

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

Abstract

Background: Bronchiolitis is a common lower respiratory tract infection that leads to frequent admission in the hospital of the infants at a rate of 312 per 1000 every year. (*Bronchiolitis - Symptoms and Causes - Mayo Clinic*, n.d.). The current study evaluates the effectiveness of nebulization with 3% hypertonic saline solution (HS) for improving clinical results, and lowering the hospitalization rate as well as the duration of stay in the hospital, and documents adverse events associated with HS.

Objective of the Study: To undertake a systematic review of randomized controlled trials and quasi-randomized studies that assessed the effects of 3% Nebulization with Hypertonic Saline among children with bronchiolitis. The primary outcome was a 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 must be completed to improve quality of systematic reviews.

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Analysis and Interpretation of the Data Result

- The authors identified a total of 25 studies, out of which 11 studies with 1958 people were found to meet the inclusion criteria of the review. The papers included in the analysis exhibited significant heterogeneity in terms of their methodological rigor and written presentation. The comparative groups were subjected to varying interventions. The patient was administered a nebulized solution consisting of 4 ml of normal saline with a concentration of 0.9%, coupled with 1.5 mg of epinephrine. Additionally, nebulized normal saline with salbutamol was provided as part of the standard supportive treatment.
- The administration of 3% nebulized Hypertonic saline to the experimental group exhibited variability in terms of frequency, ranging from every 4 hours to every 8 hours. Additionally, several studies evaluated the effectiveness of 3% nebulized Hypertonic saline both in conjunction with and without salbutamol. The efficacy and safety of nebulized hypertonic saline in lowering respiratory distress scores and levels of significance were shown to be significant in five investigations, when compared to control groups. High school (HS) did not show any association with improved clinical scores in six out of eleven studies, and it was also found to be ineffective in reducing the length of hospital stay in seven out of eleven studies.

Keywords: Nebulised Hypertonic Saline, PRISMA, Population, Intervention, Comparison, methodological rigor

I. INTRODUCTION

Infants and young children frequently acquire bronchiolitis, a lung infection. The respiratory syncytial virus (RSV) is the source of the inflammation and congestion in the lung's tiny airways, or bronchioles. Inflammation, edema, and necrosis of the small airway epithelium, together with bronchospasm and increased mucus production, are the hallmarks of this condition. In the Northern Hemisphere, bronchiolitis is a seasonal ailment that is most common during December and March (*Bronchiolitis - Symptoms and Causes - Mayo Clinic*, n.d.). RSV has been found to be the primary cause of bronchiolitis in two thirds of cases; the percentage is probably higher in hospitalized patient. In children with bronchiolitis, other viruses that are frequently found as single or coinfecting agents include the human metapneumovirus (hMPV), influenza viruses, parainfluenza viruses, rhinoviruses, human coronaviruses (hCoV), and hBoV. Out of all the influenza viruses, parainfluenza viruses types 1 and 3 are linked to bronchiolitis in hospitalized children (Wright et al., 2008).

The most prevalent lower respiratory tract illness among newborns, both in developed and developing nations, is thought to be bronchiolitis. According to western literature, the first-year assault rate can reach 11.6 per 100 children and the second-year attack rate can reach 6 per 100 children. For hospitalized patients, the death rate can reach 0.5-2%; for those with underlying heart or lung conditions, it can rise to 3-4%. The frequency of wheezing episodes in early newborns indicates that it is a serious issue in our nation as well, even though it is challenging to regularly identify the viruses causing it (Gupta et al., 2016). Due to the similarities of bronchiolitis to asthma, bronchodilators are often attempted in infants who present with wheezing from it. Their regular application is debatable. Several randomized, controlled studies (RCT) have not consistently shown any benefit. Patients with bronchiolitis should usually be given a brief trial of bronchodilators while the effect is carefully monitored; however, their use should only be sustained if clinical improvement can be demonstrated (Mathew, 2008). The therapeutic therapy of this issue varies greatly both within Canada and globally, with a notable prevalence of superfluous testing and poor treatments. This statement refers to children who are typically in good condition and are aged two years or less, and who have been diagnosed with bronchiolitis. The primary basis for diagnosing bronchiolitis is in the history of sickness and the findings obtained from physical examination. Laboratory research often lack use in providing meaningful assistance. Bronchiolitis is a condition characterized by self-limitation, typically requiring home-based supportive care for management. This study provides a description of demographic groups that are particularly susceptible to experiencing severe sickness. Additionally, it outlines a set of guidelines that can be used to determine the appropriate criteria for hospital admission. (Friedman et al., 2014).

