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NEBULIZATION THERAPY IN PEDIATRIC PATIENTS WITH BRONCHIOLITIS: A LITERATURE REVIEW

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ABSTRACT
Bronchiolitis is one of the most common causes of hospitalization in children under two years old. The main treatment for bronchiolitis is supportive therapy. Nebulization therapy in pediatric bronchiolitis is still being controversial in clinical practice and based on guideline recommendations. The purpose of this study is to determine and review the beneficial effects of saline and nebulized therapy in pediatric patients with bronchiolitis. Literature searches were obtained through reference sources from Google Scholar, PubMed, Proquest, JSTOR, ScienceDirect, and SAGE. Inclusion criteria were original articles, published in Indonesian and English, and assessed nebulization therapy's outcome in pediatric bronchiolitis patients. The treatment of administering nebulized saline NS or HS 3% can provide more effective results than treatment without nebulization. Many studies using nebulized salbutamol have found less clinical effectiveness and resulted in longer hospital stays. Combination therapy of saline and nebulization has more effective clinical results than single therapy of saline or nebulized drugs.

Keywords: bronchiolitis; combination; nebulization; pediatrics; therapy

INTRODUCTION
Bronchiolitis is a viral infection of the lower respiratory tract that most often occurs in children under two years old. This disease is one of the most common causes of hospitalization in infants (Hassan et al., 2018). Respiratory syncytial virus (RSV) is the most common etiology of bronchiolitis with an incidence rate of 50 to 90%. Bronchiolitis caused 59,600 hospital deaths in children under two years in 2015, with 99% prevalence occurring in developing countries (Crow et al., 2021). RSV spread occurs through secretions from the respiratory tract which spread through close contact with sufferers or a contaminated environment. Risk factors for bronchiolitis in babies are premature birth, chronic lung disease, congenital heart disease, immunocompromise, babies under 3 months of age, and exposure to cigarette smoke (Bradley et al., 2005).

The diagnosis of bronchiolitis is based on the history and physical examination. Bronchiolitis can show various symptoms and levels of severity, ranging from mild upper respiratory tract infections (ARI) to respiratory failure. Bronchiolitis presents with the first episode of wheezing before 12 months of age. Prodromal symptoms of the virus include fever, cough, and rhinorrhea lasting two to three days, progressing to tachypnea, wheezing, crackles, and varying degrees of respiratory distress. Signs of respiratory problems may include grunting, nostril breathing,

blueness, retractions, or abdominal breathing (Friedman et al., 2014.). Supporting examinations for bronchiolitis include oxygen saturation and chest x-ray examinations with signs of hyperinflation to atelectasis (Thorburn & McNamara, 2014).

Therapy for bronchiolitis consists of supportive management, including hydration, upper airway suction, and close monitoring for signs of respiratory failure and the need for intubation and mechanical ventilation. Supplemental oxygen is not used routinely unless oxygen saturation is consistently less than 90% (Erickson et al., 2023). Nebulization in bronchiolitis is a therapeutic option used to reduce symptoms because it reduces wheezing, shortness of breath, and edema in the airways. Nebulization can be a therapeutic option to relieve respiratory symptoms. Common therapeutic options are saline fluids, bronchodilators, epinephrine, anticholinergic agents, and corticosteroids. Each inhalation therapy has different outcomes and improves the patient's prognosis (Zhao, 2019). However, until now, no literature review has specifically and comprehensively discussed nebulization therapy using saline or other drugs for bronchiolitis. This study aims to provide a more comprehensive understanding and scientific evidence regarding nebulization therapy for bronchiolitis. It is hoped that this study can become a further reference for researchers in conducting clinical trials or in daily clinical practice.

METHODS

Literature searches were obtained through reference sources from Google Scholar, PubMed, Proquest, JSTOR, ScienceDirect, and SAGE. Researchers did not set a time limit for the study taken. The literature was searched using the keywords "nebulization, bronchiolitis, combination therapy, corticosteroids, and pediatrics" with synonyms. The inclusion criteria in this literature study are as follows:

1. Literature in the form of original articles
2. Literature published in English or Indonesian
3. The literature discusses nebulization therapy using normal saline, bronchodilators, or steroids in pediatric patients with bronchiolitis
4. Research subjects in literature are humans

The results obtained from the initial search were then reviewed by reading the title and abstract to assess the relevance of the literature. Relevance of studies was reviewed by reading the full text and assessed based on compliance with inclusion and exclusion criteria. The search results were reviewed by 5 authors (MK, TAS, RPD, AA, MRP), and if there were any disagreements between the authors, they would be resolved by discussion.

RESULTS

Bronchiolitis

Bronchiolitis is an acute lower respiratory tract infection characterized by the first episode of difficulty breathing in infants and children under two years old. Bronchiolitis is one of the causes of hospitalization for babies under one year of age. In general, bronchiolitis often begins with an upper respiratory tract infection with coryza, cough, or fever symptoms (Friedman et al., 2014). Bronchiolitis diagnosis is based on clinical symptoms, namely rhinorrhea, cough, expiratory wheezing, and respiratory distress. The first three days of symptoms are characterized by upper respiratory tract symptoms. A few days later, cough symptoms worsened, and increased respiratory effort and chest wall retraction indicated infection in the lower respiratory tract (Guitart et al., 2021). Bronchiolitis can be caused by viral, bacterial, and fungal infections. Viruses generally cause most acute bronchiolitis. Respiratory syncytial virus is the most common cause of acute bronchiolitis. Other viruses that cause include influenza virus, adenovirus, rhinovirus, human metapneumovirus, and coronavirus (Guitart et al., 2021).

