

## **ABSTRACT**

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### **EFFECTIVENESS OF 3% NEBULISED HYPERTONIC SALINE AMONG CHILDREN WITH BRONCHIOLITIS: A SYSTEMATIC REVIEW**

#### **BACKGROUND**

Bronchiolitis is a common lower respiratory infection that leads to frequent hospitalization at a rate of 312 per 1000 infants per year (1) The present review examines the effectiveness of nebulized 3% hypertonic saline solution (HS) in improving clinical scores, reducing the hospitalization rate and decreasing the length of stay (LOS), and reports adverse events attributed to HS Objective of the study: To undertake a systematic review of randomized controlled trials and quasi-randomized studies that assessed the effects of 3% Nebulized Hypertonic Saline among children with bronchiolitis. The primary outcome was reduction in mean respiratory rate and distress whilst the secondary outcomes included length of stay and readmission.

#### **METHODOLOGY**

To develop an effective search strategy, we adopted the Population, Intervention, Comparison, Outcomes and Study Design (PICOS) worksheet. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA comprises a 27-item checklist that has to be completed in order to improve quality of systematic reviews

#### **ANALYSIS AND INTERPRETATION OF THE DATA**

#### **RESULT**

- Authors identified 25 studies, of which 11 studies with 1958 participants met the review's inclusion criteria. There was wide variation in the methodological and written quality of the included studies. The comparison groups received different interventions, Nebulized with Normal saline, 4 ml. of 0.9% saline along with 1.5 mg of epinephrine, Nebulized Normal saline with salbutamol Standard

supportive care

The administration of 3% nebulized Hypertonic saline to experimental group was varied, with duration ranging from 4 hourly to 8 hourly and in some studies the efficacy of 3% nebulized Hypertonic saline was assessed along with and without salbutamol. The use of nebulized hypertonic saline in reducing the respiratory distress score and LOS was very effectively safe in five studies as compared with control groups. HS was not associated with improved clinical scores in six amongst eleven studies whereas HS was not effective in shortening the length of hospital stay in seven amongst eleven studies. Even though it was also reported in one study that HS was associated with mild adverse effects (increased coughing) in contrast of comparison group.

### **Conclusion:**

Considering the mixed findings across the studies, the effectiveness of nebulized 3% hypertonic saline solution in improving clinical outcomes for children with bronchiolitis appears to be variable. The use of HS might be beneficial in reducing respiratory distress and LOS in certain cases, but it doesn't consistently lead to improved clinical scores or significantly shorter hospital stays. Further research is needed to better understand the specific conditions or patient profiles under which nebulized hypertonic saline can provide the most benefits.

Overall, this systematic review underscores the importance of carefully considering the available evidence and individual patient factors when deciding on the use of nebulized 3% hypertonic saline solution as part of the treatment strategy for children with bronchiolitis.

# ***EFFECTIVENESS OF 3% NEBULISED HYPERTONIC SALINE AMONG CHILDREN WITH BRONCHIOLITIS: A SYSTEMATIC REVIEW***

## **INTRODUCTION**

Bronchiolitis is a common lung infection in young children and infants. It causes inflammation and congestion in the small airways (bronchioles) of the lung. Bronchiolitis is almost always caused by a virus. Typically, the peak time for bronchiolitis is during the winter months<sup>[1]</sup>. Bronchiolitis is an inflammation of the airways in the lungs. It's often caused by virus, often the respiratory syncytial virus (RSV). The first symptoms may look like a common cold. But a child develops a cough, wheezing, and breathing problems. RSV is the most frequent infecting agent. (Wright et al 1989).

This disease is characterized by inflammation, edema and necrosis of the small airway epithelium with associated bronchospasm and increased mucous production. Bronchiolitis is a seasonal illness with the highest incidence between December and March in the Northern Hemisphere.

Despite 4 decades of efforts to deal with the problem, there is no evidence-based clinically effective treatment of bronchiolitis. The standard treatment for acute bronchiolitis remains supportive care like ensuring sufficient oxygenation and maintaining adequate hydration and nutrition. Bronchodilators like salbutamol, adrenaline, anti-cholinergic drugs – ipratropium bromide and saline nebulization have been used with varying results. There is lack of sufficient evidence for almost all the interventions that are usually tried, including inhaled epinephrine, bronchodilators, steroids, anticholinergic, antibiotics, surfactant and chest physiotherapy. None of the treatment modalities is specific. Antiviral agents are available, but their use in most patients is controversial. Most of the studies using glucocorticoids in the treatment of bronchiolitis denied a positive therapeutic effect

Several studies suggested the use of nebulized 3% saline solution for infants with bronchiolitis, due to its ability to lower the viscosity of secretions, reduce airway edema, and improve mucociliary

function. Evidence alters that hypertonic saline solution favorably alters mucociliary clearance in both normal and diseased lungs.

To date, there have been various trials investigating the use of nebulized 3% hypertonic saline solution in infants with viral bronchiolitis. In some of the studies, the improvement in the clinical severity scores was significant in the group treated with hypertonic saline. In other two studies, the hypertonic saline group had a clinically significant reduction in length of hospital stay.