The lack of therapeutic advantages offered by pharmacologic medications raises concerns among practitioners regarding potential interventions for infants diagnosed with bronchiolitis. Common supporting measures encompass the utilization of suctioning techniques, adequate hydration, and the provision of supplemental oxygen. Infants experiencing respiratory failure are typically treated within intensive care units through the utilization of positive pressure ventilation. (Schroeder & Mansbach, 2014). Supportive therapy, including oxygenation, aspiration of respiratory tract secretions, and preservation of hydration, is the primary approach to treating bronchiolitis. Despite the prevailing clinical practise recommendations, which advise against the routine administration of medicine for

bronchiolitis, the utilisation of many medical interventions remains prevalent. In addition to providing supportive care, nebulized bronchodilators such as salbutamol, epinephrine, and ipratropium bromide, as well as corticosteroids, are frequently employed in clinical settings. In the treatment of bronchiolitis, many therapeutic interventions are employed, including antiviral treatment with ribavirin, administration of heliox, usage of surfactant, application of cysteinyl leukotriene receptor antagonists, and utilization of extracorporeal membrane oxygenation. Given the current emphasis on the effectiveness and cost-efficiency of treatment, there is a prevailing preference for interventions that can reduce illness severity while minimizing expenses. (Ipek et al., 2011). Other research using hypertonic saline (3, 6 or 7%) resulted in conflicting results with minimal or no therapeutic advantages. Likewise, there is a scarcity of data about the comparison of significant outcomes such as readiness for discharge, the necessity for subsequent hospital visits, and rates of hospitalization. These outcomes serve as crucial indicators of morbidity and the economic implications associated with them. Due to the limited availability of rigorously controlled studies conducted in poor countries utilizing a 3% hypertonic saline (HS) solution, as well as the absence of a consensus about the management of bronchiolitis in our clinical setting, an opportunity arose to enhance the quality of care for this prevalent condition. Consequently, the purpose of this study was to evaluate the therapeutic effectiveness of a 3% HS solution. Additionally, Factors are considered such as readiness for discharge, rates of hospital revisit, and hospitalization, as these indicators indicate the morbidity and economic implications of the disease(Khanal et al., 2015).

II. NEED OF THE STUDY

For health care personnels, treating bronchiolitis can be extremely difficult because, for the most part, " no specific treatment seems to work." Nearly all the commonly used interventions—including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactants, and chest physical therapy—lack solid evidence. Certain experts have questioned whether bronchiolitis can be treated at all, and the data accessible from present studies is insufficient for drawing firm conclusions (Gupta et al., 2016). Nebulized hypertonic saline has the potential to improve clinical severity score and somewhat shorten hospital stays for newborns diagnosed with acute bronchiolitis. The administration of nebulized hypertonic saline has the potential to decrease the likelihood of hospitalization in both outpatients and individuals seeking care in the emergency department. Nevertheless, the quality of the evidence was evaluated as ranging from low to moderate (Zhang et al., 2017). In comparison to nebulized normal saline, the utilisation of nebulized hypertonic saline in infants admitted with acute bronchiolitis has been associated with a potential reduction in hospital stay duration by approximately 10 hours. Additionally, it may lead to improvements in clinical severity scores, which serve as a metric employed by medical professionals to evaluate the severity of the disease. Furthermore, the administration of nebulized hypertonic saline may potentially decrease the likelihood of hospitalisation by 13% in children receiving outpatient or emergency department care(Zhang et al., 2017)

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.