Atypical bacteria that cause bronchiolitis are Mycoplasma pneumonia, Chlamydia trachomatis, and Chlamydia pneumoniae (Teeratakulpisarn et al., 2014; Wu et al., 2016).

According to the 2014 American Academy of Pediatrics guidelines, bronchiolitis therapy recommends that bronchiolitis management include oxygen supplementation, nutrition, and hydration. The administration of nebulized albuterol/salbutamol, epinephrine/adrenaline, hypertonic saline, and corticosteroids is not recommended for children with bronchiolitis (Ralston et al., 2014). Guidelines from other countries, such as the Italian guideline (Manti et al., 2023) and the Australian guideline (O'Brien et al., 2019), support the limitations of nebulized therapy. However, some studies still consider nebulization therapy in children with bronchiolitis to improve mucosal clearance (Guitart et al., 2021). Although some guidelines do not recommend it, researchers believe that nebulization therapy has benefits that can still be considered, so it requires more research to confirm.

Nebulization Therapy in Bronchiolitis

Nebulization therapy aims to deliver therapeutic doses of inhaled drugs derived from drug solutions or suspensions via a nebulizer through the mouth, nose, and artificial airway (tracheostomy/ETT) into the respiratory tract to the lungs. This therapy can function as additional or supporting therapy to systemic therapy. The aim of nebulization therapy is to reduce bronchospasm, coughing, and wheezing; moisturize the airways; have an anti-inflammatory effect; prevent respiratory complications such as airway inflammation, obstruction, atelectasis, infection, and asphyxia; and an expectorant. There are 3 general types of nebulizers: jet, ultrasonic, and vibrating mesh. Jet nebulizer is a type of nebulization device that is often used. This nebulizer comprises a compressed gas source (high-pressure oxygen/compressed air) and a nebulizer (Ibrahim et al., 2015; Zhao, 2019).

Table 1.
Saline nebulization in pediatric patients

Author (year)	Study Design	Subject	Nebulization Therapy	Methods	Outcome
Bakalović et al. (2023)	RCT	Children (n=380) average age (1-12) months	•NS •HS 3%	Divided into 3 groups: • NS • HS 3% • Did not receive nebulization	• LOS in NS group 5.0 (3.0-6.0) days; HS group 3% 5.0 (3.0-6.0) days; control group 5.0 (3.0-6.0) days. [NSi] • WBSS score at discharge (n=1) NS group 0.01±0.009; HS group 3% 0.01±0.01; control group 0.03±0.01. [NSi]
Pukai et al. (2020)	RCT	Children (n=199), average age 8.8 months	•NS	Divided into 2 groups: • NS • S.C	• After 4 hours, the difference in RDAI in the two groups: the average RDAI decreased (improved) by 3.41, and in the SC group, it decreased by 1.96 [S] • Improvement of hypoxemia after 4 hours, average increase in saturation in the NS group: 7%; SC group: 4% [S] • Participants who were outpatient after 4 hours in the NS group: 58%; SC group:24.2%[S]

Author (year)	Study Design	Subject	Nebulization Therapy	Methods	Outcome
Beal et al. (2019)	RCT	Children (n=103) mean age 4.2 ± 2.4 months	•HS 3% •NS	The first 24 hours, were given nebulized 3% HS every 8 hours; then participants were divided into 2 groups (nebulize every 8 hours for 2 days): • HS 3% • NS	• LOS > 6 days in the NS group: 2.9 ± 1.4 days; HS 3% : 2.2 ± 1.6 days [NSi] • WBSS at 72 hours NS: 3.4 ± 2.0; HS 3% : 2.7 ± 1.7 [NSi] • WBSS at 24 hours NS: 4.9 ± 2.1; HS 3% : 4.1 ± 2.4 [NSi] • Clinical improvement in NS: 2.9 ± 1.4 days; HS 3% : 4.1 ± 2.4 days [S]
Pilloud et al. (2019)	RCT	Children (n=121) average age 7.6 months	•HS 3%	Divided into 2 groups: • SC group (n=61) were given suctioning nasal secretions, fluid-electrolyte balance, and oxygen supplementation intervention • HS 3% group (n=59) were given 4 ml nebulization, every 6 hours until discharge	• LOS in the nebu HS group was 3% 47 hours shorter than the SC group, 50.4 hours [NSi]
Angoulvant et al. (2015)	RCT	Infants (n=777) [boys (n=468), median age 3 months]	•NS •HS 3%	Patients were nebulized for 20 minutes, and divided into 2 groups: • NS group [n=387 (49.8%)]; 5 patients did not receive therapy • HS 3% group [n=385 (49.5%)]	• After 24 hours, hospital admission was 185/385 (48.1%) HS group 3% and 202/387 (52.2%) NS group [NSi] • Mean LOS in the HS group was 3% in 3.8 (2.5) days and 3.7 (3.0) days in the NS group [NSi] • Change in HS group RDAI score 3% –3.1 (3.2) and –2.4 (3.3) in NS group [S] • HS group RACS score 3% –4.4 (4.9) and –3.4 (4.8) in NS group [S]
Silver et al. (2015)	RCT	Children (n=190) mean age 4.2 months [boys /(n=64.2%)]	•NS •HS 3%	Divided into 2 groups: • HS 3% • NS Nebulized every 4 hours	• Mean LOS in HS group: 2.1 days; NS: 2.1 days [NSi] • Average difference in RDAI after and before intervention in the HS group: 0.21; NS: 0.18 [NSi]
Teunissen et al. (2014)	RCT	Children (n=247) median age 3.4 months [boys (n=46%)]	•HS 3% •HS 6% •NS	Divided into 3 groups: • HS 3% • HS 6% • NS Nebulized every 4 hours	• Average LOS in HS 3% group: 69 hours; HS 6%: 70 hours NS: 53 hours [NSi] • Average WBSS improvement in HS group 3%: -4.55; HS group 6%: -4.54; NS group:-4.33 [NSi]