Vast majority of patients with bronchiolitis do not have asthma and the pathophysiologic features of typical bronchiolitis do not involve bronchial smooth muscle hyper responsiveness. So concern regarding bronchospasm resulting from the use of 3% saline solution among patients with bronchiolitis remains theoretical. No evidence has established that 3% saline solution induces bronchospasm in infants with bronchiolitis. The common practice is to treat hospitalised babies with acute bronchiolitis with inhalation of salbutamol diluted in normal saline solution. The present study hypothesized that simply inhalation of hypertonic saline solution without salbutamol in the form of inhalation by the babies with bronchiolitis may improves their clinical severity scores thereby shortening the length hospitalization.

## **NEED OF THE STUDY**

Management of bronchiolitis is often frustrating for physicians and care-givers because “nothing seems to work” in most cases.<sup>[4]</sup> There is lack of robust evidence for almost all the interventions that are usually tried including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. Some experts have questioned whether bronchiolitis can be treated at all and current research data is far from adequate to draw definite conclusions. It has been suggested that hypertonic saline (HS) nebulization may be useful in making secretions less viscous and promoting their excretion, thereby resulting in clinical improvement. Despite the lack of sufficient data, many physicians use this, though sometimes more for psychological than clinical benefit. Against such a background, it is relevant to ask the clinical question, “in infants with bronchiolitis (population), does HS nebulization (intervention) result in better clinical response (outcome) compared to no intervention or nebulization with normal saline (comparison).”<sup>[4]</sup> A few studies have been done to see the effectiveness of 3% HS nebulization in acute bronchiolitis.

## **Outcome**

Bronchiolitis is a common lower respiratory infection that leads to frequent hospitalization at a rate of 31.2 per 1000 infants per year (1). Salbutamol, racemic adrenaline, corticosteroids and nebulized normal saline (NS) are commonly used therapies that all appear to have questionable efficacy in specific settings (2). The present review examines the effectiveness of nebulized 3% hypertonic saline solution (HS) in improving clinical scores, reducing the hospitalization rate and decreasing the length of stay (LOS), and reports adverse events attributed to HS.

## **Objectives:**

1. To undertake a systematic review of randomized controlled trials and quasi-randomized studies that assessed the effects of 3% Nebulized Hypertonic Saline among children with bronchiolitis.

We focused on studies investigating changes in the respiratory parameters including length of stay related to use of 3% Nebulized Hypertonic Saline with or without salbutamol trials in children. The respiratory parameters taken into account in this systematic review are Breath sounds, Respiratory Pattern, oxygen saturation, forced expiratory volume and peak expiratory flow rate, assessed by using Respiratory distress assessment instrument score, Clinical bronchiolitis severity score, duration of oxygen therapy. As well Others outcome were Length of hospital stay, Readmission rate and discharge events, Medications effects and adverse effects.

## REVIEW OF LITERATURE

1) **Nurzulsarina Awang, Ariffin Nasir, Rowani Mohd Rawi and Fahisham Taib, 2020:** conducted a study to evaluate the effectiveness of treatment using nebulized salbutamol and 3% hypertonic saline (HS) compared with nebulized salbutamol and 0.9% saline (NS) solution in acute bronchiolitis. The Prospective, double-blind randomized controlled trial was conducted from April 2014 till May 2016 in previously healthy children younger than 18 months old, admitted to Hospital University Saints Malaysia with mild to moderate acute viral bronchiolitis. Patients were randomized to receive either nebulized HS with salbutamol (intervention group), or nebulized NS with salbutamol (control group). One hundred one (101) patients with acute bronchiolitis were included in this study (HS, n = 52; NS, n = 49). The mean age of the HS group was 7.1 months and NS group was 8 months. There was no difference in the clinical severity score between group ( $p = .250$ ) and the duration of hospital stay in both groups ( $p = .146$ ). It was concluded that there were no differences in term length of hospital stay and the clinical severity score for both interventional and control group.

2) **Sushmita Singh, Rupesh Masand, Girdhari Lal Sharma and Swati Mehta, 2020:** a study was conducted to compare the efficacy of nebulization with 3% hypertonic saline and 0.9% normal saline in the management of acute bronchiolitis. The objective of the study was to compare the improvement in clinical severity scores and the length of hospital stay (LOS) among children with bronchiolitis nebulized with either 3% hypertonic saline (HS) or 0.9% normal saline (NS). A total of 360 hospitalized patients of age 1–24 months, diagnosed as a case of acute bronchiolitis of moderate severity, were randomized to receive either 4 ml of 3% HS (Group A) or 4 ml of 0.9% NS (Group B) along with 1.5 mg of epinephrine in each arm, at 4 hourly intervals till the patients were ready for discharge. All the baseline characteristics were similar in both the groups. There was a significant ( $p=0.0011$ ) reduction of 13 h (12.2%), i.e., from 4 days 23 h in Group B (NS) to 4 days 10 h in Group A in the mean LOS and significant difference ( $p=0.0001$ ) in the clinical severity score was noted from the 2nd day onward in Group A as compared to Group B. No adverse events were observed or reported by the treating medical team or the patients' caregiver in both the study groups. Hence it was concluded ;Nebulization with 3% HS is superior to 0.9% NS nebulization in infants with clinically diagnosed acute bronchiolitis.