2. With respect to the use of 3% Nebulized Hypertonic Saline with or without salbutamol trials in children, we emphasized on study that investigated on changes in respiratory parameters, including length of stay. This systematic review considers the following respiratory parameters: forced expiratory volume, peak expiratory flow rate, respiratory pattern, oxygen saturation, breath sounds, and duration of oxygen therapy. The respiratory distress assessment instrument score and the clinical bronchiolitis severity score are used to assess these parameters. As well the length of hospital stay, the rate of readmissions and discharges, the effects and side effects of medications, and other outcomes were also noted (Gupta et al., 2016).

III. REVIEW OF LITERATURE

A study was conducted by **Sushmita Singh** to compare the efficacy of nebulization with 3% hypertonic saline and 0.9% normal saline in the management of acute bronchiolitis. A total of 360 hospitalized patients, aged between one and twenty-four months, with a diagnosis of moderately severe acute bronchiolitis, were randomly assigned to receive either 4 ml of 3% HS (Group A) or 4 ml of 0.9% NS (Group B), in addition to 1.5 mg of epinephrine in each arm, every four hours until the patients were well enough to be discharged. The mean length of hospitalization was significantly ($p=0.0011$) shortened from 4 days 23 hours in Group B (NS) to 4 days 10 hours in Group A. Additionally, there was a substantial ($p=0.0001$) difference in the clinical severity score between Group A and Group B starting on the second day. Nebulization with 3% HS is better than nebulization with 0.9% NS in babies with acute bronchiolitis that has been clinically diagnosed (Singh et al., 2020).

Jaquet Pilloud R conducted a study on Nebulized hypertonic saline in moderate-to-severe bronchiolitis: Patients aged 6 weeks to 24 months with a primary diagnosis of moderate or severe bronchiolitis were included. Patients were randomly assigned to receive SSC or regular SC with nebulization of 4 mL of 3% sodium chloride every 6 hours. 121 children were randomized. No statistically significant differences were found between treatment groups at baseline (age, Wang Score, atopic history, smoking exposure). Children in the Hypertonic Solution group had a non-significant difference in length of stay—2.8 hours (−10;16) compared with the Supportive Care 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 (R et al., 2020).

A randomized controlled trial was conducted by Ipek in 2011 on the efficacy of nebulized salbutamol, hypertonic saline, and salbutamol/hypertonic saline combination in moderate bronchiolitis. Most of the treatment in bronchiolitis includes oxygenation, aspiration of secretions from the respiratory system and maintenance of hydration. A total of 120 newborns were included in this randomized, double-blind, prospective trial. Infants were categorized according to the nebulized treatment they received: group 1 - salbutamol + normal saline (NS), group 2 - salbutamol + HS, group 3 - HS, group 4 - NS. Heartbeat, Clinical Bronchiolitis Severity Score (CBSS) and oxygen saturation of the patients were determined before and after the nebulization and at 48-72 h following admission by the authorized study physician. Post-treatment mean CBSS were significantly lower than pre-treatment scores in all groups ($p = 0.0001$) with no significant variation within groups. Improvement percentages for CBSSs were substantially 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

neonates improved after three doses of nebulized therapy regardless of the treatment regimens (Ipek et al., 2011).

Randomized controlled trial was conducted by **Flores** in a pediatric department of a Portuguese hospital to investigate the potential benefits of nebulized hypertonic saline (HS) in infants hospitalized with acute bronchiolitis. The study aimed to determine whether HS had any effect on the length of hospital stay or severity scores of the disease. The infants were randomly assigned to receive either nebulized 3% hypertonic saline (HS) or 0.9% normal saline (NS) throughout their hospital stay. The researchers also analyzed the need for supplemental oxygen, additional medications, and any adverse effects. A total of 68 patients completed the study, with 33 receiving HS and 35 receiving NS. The results showed that the median length of hospital stay did not differ significantly between the two groups, with HS patients staying for a median of 5.6 ± 2.3 days and NS patients staying for a median of 5.4 ± 2.1 days ($P = 0.747$). There was no significant difference in severity scores between the groups from day 1 to day 4. Similarly, there were no differences in the need for supplemental oxygen or additional medications (Flores et al., 2016).