Author (year)	Study Design	Subject	Nebulization Therapy	Methods	Outcome
Luo et al. (2011)	Case control	Children (n=126) mean age 5.8 months [girls (n=77%)]	•NS •HS 3%	Divided into 2 groups: • Group A received 4 mL NS nebulization • Group B received nebulized HS 3% 4 mL Nebulization was given every 2 hours for a dose, followed by 5 doses every 4 hours, then given every 6 hours	• LOS in the HS 3% group: 4.8 ± 1.2 days shorter than in the NS group: 6.4 ± 1.4 days [S] • WBSS in the HS group 3% at baseline, day 1, day 2, day 3, and day 4 (8.5 ± 1.5; 5.7 ± 1.5; 3.5 ± 1.1; 2.4 ± 0.9 and 1.7 ± 0.6) was reduced compared to WBSS in the NS group at baseline, day 1, day 2, day 3, and day 4 (8.5 ± 1.5; 7.3 ± 1.7; 5.9 ± 1.5; 4.1 ± 1.1 and 3.1 ± 0.7) [S]

Table 1 shows several studies comparing NS and HS nebulization therapy in pediatric bronchiolitis. Significant clinical improvement results in the NS nebulization group were obtained in the RCT study of Pukai et al. (2020), with improvements in RDAI scores and oxygen saturation compared to SC (standard care) (Pukai & Duke, 2020). Based on studies by Angoulvant et al. (2015) and Luo et al. (2011), which compared HS nebulization and NS. It was found that HS nebulization was significantly more effective than NS in reducing symptoms based on the scoring system (Angoulvant et al., 2017; Luo et al., 2011). However, several studies did not obtain significant clinical improvement results in the HS group compared to NS using the WBSS (Bakalović et al., 2023; Beal et al., 2019; Teunissen et al., 2014) and RDAI (Silver et al., 2015) scoring systems. Meanwhile, based on hospital length of stay (LOS), six studies showed no significant difference in hospital LOS between the NS and HS nebulization groups (Angoulvant et al., 2017; Bakalović et al., 2023; Beal et al., 2019; Silver et al., 2015; Teunissen et al., 2014). Meanwhile, only one study in 2011 obtained significantly higher LOS results in the HS group. Short compared with the NS group (Pukai & Duke, 2020).

Table 2.
Nebulization of saline, corticosteroids, epinephrine, bronchodilators and nebulization combinations

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
Danish et al. (2022)	RCT	Children (n=180) average age 9.1 years	•Salbutamol + Ipratropium bromide + NS • Epi + NS	Divided into 2 groups: • Group 1 received nebulized salbutamol (0.15mg/kg) + ipratropium bromide (250 micrograms per dose) and NS 2mL • Group 2 received nebulized epinephrine 0.5mg/kg dissolved in 1:1000 NS a maximum of 5 mg	• RDAI score in group 1 decreased after nebulization for 30 minutes (mean 3.23+0.52) [NSi] • RDAI score in group 2 decreased after nebulization for 30 minutes (mean 2.67+0.47) [S]
Aksatha et al. (2022)	RCT	Children (n=200) average age (2-24)	•Epi + NS + DEXA injection •HS 3%	Divided into 2 groups: • 4 ml HS 3% (n=100)	• The average LOS of the Epi & DEXA group was 4.58 days shorter than the HS