3) **Raphaelle Jaquet-pilloud, Marie-Elise Verga, Michel Russo et. al, 2020:** conducted a study on Nebulised hypertonic saline in moderate-to-severe bronchiolitis: a randomised clinical trial to investigate whether nebulised hypertonic saline (HS) treatment would decrease length of hospital stay (LOS) among infants with moderate-to severe-bronchiolitis compared with standard supportive care (SC). An open, multicentre, randomised clinical trial, in Swiss children's hospitals. Patients aged 6 weeks to 24 months with a primary diagnosis of moderate or severe bronchiolitis were included. Patients were randomised to receive standard SC with nebulisation of 4 mL of 3% sodium chloride every 6 hours versus SSC. Main outcomes and measures

were LOS duration of oxygen therapy, transfer to intensive care unit (ICU), readmission within 7 days following discharge and adverse events. 121 children were randomised. No statistically significant differences were found between treatment groups at baseline (age, Wang Score, atopic history, smoking exposure). Children in the HS group had a non-significant difference in length of stay  $-2.8$  hours ( $-10$ ;  $16$ ) compared with the SC group. There were no differences in oxygen therapy duration, transfer to ICU, readmission rate or adverse events. The intervention was discontinued at the parents' request in 16% of the cases. The study does not support the use of HS nebulisation in children with moderate to severe bronchiolitis.

**4) IlkeOzahiIpek, Emek Uyur Yalcin, Rabia Gonul Sezer and Abdulkadir Bozaykut, 2011:** A randomized controlled trial was conducted, on the efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. The mainstay of treatment in bronchiolitis includes oxygenation, aspiration of secretions from the respiratory tract and maintenance of hydration. The first choice medical agent in clinical practice is nebulized bronchodilators, although their place in treatment is controversial. We investigated the therapeutic benefit of nebulized hypertonic (3%) saline (HS), by comparing four different nebulized regimens in the treatment of bronchiolitis in the emergency department. A total of 120 infants were included in this randomized, double-blind, prospective study. Infants were grouped according to the nebulized treatment they received: group 1 - salbutamol + normal saline (NS), group 2 - salbutamol + HS, group 3 - HS, group 4 - NS. Heart beat, Clinical Bronchiolitis Severity Score (CBSS) and oxygen saturation of the patients were determined before and after the nebulizations and at 48-72 h after admission by the designated study physician. Post-treatment mean CBSS were significantly lower than pre-treatment scores in all groups ( $p = 0.0001$ ) with no significant difference within groups. Improvement percentages for CBSSs were significantly higher in infants without a history of atopy treated with HS and NS ( $p = 0.023$ ,  $p = 0.0001$ , respectively). The CBSSs of all the infants improved after three doses of nebulized therapy regardless of the treatment regimens. The combination of salbutamol with hypertonic saline did not lead to an additive effect in the improvement of CBSSs compared to the standard salbutamol + NS combination. Atopic children benefited from salbutamol/NS combination whereas non-atopic children improved with HS and NS nebulizations based on improvement percentages of CBSS.

**5) Pedro Flores, Ana Lusía Mendes, Ana S Netol, 2015:** conducted a randomized trial of nebulized 3% hypertonic saline with salbutamol in the treatment of acute bronchiolitis in hospitalized infants. Acute bronchiolitis is a common disorder of infants that often results in hospitalization. Apart from supportive care, no therapy has been shown to influence the course of the disease, except for a possible effect of nebulized hypertonic saline (HS). To determine whether this does have beneficial effects on length of stay in hospital or on severity scores, we undertook a double-blind, randomized, controlled trial in a pediatric department of a Portuguese hospital. Previously healthy infants, younger than 12 months, hospitalized with mild-to-moderate acute viral bronchiolitis were randomized to receive either nebulized 3% (hypertonic, HS) or 0.9% (normal,

NS) saline during their entire hospital stay. Primary endpoints were: length of hospital stay and severity scores on each day of hospitalization. Need for supplemental oxygen, further add-on medications and adverse effects were also analyzed. Sixty-eight patients completed the study (HS: 33; NS: 35). The median length of hospital stay did not differ between groups: HS:  $5.6 \pm 2.3$  days; NS:  $5.4 \pm 2.1$  days ( $P = 0.747$ ). We found no difference between groups in severity scores from day 1 to day 4. There were no differences in need for supplemental oxygen or add-on medications. Patients in HS group had significantly more cough (46% vs. 20%,  $P = 0.025$ ) and rhinorrhoe (58% vs. 31%,  $P = 0.30$ ). This study does not support the use of nebulized HS over NS in therapy of hospitalized children with mild-to-moderate acute viral bronchiolitis.