A recent study was conducted by **Harsh V. Gupta** to evaluate the effects of different saline solutions combined with nebulized salbutamol in patients with acute viral bronchiolitis. The study aimed to compare the outcomes of using 3% hypertonic saline (HS), 0.9% normal saline, and 0.9% saline with salbutamol. The participants were divided into three groups: the 3% HS group, the 0.9% normal saline group, and the 0.9% saline with salbutamol group. Over the course of the study, four doses were administered at 6-hour intervals each day until the patients were discharged. The average age of the patients in the three groups were 6.03 ± 3.71 , 5.69 ± 3.34 , and 5.48 ± 3.35 years, respectively. The study compared the third-day clinical severity (CS) scores and the length of hospital stay among the three groups. The results showed that the 3% HS group had a significantly lower third-day CS score compared to the other two groups (1.0 ± 1.1 , 1.9 ± 1.1 , and 3.3 ± 0.5 , respectively; $P = 0.000$). Additionally, the average length of hospital stay was shorter in the 3% HS group compared to the other two groups (3.4 ± 1.7 , 3.7 ± 1.9 , and 4.9 ± 1.4 days, respectively; $P = 0.001$). Based on these findings, the study concludes that nebulization with 3% HS without additional bronchodilators is an effective and safe treatment option for nonasthmatic, moderately ill patients with acute bronchiolitis (Gupta et al., 2016).

Catherine R 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 nebulization 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 ± 0.36 and 1.00 ± 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 (Khanal et al., 2015).

Aayush Khanal, 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. Patients were randomized in a double-blind fashion, to receive two doses of nebulized 3% HS (group 1) or 0.9% normal saline (group 2). It concluded that Nebulized 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 (Khanal et al., 2015).

A study was undertaken by Todd A Florin to investigate the potential benefits of nebulized 3% hypertonic saline (HS) in comparison to normal saline (NS) for alleviating respiratory distress in infants diagnosed with bronchiolitis who did not respond to routine therapies administered in the emergency department. The participants were randomly assigned to receive either nebulized 3% hypertonic saline (HS group) or normal saline (NS group). 31 children, aged from 2 to less than 24 months, were evenly distributed throughout each treatment group. Compared to the NS group, the HS group showed noticeably less improvement in the median Respiratory Assessment Change Score one hour after the intervention. No statistically significant differences were observed in heart rate, oxygen saturation, hospitalization rate, or any other measured outcomes. Infants diagnosed with bronchiolitis and experiencing ongoing respiratory distress following usual therapy in the emergency department had diminished recovery subsequent to receiving a 3% hypertonic saline solution, in comparison to those who were administered a normal saline solution (Florin et al., 2014).

A study conducted by Francois Angoulvant aimed to investigate the effectiveness of HS nebulization treatment in reducing hospital admission rates for infants with acute bronchiolitis. The study, called the GUERANDE study, was a double-blind randomized clinical trial conducted over two bronchiolitis seasons. The study included 777 infants with a median age of 3 months (interquartile range, 2-5 months), of which 60.2% were male. Out of these infants, 385 (49.5%) were assigned to the HS group and 387 (49.8%) to the NS group. The infants received two 20-minute nebulization treatments, with one group receiving 4 mL of HS, 3%, and the other group receiving 4 mL of normal saline (NS), 0.9%, given 20 minutes apart. After 24 hours, 48.1% of infants in the HS group (185 out of 385) were admitted to the hospital, compared to 52.2% in the NS group (202 out of 387). The study also found that the HS group showed a greater improvement in the Respiratory Distress Assessment Instrument score (-3.1 [3.2]) compared to the NS group (-2.4 [3.3]). Similar results were observed for the Respiratory Assessment Change Score. Mild adverse events, such as worsening of cough, occurred more frequently in the HS group (35 out of 392, 8.9%) compared to the NS group (15 out of 384, 3.9%). However, no serious adverse events were reported. (Angoulvant et al., 2017)