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
		months		• 0.5m/kg Epi + 4ml NS + DEXA injection 1x/day in the first 5 days (n=100)	3% group 4.96 days [S]
Majagaiya et al. (2022)	RCT	Children (n=124) mean age 6.92±0.24	•HS 3% + salbutamol + budesonide •NS + salbutamo + budesonide	Divided into 2 groups: • HS 3% with 0.25 mL salbutamol + 0.5 mg budesonide (n=62) • NS with 0.25 mL salbutamol + 0.5 mg budesonide (n=62)	• WBSS in the HS group 3% + budesonide and salbutamol 7.34 ± 0.1 while in the NS + budesonide and salbutamol group 7.39 ± 0.99 [NSi] • LOS group HS 3% + budesonide and salbutamol 4.27 ± 0.90 days, while group NS + budesonide and salbutamol 5.39 ± 0.610 days [S]
Sharma et al. (2021)	RCT	Children (n=248) mean age 4.55 [boys (n=94.5%)]	•HS3% + Salbutamol •NS + Salbutamc	Divided into 2 groups: • 4 ml HS 3% plus 2.5 mg salbutamol for 4 hours • 4 ml NS plus 2.5 mg salbutamol for 4 hours	• LOS in NS group: 63.93 ± 22.43 and HS 3% group: 63.51 ± 21.27 [NSi] • Median WBSS between 2 groups monitored every 12 hours to 132 hours [NSi]
Yasin et al. (2021)	RCT	Children (n=34) average age 4.7 months	•Epi •HS 3%	Divided into 2 groups: • Epi group (n=99) was given epinephrine acid tartrate 1% with sodium metabisulfite and vehicle (n=99) • The placebo group (n=95) was given chlorobutanol, edetate disodium, sodium chloride, and purified water	• Mean LOS in the epinephrine group: 45 hours; HS 3% group: 74.3 hours [S]
Singh et al. (2020)	RCT	Children (n=351) mean age 8.95 months [boys (n= 208)]	•HS 3% + Epi •NS + Epi	Divided into 2 groups: • 4 ml HS 3% + 1.5 mg Epi (n=172) • NS + 1.5 mg Epi (n=179) Nebulization every 4 hours until the patient was outpatient	• LOS in the HS3%+ Epi group (106.03±18.19) hours was shorter compared to the NS + Epi group (119.19±22.08) hours [S] • Mean WBSS in HS3%+ Epi group and NS + Epi group day 0 (5.34±0.73 & 5.29±0.75) [NSi]; day 1 (4.77±0.86 &

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
					4.90±0.89) [NSi]; day 2 (3.506±0.767 & 4.024±1.020) [S]; day 3 (2.39±0.84 & 2.78±1.14) [S];]; day 4 (1.25±0.96 & 1.72±1.16) [S]; day 5 (0.56±0.75 & 0.94±0.86) [S]
Ali et al. (2017)	RCT	Children (n=120) mean age 13.01 months [male (n=61)]	•Salbutamol •HS 3%	Divided into 2 groups • Salbutamol (0.15 mg/kgBB) • HS 3%	• After 24 hours, the mean WBSS of the salbutamol group was 6,132.47 heavier than the HS 3% group 4,882.04 [S] • Mean LOS in the salbutamol group: 3,920.81 days longer than the HS 3% group 3,050.77 days [S]
Uysalol et al. (2017)	RCT	Children (n=378) mean age 7.63 ± 4.6 months [male (n=54.8%)]	•HS 3% •Epi •HS 3% + Epi •Salbutamol •NS	Divided into 5 groups: • Group 1 nebulized HS 3% • Group 2 is Epi nebulization • Group 3, namely nebulized Epi+HS 3% • Group 4 is salbutamol nebulization • Group 5 is NS nebulization	• Average LOS group HS 3% 8 hours, Epi 4 hours, Salbutamol 16 hours, Epi + HS 3% 4 hours and Normal saline 16 hours. [S]
Flores et al. (2016)	RCT	Children (n=68) mean age 3.5 months [boys (n=36)]	•HS 3% + salbutamol •NS + salbutamol	Divided into 2 groups: • HS 3% + salbutamol (n=33) • NS + salbutamol (n=35)	• HS group WBSS 3% days 1,2,3 (5.8± 2.1, 5.9 ±2.3, 5.5 ±3.2), NS group WBSS days 1,2,3 (6.3 ±1.7, 6.8 ±2.4, 5.6 ±2.7) [TS] • LOS group HS 5.6 ± 2.3, NS 5.4 ± 2.1 [NSi]
Gupta et al. (2016)	RCT	Children (n=99) mean age 6.03 ± 3.71 [boys n=69.73%)	•HS 3% •NS •NS + salbutamo	Divided into 3 groups: • HS 3% • NS • NS + Salbutamol Nebulized every 6 hours	• WBSS scores after 3 days of treatment in the HS 3%, NS, and NS+ salbutamol groups: 1.0 ± 1.1, 1.9 ± 1.1 and 3.3 ± 0.5 [S] • LOS in the HS 3%, NS, and NS+ salbutamol groups 3.4 ± 1.7, 3.7 ± 1.9

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
					and 4.9 ± 1.4 days [S]
González et al. (2015)	RCT	Children (n=185) mean age 2.11 ± 2.22 months [boys (n= 49.7%)]	•Epi + HS 3% •HS 3% + sterile water	Divided into 2 groups: • Epi (3 ml ratio 1:1000), in HS 3% (7 mL) (n=94) • HS 3% (7 mL) plus 3 mL of sterile water (n=91)	• WBSS on the third day of the Epi group 3.93.95% CI (3.68–4.17) and placebo (4.31.95% CI(4.014.59) [NSi] • LOS HS group 3% + Epi (3.94 ±1.37), HS group 3% + Placebo (4.82 ± 2.3) [S]
Bawazeer et al. (2014)	RCT	Children (n=162 children) average age 4.59 [male (n=53%)]	•Epi + oral DEXA •Salbutamol + oral DEXA •Epi + oral placebo •Salbutamol + oral placebo	Divided into 4 groups • Nebulized Epi + oral DEXA • Nebulization Salbutamol + oral DEXA • Nebulized Epi + oral placebo • Nebulized salbutamol + oral placebo	• RDAI scores at 0 minutes and 240 minutes: nebu Epi+ oral DEXA group (7.69;4.41), nebu salbutamol + oral DEXA group (8.6;5.14), nebu Epi+ oral placebo group (8.18;4.79), nebu salbutamol + oral placebo group (8;5.03) [NSi]
Giudice et al. (2012)	RCT	Children (n=136 children) average age 4.5 months [boys (n=69)]	•NS + Epi •HS 3% + Epi	Divided into 2 groups: • NS + Epi 1.5mg + conventional therapy • HS 3% + Epi 1.5mg + conventional therapy Every 6 hours nebulization was done. CSF assessment was carried out twice a day before and after nebuization.	• LOS Group 1: 5.6±1.6 days, group 2: 4.9±1.3 [S] • WBSS day 1, day 2, day 3 in the NS group before nebulization (8.8 ± 1.5; 8.3 ± 1.7; 7.7 ± 1.6) and after nebulization (8.8 ± 1.6; 8.2 ± 1.7; 7.6 ± 1.6) [NSi] • WBSS HS group 3% before inhalation (8.5 ± 1.4; 7.4 ± 1.6; 6.5 ± 1.6) and after inhalation (8.0 ± 1.3; 6.8 ± 1.4; 5.8 ± 1.4) [S] • WBSS difference between the two groups on days 1,2,3 [S]
Kiper et al. (2011)	RCT	Children (n=75) mean age 7.6 months [boys (n=64%)]	•Epi + NS •Salbutamol + N	Divided into 2 groups: • Group 1: Nebulization Epi/30 minutes (L-epinephrine 1:1000, 2.5 mg/dose combined with 0.9%	• RDAI scores decreased in both groups. Group 1: first 1 hour (mild 21, moderate 13, severe 2); first 4 hours (mild 30, moderate 3, severe