6) **Harsh V. Gupta, Vivek V. Gupta , Gurmeet Kaur et.al, 2016:** conducted a study on effectiveness of 3% hypertonic saline nebulisation in acute bronchiolitis among Indian children. The objective of the study is to compare the effects of 3% hypertonic saline (HS) and 0.9% normal saline with nebulized 0.9% normal saline with salbutamol in patients of acute viral bronchiolitis. A quasi-experimental study design was used. Participants were divided into three groups, that is, 3% HS group, 0.9% normal saline group and 0.9% saline with salbutamol group. Four doses at interval of 6 hr were given daily until discharge. Average CS score and length of hospital stay were compared. One-way analysis of variance paired t-test and Chi-square test were utilized for statistical analysis. It concludes that 3% HS nebulisation (without additional bronchodilators) is an effective and safe treatment for non-asthmatic, moderately ill patients of acute bronchiolitis.

7) **Catherine R and Manju Bala Dash, 2018:** conducted a study on the effectiveness of Salbutamol vs Hypertonic Saline Nebulization on breathing pattern among children with LRTIs. The objective is to assess the respiratory pattern of children in Group-1 (Salbutamol) and Group-2 (Hypertonic saline) before and after the interventions. Quantitative approach and pre and post with two group research designs was used. The study samples were 1 month to 12 years children. Salbutamol and Hypertonic saline nebulisation were given and children were assessed before and at 1 hr after intervention using oxygen saturation level, heart rate and respiratory patterns. The results showed that the post-test mean oxygen saturation level was  $1.15 \pm 0.36$  and  $1.00 \pm 0.00$  in group-1 and 2 respectively with 't' value of 2.63 ( $p < 0.05$ ) shows that there is a statistically significant difference between group 1 and 2 nebulization toward oxygen saturation level. It concludes that each method of nebulization i.e. Salbutamol and Hypertonic saline shows significant difference in the post-test oxygen saturation level, heart rate, and respiratory pattern of the children than pre-test but salbutamol shows better result compared to hypertonic saline nebulisation.

8) **Aayush Khanal, Arun Sharma, Srijana Basnet et.al, 2015:** conducted a study to assess the efficacy of nebulised hypertonic saline (HS) 3% among children with mild to moderately severe bronchiolitis. A double-blind randomised controlled trial method was used in this study. Infants aged 6 weeks to 24 months, with a first episode of wheezing and Clinical severity scores between 1 and 8, were enrolled over 4 months duration.



Those with severe disease, co-morbidities, prior wheezing, recent bronchodilator and steroid use were excluded. Patients were randomized in a double blind fashion, to receive two doses of nebulised 3% HS (group1) or 0.9% normal saline (group 2). It concluded that Nebulised 3% HS is effective, safe and superior to normal saline for outpatient management of infants with mild to moderately severe viral bronchiolitis in improving clinical severity scores, Facilitating early out-patient department discharge and preventing hospital re-visits and admissions in the 24hr of presentation.

**9) Todd A Florin, Kathy N Shaw, Marlena Kittick , 2014:** conducted a study to determine whether nebulized 3% HS compared with normal saline (NS) improves respiratory distress in infants with bronchiolitis not responding to standard treatments in the emergency department. A randomized clinical trial with blinding of investigators, health care providers, and parents was conducted at a single urban pediatric ED. The participants included children aged 2 to less than 24 months with their first episode of bronchiolitis and a Respiratory Distress Assessment Instrument score of 4 to 15 after nasal suctioning and a trial of nebulized albuterol. Patients were randomized to receive either nebulized 3% HS (HS group) or NS (NS group). The 31 patients enrolled in each treatment arm had similar baseline demographic and clinical characteristics. At 1 hour after the intervention, the HS group demonstrated significantly less improvement in the median Respiratory Assessment Change Score compared with the NS group (HS, -1 [interquartile range, -5 to 1] vs. NS, -5 [interquartile range, -6 to -2];  $P = .01$ ). There were no significant differences in heart rate, oxygen saturation, hospitalization rate, or other outcomes. Infants with bronchiolitis and persistent respiratory distress after standard treatment in the emergency department had less improvement after receiving 3% HS compared with those who received NS. Based on these results and the existing evidence, administration of a single dose of 3% HS does not appear to be indicated to treat bronchiolitis in the acute care setting.

