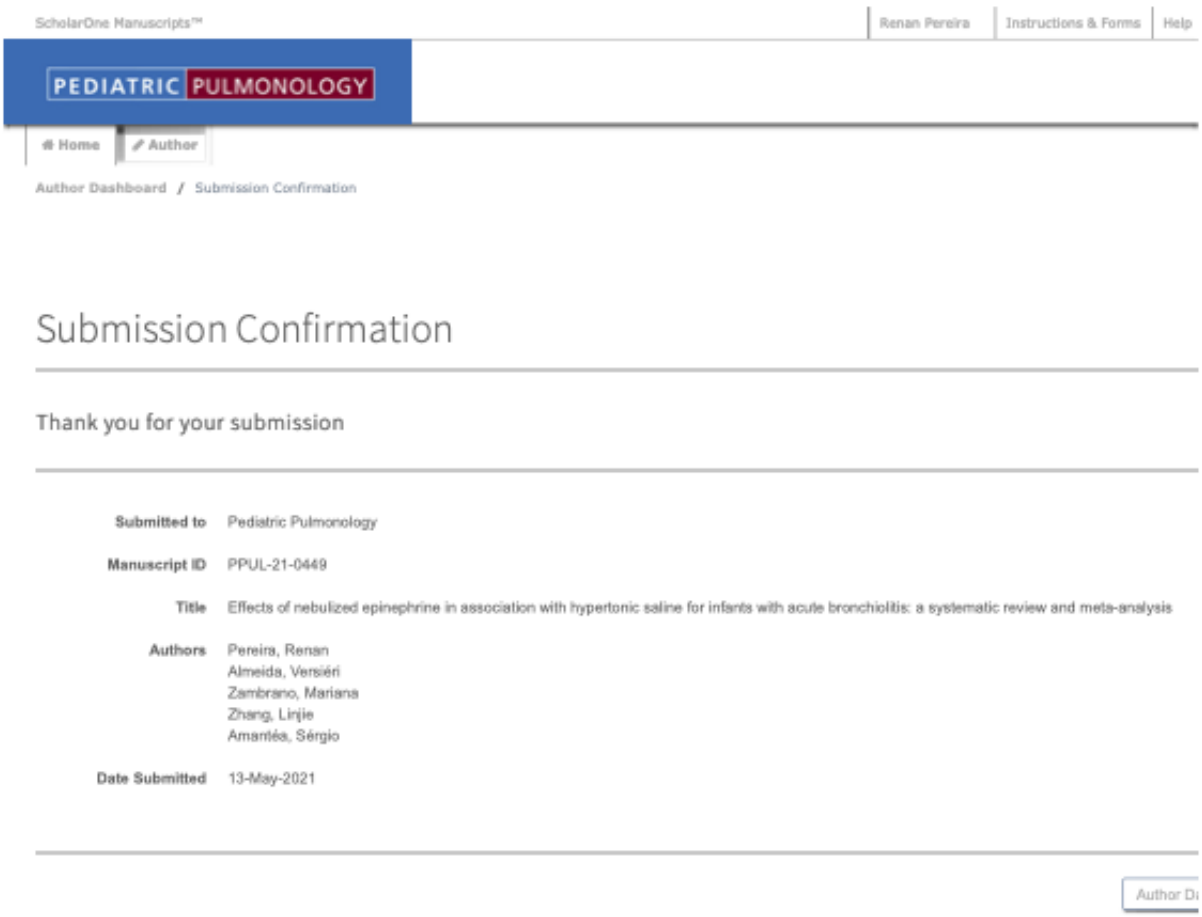
We recognize the importance of developing the highest ethical standards and we are committed to ethical publication practice. For more information on the publisher’s policies, please see Wiley-Blackwell Guidelines on Publication Ethics and Best Practices **www.wiley.com/bw/publicationethics**. Of particular importance is the section on Research Misconduct, which includes data fabrication, falsification, plagiarism, and inappropriate image manipulation.