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
				saline solution). • Group 2: 2 doses of salbutamol given every 30 minutes (salbutamol 0.15 mg/kg/dose combined with 0.9% saline solution).	3). Group 2: first 1 hour (mild 19, moderate 19, severe 3); First 4 hours (mild 32, moderate 5, severe 2) [NSi] • Hospitalization rate in group 1: 8.3%; group 2: 5.1% [NSi] • Average LOS in group 1: 18.5 hours; group 2: 14.5 hours [NSi]
Plint et al. (2009)	RCT	Children (n=800) median age 5 months [boys (n=60%) in each group]	•Epi + oral DEXA •Epi + oral placebo •Placebo + oral DEXA •Placebo + oral placebo	Divided into 4 groups • Epi + oral DEXA nebulization group • Epi nebulization group + oral placebo • Placebo nebulization + oral DEXA group • Nebulization placebo + oral placebo group Nebulization was given for 30 minutes, nebulization 3ml Epi 1:1000 in 3cc saline, oral dexamethasone 1mg/kgBB (maximum 10 mg). The placebo consisted of Ora-Plus and Ora-Sweet.	• Hospital admission after 7 days of intervention in the ER: Group 1 (17.1%), group 2 (23.7%), group 3 (25.6%), group 4 (26.4%) [S] • RDAI score after 30 minutes: Group 1 (−1.62±2.23), group 2 (−1.44±1.94), group 3 (−0.98±2.07), group 4 (−1.06±2.16) [S] • RDAI score after 60 minutes: Group 1 (−2.50±2.58), group 2 (−2.45±2.32), group 3 (−1.75±2.40), group 4 (−1.65±2.42) [S] • Discharge time from the ER/Hospital in group 1 (4.6 hours) was shorter than in group 4 (5.3 hours) [S] • Discharge time from emergency room/hospital in group 3 (5.1 hours), group (2.9 hours) compared with group 4 [NSi]
Mull et al. (2004)	RCT	Children (n=68) average age 4.7 months	•Epi + NS •Albuterol + NS	Divided into 2 groups: •Epi 0.9 mg/kg + 2ml NS together with O2 6 lpm •Albuterol 0.15 mg/kg + 2 ml NS together with O2 6 lpm	• Mean RDAI Score in both groups decreased [S] • Mean SpO2 improved more quickly in the Epi group (90 minutes) compared to albuterol (120

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
					minutes) [S]
Wainwright et al. (2003)	RCT	Children (n=194) mean age 4.43 months [boys (n=60%)]	•Epi •Plasebo	Divided into 2 groups •Epi group (n=99) was given epinephrine acid tartrate 1% with sodium metabisulfite and vehicle (n=99) •Placebo group (n=95) was given chlorobutanol, edetate disodium, sodium chloride, and purified water	•Mean LOS in Epi group: 58.8 (49.4–70.0) hours; placebo group: 69.5 (59.3–81.4) hours [NSi] •Mean time ready for discharge in the Epi group: 46.5 (38.3–56.5) hours; placebo group: 47.7 (39.0–58.3) hours [NSi]
Ho et al. (1991)	RCT	Children (n=21) average age 3 months	•Salbutamol •NS	Participants were randomly given nebulization: •Salbutamol 2.5 mg/2ml plus oxygen 6 lpm •Placebo (2ml normal saline) plus 6 lpm oxygen SpO2 checking were carried out every 30 minutes before nebulization, 10 minutes during nebulization, 30 minutes after nebulization	•Oxygen saturation (SpO2) of the group receiving nebulized salbutamol experienced desaturation [S] •Oxygen saturation (SpO2) in the group receiving placebo nebulization experienced desaturation [S]
Stokes et al. (1983)	RCT	Children (n=25) average age 17 months	•*Aquadest* •Salbutamol •Ipratropium bromide	Divided into 3 groups: • Nebulize 2 ml distilled water • Nebulization of 2 ml salbutamol • Nebulization of 2 ml ipratropium bromide Patients were given otorvine nasal drops 30 minutes before nebulization to clear the upper respiratory tract	•The average total effort of breathing did not change before and after nebulization with distilled water and salbutamol [NSi] •The average total effort of breathing changed before and after nebulization by 18.2% with Ipratropium bromide [S]
Sapkota et al. (2021)	Prospective Cohort	Children (n=100) mean age in the HS group was 3% (7.17±4.46) months, and in the	•HS 3% + Salbutamol •NS + Salbutamc	Divided into 2 groups • HS 3% nebulization group + 2.5mg salbutamol • NS nebulization group + 2.5 mg salbutamol Every 4 hours until	•LOS in the HS 3% + salbutamol group was shorter than in the NS + salbutamol group [S] •Symptoms in Group HS 3% + salbutamol