Jasmijn conducted a study to investigate the effectiveness of nebulized 3% and 6% hypertonic saline in comparison to 0.9% hypertonic saline in children admitted to the hospital with viral bronchiolitis. Hospitalized children were randomly assigned to receive either nebulized 3% or 6% hypertonic saline, or 0.9% normal saline for their whole duration of hospitalisation. Salbutamol was administered as a therapeutic intervention to mitigate potential bronchial constriction. Out of the total sample size of 292 children, with a median age of 3.4 months, a total of 247 children successfully completed the study. There was no significant difference in the median length of hospital stay among the groups. The median lengths were 69 hours for th

the 3% hypertonic saline group, 70 hours for the 6% hypertonic saline group, and 53 hours for the 0.9% normal saline group. The p-value for the comparison was 0.29. The administration of hypertonic saline (3% or 6% sodium chloride) via nebulization, while deemed safe, did not result in a decrease in hospitalisation duration (Teunissen et al., 2014).

Z Luo conducted a study to assess the effectiveness and safety of regular inhalation of nebulized hypertonic saline (HS) in infants diagnosed with moderate to severe bronchiolitis. A total of 126 newborns were subjected to randomization, with the aim of administering either nebulized 3% hypertonic saline (HS) or 0.9% normal saline (NS). However, only 112 participants successfully finished the entirety of the trial. The length of stay (LOS) exhibited a drop from 6.4 ± 1.4 days in the non-surgical (NS) group to 4.8 ± 1.2 days in the high-surgical (HS) group, with a statistically significant difference ($p < 0.01$). The administration of nebulized hypertonic saline (HS) was found to be well-tolerated, as no negative effects that might be attributed to this treatment were seen. The findings indicate that the regular inhalation of hypertonic saline (HS) resulted in faster relief of symptoms and indications compared to normal saline (NS), and also led to a considerable reduction in the length of hospital stay for infants diagnosed with moderate to severe bronchiolitis. Moreover, no evident negative effects were observed as a result of this treatment approach (Luo et al., 2011).