**10) Francois Angoulvant, Xavier Bellettre, Karen Milcent et al, 2017:** conducted a study to examine whether HS nebulization treatment would decrease the hospital admission rate among infants with a first episode of acute bronchiolitis. The Efficacy of 3% Hypertonic Saline in Acute Viral Bronchiolitis (GUERANDE) study was a multicenter, double-blind randomized clinical trial on 2 parallel groups conducted during 2 bronchiolitis seasons (October through March) from October 15, 2012, through April 15, 2014, at 24 French pediatric EDs. Among the 2445 infants (6 weeks to 12 months of age) assessed for inclusion, 777 with a first episode of acute bronchiolitis with respiratory distress and no chronic medical condition were included. Two 20-minute nebulization treatments of 4 mL of HS, 3%, or 4 mL of normal saline (NS), 0.9%, given 20 minutes apart. Hospital admission rate in the 24 hours after enrolment was the measured outcome. Of the 777 infants included in the study (median age, 3 months; interquartile range, 2-5 months; 468 [60.2%] male), 385 (49.5%) were randomized to the HS group and 387 (49.8%) to the NS group (5 patients did not receive treatment). By 24 hours, 185 of 385 infants (48.1%) in the HS group were admitted compared with 202 of 387 infants (52.2%) in the NS group. The risk difference for hospitalizations was not significant according to the

mixed-effects regression model (adjusted risk difference, -3.2%; 95% CI, -8.7% to 2.2%; P = .25). The mean (SD) Respiratory Distress Assessment Instrument score improvement was greater in the HS group (-3.1 [3.2]) than in the NS group (-2.4 [3.3]) (adjusted difference, -0.7; 95% CI, -1.2 to -0.2; P = .006) and similarly for the Respiratory Assessment Change Score. Mild adverse events, such as worsening of cough, occurred more frequently among children in the HS group (35 of 392 [8.9%]) than among those in the NS group (15 of 384 [3.9%]) (risk difference, 5.0%; 95% CI, 1.6%-8.4%; P = .005), with no serious adverse events. Nebulized HS treatment did not significantly reduce the rate of hospital admissions among infants with a first episode of acute moderate to severe bronchiolitis who were admitted to the pediatric ED relative to NS, but mild adverse events were more frequent in the HS group.

**11) Khandaker Tarequal Islam, Abid Hossan Mollah , Abdual Matin , and Mahmuda Begum, 2018 :** Comparative Efficacy of Nebulized 3% Hypertonic Saline versus 0.9% Normal Saline in Children with Acute Bronchiolitis. A randomized control trial carried out in the Department of Pediatrics, Dhaka Medical College Hospital from January 2013 to December 2013. Ninety children from 1 month to 2 years of age hospitalized with clinical bronchiolitis were randomized to receive 3% nebulized hypertonic saline (Group-I) or 0.9% nebulized normal saline (Group-II). Nebulization was done 8 hourly until discharge. Outcome variables were clinical severity score, duration of oxygen therapy and length of hospital stay. Baseline clinical severity score and O<sub>2</sub> saturation were in group-I 9.0±1.0 and 94.9±1.7 and in group-II 9.3±1.8 and 94.6±2.6 respectively (p>0.05). At 72 hours, the mean severity score for the group-I was 1.64±0.99 and that for the group-II was 3.0 ± 1.48 (95% CI -2.17 to -0.53, p=0.002). The cases of group-I required a shorter duration of oxygen therapy compared to those of group-II (15.0±6.0 hours vs 26.4±5.37 hours, 95% CI -20.35 to -2.44). Forty two (93.3%) of the group-I children recovered by the end of 72 hours and discharged whereas 26 (57.8%) of the group-II children recovered during the same period. Length of hospital stay was shorter in group-I compared to group-II (58.1±22.0 hours vs 74.7±27.2 hours, 95% CI -26.89 to -6.17, p=0.002). None of the cases encountered any side-effects. Hence, Nebulization with 3% hypertonic saline significantly reduced clinical severity, length of hospital stay and duration of oxygen therapy in case of acute bronchiolitis in comparison to 0.9% normal saline and was safe.