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
		NS+2.5 mg salbutamol group (6.6±3.74) months. [male (n=55%)]		the patient was discharged	(coughing, wheezing) improved more quickly compared to Group NS + salbutamol [S]
Song et al. (2021)	Prospective Cohort	Children (n=127) mean age 16.1 months [boys (n=77)]	•Budesonide + Salbutamol •No nebulization	Divided into 2 groups: • Control group (n=59): patients with conventional management (antivirals, sputum aspiration, several methods to reduce disease progression) • Intervention group (n=68): patients were given nebulized Budesonide 2x1 at a dose of 200 μg/15 minutes/inhalation, and nebulized salbutamol 2x1 at a dose of 200 μg/15 min/inhalation for 2 weeks	• Time to disappearance of complaints was shorter in the intervention group compared to the control group [S]
Mojtaba et al. (2016)	Prospective Cohort	Children (n= 67) average age 4 months [boys (n= 39), girls (n= 28)	•Ventolin + NS •HS 5%	The duration of the study was 6 months divided into 2 groups: • Ventolin (500 mg/mL in NS) • HS 5% using a jet nebulizer	• Average LOS in the Ventolin nebulization group: 4.2 days longer than the group with 5% HS nebulization: 3.8 days [NSi]
Pinto et al. (2016)	Retrospective Cohort	Children (n=195) average age 4.95 months	•Albuterol •Albuterol + HS 3% •HS 3% •No nebulization	Divided into 4 groups: • Group 1 received nebulized Albuterol • Group 2 received nebulized Albuterol + HS 3% • Group 3 received HS 3% nebulization • Group 4 without nebulization	• LOS for children in Groups 1 and 4 was shorter (29.3-50.9 hours; 33.7-48.8 hours), and compared to that in Groups 2 and 3 (47.9-88.7 hours; 48.6-90.5 hours) [S] • Respiratory scores in group 4 are lower than groups 1,2,3 [S]
Tinsa et al. (2009)	Prospective Cohort	Children (n=35) mean age 6.25 months [boys (n=54.95%)]	•Terbutaline •NS	Divided into 2 groups: • Terbutaline nebulization group • NS nebulization group	• RDAI scores in the terbutaline group: baseline (7.4 ± 2.4), 30th minute (6.73 ± 2.5), 60th minute (6.05 ± 2.8), and 120th minute (4.7 ± 2.4). RDAI scores

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
					in the NS group: baseline (7.5 ± 0.9), 30 minutes (6.5 ± 0.7), 60 minutes (5.5 ± 1), and 120 minutes (4.6 ± 1.3) [NSi] • Length of stay in the NS group was 2.57 days shorter than in the terbutaline group, 3.3 days [NSi]

There were 3 studies that carried out nebulized combinations of epinephrine with saline and oral or injectable dexamethasone (Table 2) (Akshatha et al., 2022). Plint et al.(2009) study with nebulized epinephrine, NS and oral dexamethasone found reduced hospital admissions in 7 days , RDAI score, and discharge time were significantly compared with other groups (Plint et al., 2009). Meanwhile, Bawazeer's (2014) study with nebulized epinephrine and oral dexamethasone found that the RDAI score was not significantly reduced compared to the nebulized salbutamol and oral dexamethasone groups; nebulized epinephrine and oral placebo; nebulized salbutamol and oral placebo (Bawazeer et al., 2014). Other nebulization therapies with various agent were also reported as shown in Table 3.

Table 3.
Other Nebulization Therapies in Pediatric Patients with Bronchiolitis

Author (year)	Study Design	Subject	Therapy	Methods	Outcome
Debbarma et al. (2021)	RCT	Children (n=60) average age 7.5 months	• Mg SO4 • No nebulization	Divided into 2 groups (total subjects = 60): • Intervention Group: nebulization 3ml 3.2% MgSO4 every 4 hours for 24 hours + SC • SC Group	• Mean LOS was 2.89 ± 2.25 days in the MgSO4 group and 2.96 ± 1.86 days in the SC group [NSi] • BSS monitored in two groups [NSi]
Chen et al. (2020)	RCT	Children (n=600) mean age 244 days [boys (n=407)]	• IFN injection IM • Low dose IFN 1 µg/kg • High dose IFN 2 µg/kg	Randomly divided into 4 groups: • Control Group • IM IFN injection group • Nebulization group 1 (IFN low dose) 1 µg/kg • Nebulization group 2 (IFN high dose) 2 µg/kg	• Cough score on days 1 and 3; 3 and 5; 5 and 7 (P value: 0.003, 0.005, 0.28. Differences in cough score on days 1 and 3: nebulization 2 (P<0.001), days 3 and 5: IFN injection, IFN nebulization 1, nebulization IFN 2 0.004, 0.003 and 0.009) [S] • •Lowell wheezing scores on days 1 and 3; 3 and 5, 5 and 7 (P<0.001, 0.165, 0.149) [S]
Naz et al. (2014)	RCT	Children (n=100) average age 3 months	• N-acetylcysteine • Salbutamol	Divided into 2 groups: • Group 1 received nebulized N-acetylcysteine • Group 2 received nebulized salbutamol	• Clinical severity score in group 1 (Day 1: 15.38 ± 2.62, day 3: 2.9 ± 1.48, day 5: 3.30 ± 1.77) [S] • Clinical severity score in group 2 (Day 1: 4.68 ± 2.2, day 0.88 ± 1.08, day 3: 1.90 ± 1.32) [S] • Average LOS of group 1: 4.36 ± 1.66 shorter than group 2: 4.98 ± 2.6 [NSi]