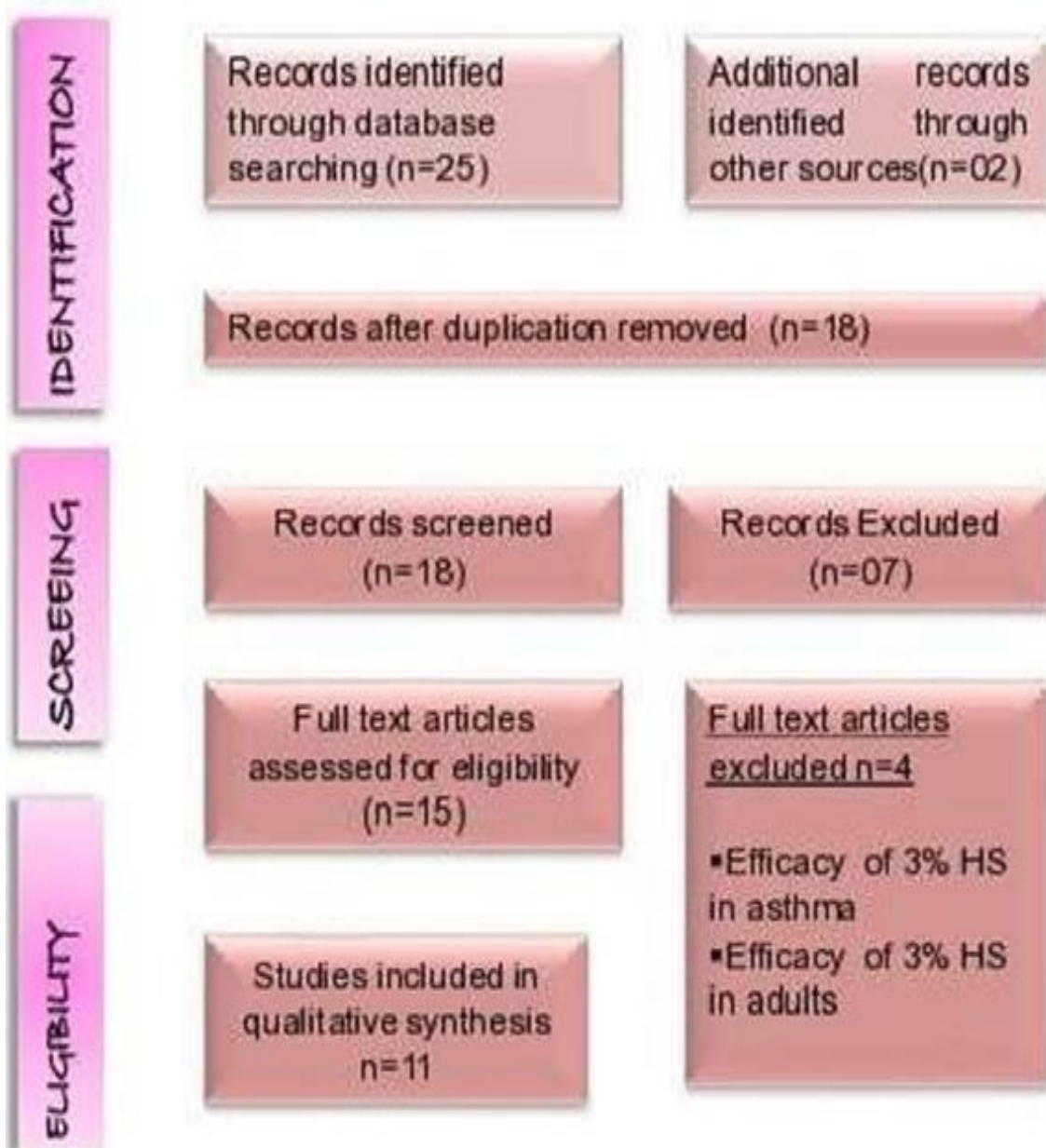
- 1. Methodology:** The primary outcome was a reduction in mean respiratory rate and distress whilst the secondary outcomes included length of stay and readmission. To develop an effective search strategy, we adopted the Population, Intervention, Comparison, Outcomes and Study Design (PICOS) worksheet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

Table 1: Shows PICOS criteria: Population, Intervention, Comparison and Outcome

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

2. 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 RCT 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 albuterol.

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



3. 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.

4. Inclusion Criteria

- Children upto 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.

5. 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

6. 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

7. Risk of Bias in Individual Studies: The authors independently evaluated the risk of bias by employing the Cochrane risk of bias method. The present method evaluates the potential for bias by the use of seven criteria, each rated as having a low, uncertain, or high risk of bias. These criteria include random sequence generation, allocation

concealment, blinding of participants and workers, blinding of outcome assessment, incomplete outcome data, selective reporting, and other forms of bias. The discrepancies were subjected to reevaluation by a third reviewer, and an agreement was reached through a process of discussion.

- Authors identified 25 studies, of which 11 studies with 1958 participants met the review's inclusion criteria.
- The methodological and writing quality of the included research varied greatly. 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.
- All the studies that were included had only children as participants, with numbers ranging from 80 to 777. The average ages of the children involved in the investigations varied between 2.6 months and 12 months. All studies employed random assignment to allocate children into nebulized therapy groups, with options including 3% hypertonic saline (HS) or 0.9% normal saline (NS). All of the studies included in the analysis employed the reduction in the Clinical Respiratory Assessment Scale and length of hospital stay as outcome measures, with the exception of one research that utilized O₂ saturation rate and Respiratory patterns as indicators of effectiveness.
- Finally, eleven Randomized controlled trials with a total of 1958 patients were included. Compared with usual care and other intervention groups (0.9% NS, Salbutamol). Trials durations ranged from 4 hourly 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 some studies, 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 duration.