## METHODOLOGY

## Methodology

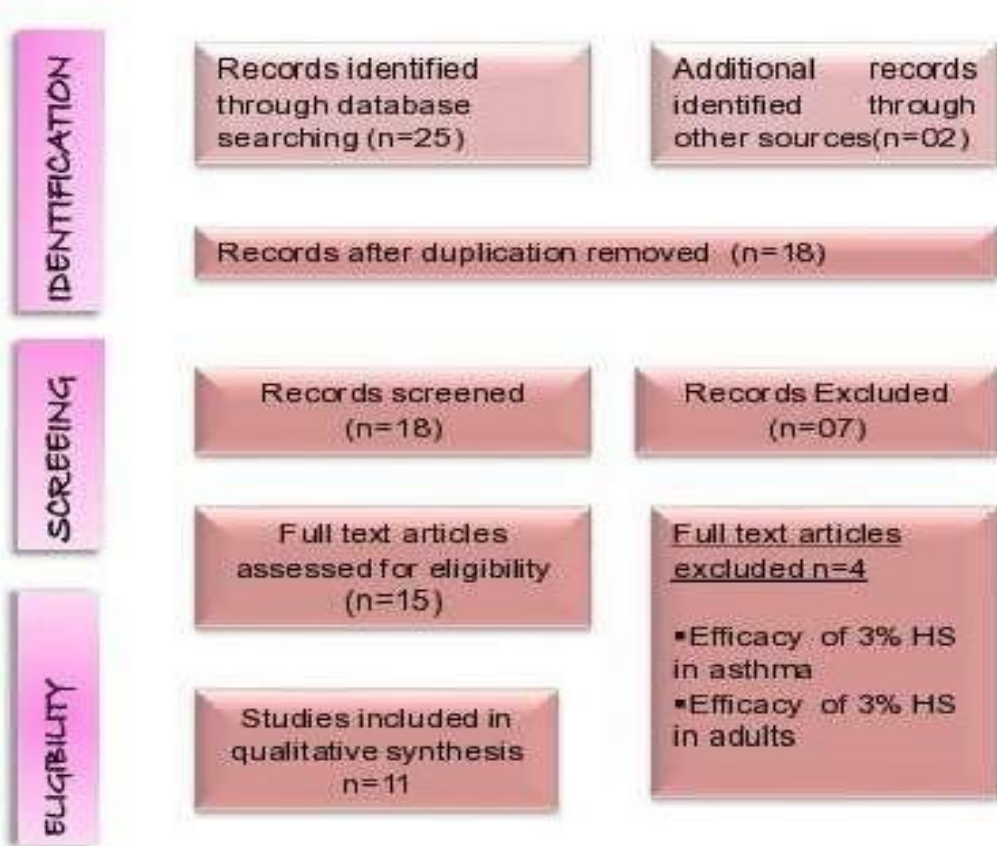
The primary outcome was reduction in mean respiratory rate and distress whilst the secondary outcomes included length of stay and readmission. To develop an effective search strategy, we adopted the Population, Intervention, Comparison, Outcomes and Study Design (PICOS) worksheet in a **Table 1**.

PARAMETER	INCLUSION CRITERIA	EXCLUSION CRITERIA
POPULATION	Children of age ranges from 1 month-12 years having bronchiolitis.  Children with mild to severe bronchiolitis, Lower respiratory tract infections.	Children of age less than 1 month, Adolescents & Adults with acute bronchiolitis.  Children with acute and chronic exacerbations conditions and asthma
INTERVENTION	<b>Experimental Group:</b> Nebulized 3% hypertonic saline, which is in seldom use in the treatment of acute bronchiolitis	The studies which use Nebulization with 7% Hypertonic saline for the treatment of bronchiolitis were not included
COMPARISON GROUP	<b>Comparison groups:</b>  <b>1. Either use of nebulized 0.9% Normal saline alone or with combination of Sallbutamol.</b>  <b>2. Supportive care of bronchiolitis..</b>	<b>Placebos were excluded</b>
OUTCOME	<b>Primary Outcome:</b> Reduction in clinical respiratory severity score instrument  <b>Secondary Outcome:</b> Length of hospital stay, Duration of oxygen therapy, duration of Readmissions.	Physiological parameters is of no interest  Heart rate, Blood pressure. Effects of bronchodilator.
STUDY DESIGN	Randomized Controlled trial, Double blind randomized clinical trial, Prospective study, Quasi experimental study.	Case Report, Lack of rigorous description of the methodology and experimental set up impeding replicability.

TABLE NO.1 shows PICOS criteria: Population, Intervention, Comparison and Outcome

**Search strategy:** we searched the MEDLINE/PubMed, Scopus, CENTRAL Cochrane, Google scholar, electronic database searches and hand searches of relevant journals and abstract book of conference proceedings for RCTs on effectiveness of 3% nebulized hypertonic normal saline compared with usual care or any active control intervention. The challenge of the review is the heterogeneity of these studies. The keywords used in search strategy were 3% Nebulized Hypertonic saline, bronchiolitis, Nebulized normal saline, Nebulized salbutamol.

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA comprises a 27-item checklist that has to be completed in order to improve quality of systematic reviews. The check-list is reported in Supplementary **Table 2**



Date of most recent search: April –July 2020

**Selection Criteria:** We included Randomized controlled trials and quasi experimental and Pre Experimental studies comparing 3% Nebulized Hypertonic Saline with a control group in children with bronchiolitis.

### **Inclusion Criteria**

- Children up to the age of 12 years with a clinical diagnosis of mild to severe bronchiolitis were eligible for inclusion.
- **3% Nebulized Hypertonic Saline was given along with supportive care of bronchiolitis**
- Effect of 3% Nebulized Hypertonic Saline on respiratory status/parameters, along with length of stay and readmissions.
- RCT, Case control, quasi experimental, pre-experimental, true experimental design studies.
- Studies reported within the period of 2011 to 2020 were included.

### **Exclusion criteria**

- Adult as a participant
- Children with other diagnosis such as asthma or respiratory exacerbations.
- 0.9% Nebulized Normal saline as intervention
- 7% Nebulized Hypertonic saline .
- Studies reported before the period of 2011 were excluded.
- Case reports.
- Any intervention where 3% Nebulized Hypertonic Saline were not key to the intervention was excluded.