Authors who submit to Pediatric Pulmonology should take heed of the following:

Conflict of Interest: Authors must indicate at the time of submission any potential conflict of interest (particularly of a fiscal nature) that may have a perceived influence on the results of the research. The existence of such does not automatically preclude publication. A conflict of interest statement should appear in the

Acknowledgment section. For further information on Conflict of Interest please visit **www.icjme.org**

ANEXO B – Comprovante de submissão do artigo a Revista.



ANEXO C – Comprovante Registro PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Renan Pereira, Versiéri Oliveira de Almeida, Sérgio Luís Amantéa. Effects of nebulized adrenaline in association with hypertonic saline for infants with acute bronchiolitis: a systematic review. PROSPERO 2020 CRD42020211518 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020211518

Review question

To systematically review the effects of nebulizer adrenaline associated with hypertonic saline on patientswith acute bronchiolitis.

Searches

Studies will be identified using electronic search databases: MEDLINE, SciELO, LILACS and ClinicalTrials.gov to find eligible studies for review.

Search terms will include the general subject term ‘bronchiolitis’ as well as for the target intervention that isof interest. Each search strategy will be tailored depending to the search database because syntax, limits and available fields vary between databases.

There will be no restriction for language or publication date.

Types of study to be included

Randomized Control Trials

Condition or domain being studied

Acute Bronchiolitis

Participants/population

Children aged less than or equal to 2 years old diagnosed with acute bronchiolitis, according to previousstablished criteria.

Intervention(s), exposure(s)

Nebulization of hypertonic saline (in any concentration) plus adrenaline (in any concentration)

Comparator(s)/control

Placebo (0.9% normal saline or standard treatment without saline inhalation) or isolated therapy withhypertonic saline or adrenaline

Main outcome(s)

Rate of hospitalization (ROH)

Measures of effect

As given in the source documents

Additional outcome(s)

Length of stay

Clinical severity scores

Adverse effects

Measures of effect

As given in the source documents

Data extraction (selection and coding)

The studies retrieved during the searches will be screened for relevance, and those identified as beingpotentially eligible will be fully assessed against the inclusion/exclusion criteria.

All abstracts and titles will be screened independently by two reviewers to determine potential studies forreview.

Any differences arising between the two reviewers will be resolved through discussion until agreementis reached.

Risk of bias (quality) assessment

We will assess the risk of bias in the included studies using to the tools available in RevMan 5.3, and the criteria set out in the Cochrane Handbook for Systematic Reviews of Interventions. Generation of allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of data, selective reporting and other risks of bias will be evaluated for all included studies, and every item assessed as being of a high, low or unclear risk of bias.

Two reviewers will independently perform the risk of bias assessment, with any disagreements being settledby discussion.

Strategy for data synthesis

Characteristics from studies will be presented in tables and narrative forms, guided by the use of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement.

Mean difference (MD) will be used for continuous variables, and standard mean difference (SMD) will be used for the continuous data analysis, if the criterion or measurement for evaluating the results among thedifferent studies is different.

Risk ratio (RR) will be used for dichotomous variables, and we will calculate 95% CI for each effect sizeestimate.

We anticipate heterogeneity between studies due to different study designs, methods of analysis, lag exposures, and geographical and population differences. A random effects model will therefore be used toaccount for heterogeneity between and within studies. We will use the I^2 statistic to assess the statistical heterogeneity within studies, with a value less than 50% (I^2<50) indicating low statistical heterogeneity.

Analysis of subgroups or subsets

Pre-specified subgroup analyses will be performed to determine whether the observed associations were modified by these factors, and will calculate a P interaction for the differences between the subgroups through meta-regression.

Subgroup analyses will be considered for concentration of hypertonic saline/adrenaline and type of controlmedications (isolated hypertonic saline or placebo or isolated adrenaline)

Contact details for further information

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Organisational affiliation of the review

Universidade Federal de Ciências da Saúde de Porto Alegre

Review team members and their organisational affiliations

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Type and method of review

Intervention, Systematic review

Anticipated or actual start date

29 September 2020

Anticipated completion date

30 June 2021

Funding sources/sponsors

Universidade Federal de Ciências da Saúde de Porto Alegre

Conflicts of Interest

None

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

13 November 2020

Date of first submission

13 October 2020

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may beconstrued as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will addpublication details in due course.

Versions

13 November 2020