DISCUSSION

Nebulizing Fluids and Medications in Bronchiolitis Patients

Saline

Nebulized saline was first introduced in 2002. The saline fluids that can be used are NS (normal saline) and HS (hypertonic saline). Nebulization of saline fluid has several benefits regarding the treatment of bronchiolitis. The first benefit of saline nebulization is that it can increase mucus clearance by destroying mucus ionic bonds, reducing the thickness and elasticity of mucus, inducing osmotic fluid flow from the mucus layer, and stimulating the release of prostaglandins thereby rehydrating the airway lining and improving mucociliary clearance (Sapkota et al., 2021). The second benefit of saline nebulization is that it can absorb fluid from the mucosal and submucosal layers to reduce edema in the respiratory tract. Saline nebulization is safe with rare side effects such as temporary bradycardia and desaturation (Zhang et al., 2017). Due to the good safety profile, low cost, and non-invasive administration, nebulized administration of hypertonic saline is considered good to apply (Alharbi et al., 2018).

Epinephrine

Based on theory, the rational reason for using epinephrine as a nebulized drug is that it can cause vascular vasoconstriction and reduce respiratory tract edema so that it has a dilating effect on bronchial smooth muscle through alpha and beta adrenergic receptors. Epinephrine as an adrenergic agent can cause tachycardia, cold sweat, paleness, trembling, and arrhythmia (Skjerven et al., 2015). Two studies using nebulized epinephrine found that LOS RS was significantly shorter than nebulized HS 3%, NS, and salbutamol (Uysalol et al., 2017; Yasin et al., 2021). However, in contrast to the study by Wainwright et al.(2003), the LOS and average discharge time in the epinephrine nebulization group were not significantly shorter than those in the placebo group (Wainwright et al., 2003).

Many studies have been conducted regarding nebulization of saline and epinephrine. The saline fluids used together with epinephrine are normal saline and 3% hypertonic saline. Danish et al.(2022) carried out nebulization of epinephrine and NS with a significant reduction in the RDAI score (Danish et al., 2022). This was supported by a study by Mull et al.(2004), which found that the mean RDAI and mean SpO2 improved significantly compared to the albuterol and NS nebulization groups (Mull et al., 2004). However, the Kiper study et al. (2011) with epinephrine nebulization and NS obtained an RDAI score, the hospitalization rate and hospital LOS did not significantly improve compared to the salbutamol nebulization and NS group (Özlem Şimşek-Kiper et al., 2011). Another study by Giudice et al. (2012) obtained a WBSS score for the group with epinephrine nebulization and NS on day 1 , 2, and 3 were not significantly reduced (Giudice et al., 2012). There were four studies with nebulized epinephrine and HS 3% which showed that it could significantly reduce hospital LOS compared to the nebulized saline group and other drugs (Flores-González et al., 2015; Giudice et al., 2012; Singh et al., 2020; Uysalol et al., 2017). Study by Singh et al.(2020) with epinephrine nebulization and 3% HS had significantly reduced WBSS scores on days 3, 4 and 5 compared to the epinephrine nebulized and NS groups (Singh et al., 2020). This study is supported by the study of Giudice et al.(2013) which obtained significantly reduced WBSS scores after nebulization (Giudice et al., 2012). However, the González et al.(2015) study found that the WBSS score was not significantly reduced compared to 3% HS nebulization and sterile water on the third day(Flores-González et al., 2015).

Corticosteroids

The use of nebulized corticosteroids causes faster effects and less degradation than oral corticosteroids. Researchers only received studies using the nebulized combination of budesonide as a nebulized corticosteroid drug in pediatrics with bronchiolitis. Budesonide as a

glucocorticoid has anti-inflammatory and allergic effects which can improve respiratory tract inflammatory responses. A cohort study by Song et al. (2021) with nebulized budesonide combined with salbutamol for 2 weeks found that complaints decreased significantly more quickly compared to the group without nebulization (Song & Li, 2021). An RCT study by Majagaiya et al. (2022) with a nebulized combination of budesonide and salbutamol in saline showed WBSS scores in the nebulization group in HS 3% was not significantly better than the nebulization group in NS. Meanwhile, the RS LOS of the budesonide and salbutamol nebulization group in HS 3% was significantly shorter than in NS (Joshi et al., 2022).