## **Data Collection and analysis:**

Review authors independently selected articles for inclusion, evaluated the methodological quality of the studies, and extracted data. Data were pooled in random effect meta-analysis whenever possible. Data extraction comprises of:

- Study name
- Year of publication
- Sampling technique
- Outcome measured
- Study group Mean
- Study group Standard difference
- Comparison group Mean
- Comparison group standard difference
- Difference between two means

## **Risk of bias in individual studies:**

Risk of bias was assessed by authors independently using the Cochrane risk of bias tool. This tool assesses risk of bias using 7 criteria (rating: low, unclear, or high risk of bias): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Discrepancies were rechecked with a third reviewer and consensus achieved by discussion.

- Authors identified 25 studies, of which 11 studies with 1958 participants met the review's inclusion criteria. There was wide variation in the methodological and written quality of the included studies.
- The comparison groups received different interventions:
  - Nebulized with Normal saline
  - 4 mL of 0.9% saline along with 1.5 mg of epinephrine
  - Nebulized Normal saline with salbutamol
  - Standard supportive care
  - The majority of trials stated that they administered 0.9 % of normal saline as the control group except one where standard supportive care was the control
- The administration of 3% nebulized Hypertonic saline to experimental group was varied, with duration ranging from 4 hourly to 8 hourly and in some studies the efficacy of 3% nebulized Hypertonic saline

was assessed along with and without salbutamol.

- Participant numbers ranged from 80 to 777 in the included studies; all studies were in children only. The mean ages of the children in the studies ranged from 2.6 months to 12 months. All studies randomly assigned children to nebulized treatment groups of either 3% HS or 0.9% NS. All of the included studies used reduction in Clinical Respiratory Assessment Scale and length of hospital stay except one study which utilized O<sub>2</sub> saturation rate and Respiratory patterns as an outcome.
- Finally, eleven Randomized controlled trial with a total of 1958 patients were included. Compared with usual care and other intervention group (0.9%NS, Salbutamol). Trials durations ranged from 4hourly to 6 hourly/ day for 4 to 6 days. We applied no restrictions based on the concentration, dose or administration of the intervention or control.
- In four studies (1-3,7), a protocol-specified bronchodilator was mixed and nebulized along with a 3% hypertonic solution, including salbutamol, 1.5mg epinephrine, and standard supportive care at variable dosing frequencies and durations.



## SUMMARY OF STUDIES:

Study Title	Author & Publications	Design of study & Technique	Sample	Results
RCT Compared treatment with Nebulized 3% Hypertonic Saline Plus Salbutamol versus Nebulized 0.9% Saline Plus Salbutamol	NurzulsanaAwang, AriffinNasir, RowaniMohdRawi FahishamTaib,2020	Double blind RCT  <b>Exp group:</b> nebulized 3% HS with salbutamol  <b>control group</b> nebulized NS with salbutamol.	101previously healthy children younger than 18 months old, with mild to moderate acute bronchiolitis.	There was no difference in the clinical severity score between group (p = .250) and the duration of hospital stay in both groups (p = .146).
Comparative efficacy of nebulization with 3% hypertonic saline and 0.9% normal saline	Sushmita Singh, Rupesh Masand, Girdhari Lal Sharma and Swati Mehta, 2020	RCT: Exp.group: 4 ml of 3% HS  Control group: 4ml of 0.9% NS  *along with 1.5 mg of epinephrine in each arm, at 4 hourly intervals	A total of 360 hospitalized patients of age 1–24 months, diagnosed as a case of acute bronchiolitis of moderate severity.	There was a significant (p=0.0011) reduction of 13 h (12.2%), i.e., from 4 days 23 h in Group B (NS) to 4 days 10 h in Group A in the mean LOS and significant difference (p=0.0001) Nebulization with 3% HS is superior to 0.9% NS nebulization in infants with clinically diagnosed acute bronchiolitis.

<p>RCT on Nebulised hypertonic saline in moderate-to-severe bronchiolitis among infants.</p>	<p>Raphaelle Jaquet-pilloud, Marie-Elise Verga, Michel Russo et. al, 2020</p>	<p>RCT Patients were Exp.group: randomised to receive standard Supportive care (SSC) with nebulization of 4 mL of 3% sodium chloride every 6 hours  Control: SSC</p>	<p>121 Patients aged 6 weeks to 24 months with a primary diagnosis of moderate or severe bronchiolitis were included.</p>	<p>No statistically significant differences were found between treatment groups at baseline .Children in the HS group had a non-significant difference in length of stay –2.8 hours (–10; 16) compared with the SSC group.</p>
<p>A randomized controlled trial on the efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis.</p>	<p>IikeOzahiIpek, Emekuyur Yalcin, Rabia GonulSezer, Abdulkadir Bozaykut et. al, 2011</p>	<p>randomized, double-blind, prospective study  Group 1 - salbutamol + normal saline (NS),  Group 2 - salbutamol + HS,  Group 3 - HS,  Group 4 - NS.</p>	<p>A total of 120 infants were included in this randomized, double-blind, prospective study.</p>	<p>No significant difference between different treatment groups were observed but there was reduction in CSS and duration of oxygenation in all treatment groups.</p>
<p>A RCT of nebulized 3% hypertonic saline with salbutamol</p>	<p>Pedro Flores, Ana Lusía Mendes, Ana S Netol, 2015:</p>	<p>RCT Exp.Group: nebulized 3% (hypertonic, HS)  Control: 0.9% (normal, NS) saline during their entire hospital stay</p>	<p>68 Previously healthy infants, younger than 12 months, hospitalized with mild-to-moderate acute viral bronchiolitis were randomized.</p>	<p>No difference between groups in severity scores from day 1 to day 4.</p>