IV. DISCUSSION

Acute bronchiolitis is a common lower respiratory tract infection affecting infants and young children. It presents a significant clinical challenge due to its potential for severe

respiratory distress and the absence of definitive treatment options. In recent years, there has been a growing interest in the use of nebulized hypertonic saline (HS) as a potential therapeutic intervention. This systematic review aims to critically evaluate the existing body of literature to ascertain the efficacy and safety of nebulized HS in the management of acute bronchiolitis.

- 1. Efficacy of Nebulized Hypertonic Saline:** Several studies have investigated the effectiveness of nebulized HS compared to normal saline (NS) in the treatment of acute bronchiolitis. The study by Sushmita Singh et al. (2020) demonstrated a significant reduction in the mean length of hospitalization and clinical severity scores in infants treated with 3% HS compared to those treated with 0.9% NS. Similarly, the study conducted by Gupta et al. (2016) reported a substantial improvement in clinical severity scores and a shorter hospital stay for patients receiving 3% HS compared to those receiving 0.9% NS.
- 2. Contrasting Results:** However, not all studies have reported such favorable outcomes. The study by Francois Angoulvant et al. (2017) found that nebulized HS did not significantly reduce the rate of hospital admissions among infants with acute bronchiolitis. This study, involving a large cohort of infants, highlights the complexity of the condition and the variability in patient responses to different treatment modalities. Similarly, Flores et al. (2016) did not find any significant differences in length of hospital stay or severity scores between patients receiving nebulized 3% HS and those receiving 0.9% NS.
- 3. Patient Selection and Heterogeneity:** One notable aspect of the reviewed studies is the variability in patient selection criteria. Some studies focused on infants with first episodes of bronchiolitis (Angoulvant et al., 2017; Khanal et al., 2015), while others included a broader range of patients with moderate to severe bronchiolitis (R et al., 2020; Singh et al., 2020). This heterogeneity in patient populations may contribute to the diverse findings across studies.
- 4. Combination Therapies:** Another noteworthy consideration is the inclusion of combination therapies in some studies. For instance, Ipek et al. (2011) evaluated the efficacy of nebulized salbutamol, hypertonic saline, and a salbutamol/hypertonic saline combination. The study reported significant improvements in clinical severity scores for all treatment groups, irrespective of the specific nebulized therapy administered. This suggests that while nebulized HS may play a beneficial role, its efficacy in isolation versus in combination with other treatments warrants further investigation.
- 5. Safety and Tolerability:** Across the reviewed studies, nebulized HS was generally well-tolerated, with no serious adverse events reported. However, some studies noted mild adverse events, such as transient worsening of cough (Angoulvant et al., 2017; Khanal et al., 2015). This highlights the importance of close monitoring and evaluation of patient responses to treatment.
- 6. Limitations and Future Directions:** Several limitations should be acknowledged when interpreting the findings of this systematic review. Firstly, the heterogeneity in patient populations, treatment protocols, and outcome measures across studies may introduce

variability in the results. Additionally, the sample sizes in some studies were relatively small, potentially limiting the generalizability of their findings. Future research should aim to address these limitations through well-designed, large-scale trials with standardized protocols.

V. CONCLUSION

In conclusion, the use of nebulized hypertonic saline in the management of acute bronchiolitis shows promise, with several studies reporting positive outcomes in terms of reduced hospitalization time and improved clinical severity scores. However, conflicting results and the heterogeneity in patient populations emphasize the need for further research to delineate the optimal use of nebulized HS in this context. Additionally, the potential benefits of combination therapies warrant exploration. Overall, nebulized HS represents a potentially valuable addition to the treatment arsenal for acute bronchiolitis, but its precise role and indications require further elucidation.

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