Effectiveness of 3% hypertonic saline nebulisation in acute bronchiolitis among Indian children.	Harsh V. Gupta, Vivek V. Gupta, Gurmeet kaur et.al, 2016.	Quazi 1 <sup>st</sup> 3% HS group, 2 <sup>nd</sup> 0.9% normal saline 3 <sup>rd</sup> 0.9% saline with salbutamol group.	99 children were enrolled	3% HS nebulisation (without additional bronchodilators) is an effective and safe treatment for moderately ill patients of acute bronchiolitis.
Effectiveness of Salbutamol vs Hypertonic Saline Nebulization on breathing Pattern among children with LRTIs	Catherine Rand Manju Bala Dash, 2018:	Quazi pre and post with two group research design	80 children were enrolled age of 1month to 12years children.	It concludes that each method of nebulisation i.e. Salbutamol and Hypertonic saline shows significant difference in the post-test oxygen saturation level, heart rate, and respiratory pattern of the children than pre-test but salbutamol shows better result compared to hypertonic saline nebulisation.
Efficacy of nebulised hypertonic saline (HS) 3% among children with mild to moderately severe bronchiolitis.	Aayush Khanal, Arun Sharma, Srijana Basnet et.al, 2015.	A double-blind RCT Patients were randomized in a double blind fashion, to receive two doses of nebulised 3% HS (group1) or 0.9% normal saline (group 2)	80 Infants aged 6 weeks to 24 months.	It concluded that Nebulised 3% HS is effective, safe and superior to normal saline for outpatient management of infants with mild to moderately severe viral bronchiolitis in improving clinical severity scores,

<p>To determine whether nebulized 3% HS compared with normal saline (NS) improves respiratory distress in infants with bronchiolitis</p>	<p>Todd A Florin, Kathy N Shaw, Marlana Kittick,2014</p>	<p>A randomized clinical trial  Patients were randomized to receive either nebulized 3% HS (HS group) or NS (NS group).</p>	<p>62 children aged 2 to less than 24 months with their first episode of bronchiolitis.</p>	<p>Based on these results and the existing evidence, administration of a single dose of 3% HS does not appear to be indicated to treat bronchiolitis in the acute care setting.</p>
<p>Study to examine whether HS nebulization treatment would decrease the hospital admission rate among infants with a first episode of acute bronchiolitis.</p>	<p>Francois Angoulvant,XavierBelletre,KarenMilcent et al, 2017.</p>	<p>double-blind randomized clinical trial on 2 parallel groups  Two 20-minute nebulization treatments of 4 mL of HS, 3%, or 4 mL of normal saline (NS), 0.9%, given 20 minutes apart</p>	<p>777 with a first episode of acute bronchiolitis with respiratory distress.</p>	<p>Nebulized HS treatment did not significantly reduce the rate of hospital admissions among infants</p>
<p>Comparative Efficacy of Nebulized 3% Hypertonic Saline versus 0.9% Normal Saline in Children with Acute Bronchiolitis</p>	<p>KhandakerTarequal Islam, Abid HossanMollah , AbdualMatin , and Mahmuda Begum, 2018</p>	<p>were randomized to receive 3% nebulized hypertonic saline(Group-I) or 0.9% nebulized normal saline (Group-II). Nebulization was done 8 hourly until discharge.</p>	<p>90 children  1 month to 2 years of age.</p>	<p>Nebulization with 3% hypertonic saline significantly reduced clinical severity, length of hospital stay and duration of oxygen therapy in case of acute bronchiolitis in comparison to 0.9% normal saline and was safe.</p>

## Discussion

- The use of nebulized hypertonic saline in reducing the respiratory distress score and LOS was effectively safe in five studies as compared with control groups.
- In summary, HS was not associated with improved clinical scores in six amongst eleven studies whereas HS was not effective in shortening the length of hospital stay in seven amongst eleven studies.
- Even though it was also reported in one study that HS was associated with mild adverse effects (increased coughing) in contrast of comparison group. Table 3:

## Author's Conclusion :

- In this trial, HS had no clinical benefit on LoS or readiness for discharge and was not a cost-effective treatment for acute bronchiolitis. Claims that HS achieves small reductions in LoS must be treated with scepticism.

## Further research:

- Our aggregate level data analysis was unable to identify specific study characteristics which influence the effect of HS on LoS and reduction in Clinical severity respiratory scale.

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