Short-acting beta2 agonists (SABAs)

The administration of SABAs, namely salbutamol, also known as albuterol or ventolin, to bronchiolitis patients has a lot of controversy. Single administration of salbutamol in the RCT study by Ali et al.(2017) resulted in significantly higher WBSS scores and longer LOS RS compared to the 3% HS nebulization group (Ali et al., 2022). Significantly longer LOS RS in the salbutamol nebulization group was also obtained in the study by Uysalol et al. (2017) (Uysalol et al., 2017).28 Stokes et al.'s (1983) study with salbutamol nebulization found that there was no significant reduction in respiratory effort (Stokes et al., 1983). The Tinsa et al. (2009) cohort study found that the RDAI score improved after terbutaline nebulization at 30, 60 and 120 minutes. However, LOS RS results were obtained longer than children who received NS nebulization (Tinsa et al., 2009).

These unfavorable results were also obtained in the study of salbutamol nebulization in saline by Gupta et al.(2016), which showed significantly higher WBSS scores and longer LOS RS in the NS + salbutamol nebulization group compared to the 3% HS nebulization and NS alone group. NS (Gupta et al., 2016). A cohort study by Mojtaba et al.(2016) with ventolin nebulization in NS resulted in a non-significant longer LOS RS compared to the 5% HS nebulization group (Mojtaba et al., 2016). An RCT study by Mull et al.(2004) resulted in a significantly reduced RDAI score. as well as a longer improvement in oxygen saturation in the albuterol nebulization group in NS compared to epinferin nebulization in NS (Mull et al., 2004). A study with salbutamol nebulization in NS did not significantly show a decrease in RDAI, fewer hospitalization rates and shorter LOS compared to the nebulization group epinephrine in NS (Özlem Şimşek-Kiper et al., 2011). Nebulization of albuterol in HS 3% by Pinto et al. (2016) resulted in significantly longer LOS than groups without nebulization and albuterul alone (Pinto et al., 2016). Studies by RCT Sharma et al. (2021) and Flores et al.(2016) compared nebulization of salbutamol based on the additional type of saline fluid, namely NS and HS 3%. It was found that the WBSS score was not significantly lower in the salbutamol nebulization group in HS 3% and the LOS was not significantly different (Flores et al., 2016; Sharma et al., 2013). Meanwhile, a cohort study by Sapkota et al. (2021) obtained significant results with shorter hospital LOS and cough and wheezing symptoms improving more quickly in the salbutamol nebulization group in HS 3% (Luo et al., 2011).

An RCT study with a combination of salbutamol and budesonide in 3% NS or HS fluid by Majagaiya et al. (2021) found that the LOS of the salbutamol and budesonide nebulization group in 3% HS fluid was significantly shorter than in NS fluid. The WBSS score of the salbutamol and budesonide group in HS was 3% better than in NS, but not significant (Joshi et al., 2022). A cohort study by Song et al. (2021) found that combined nebulization of budesonide and salbutamol could significantly shorten healing compared to no nebulization (Song & Li, 2021).

Short-acting muscarinic antagonists (SAMAs)

Ipratropium bromide is an anticholinergic drug that acts as a SAMAs. Ipratropium Bromide is known to have good effectiveness in reducing airway obstruction caused by wheezing in both pediatric and infant patients. A study by Stokes et al.in 1983 found a significant improvement in breathing effort in the group that underwent nebulization of 2 ml of ipratropium bromide (Stokes et al., 1983). Danish et al. (2022) study with nebulization of a combination of salbutamol and ipratropium bromide in NS reduced the RDAI score which was not significant after nebulization for 30 min (Danish et al., 2022).

Other therapies

N-Acetylcysteine (Mucolytic Agent)

N-acetylcysteine is the main precursor of the antioxidant glutathione which reduces the formation of proinflammatory cytokines such as IL-9 and TNF-a; is a vasodilator by increasing cyclic GMP and playing a role in the regeneration of endothelial-derived relaxing factor. Research conducted by Naz Farrah et al found that N-Acetylcystein can significantly improve the clinical severity score so that it is effective as a therapy for acute bronchiolitis compared to the salbutamol nebulization group. LOS RS of the N-acetylcystein nebulization group was shorter than the salbutamol nebulization group, but not significantly different (Naz et al. 2014).

Interferon -α1b

Interferon -α1b is an anti-viral drug that can induce the production of antiviral proteins and activate cell-mediated immunity. Administration of IFN drugs by intramuscular injection has been widely studied (Chen et al., 2020; Zhou et al., 2020). Nebulization of IFN in bronchiolitis aims to accelerate the onset of therapeutic effects; directly acts on various receptors in the mucosa and submucosa of the respiratory tract; reducing the use of systemic drugs; phlegm thinning effect; moisten the airway and reduce injection trauma in pediatric patients so that treatment compliance increases. In research conducted by Chen et al, it was found that IFN nebulization was significantly effective in reducing complaints of coughing up to day 5 and wheezing in bronchiolitis up to day 3 (Chen et al., 2020).

Magnesium Sulphate

Magnesium has a role in physiological processes such as modulation of muscle excitability and calcium influx across cell membranes. The role of magnesium as a bronchodilator has been used in bronchial asthma. MgSO4 provides benefits in those who are unresponsive to β-agonists. The efficacy of nebulized MgSO4 treatment for bronchiolitis has not been tested. Based on an open label RCT study by Debbarma et al.(2021), it was found that the duration of hospitalization in the group given nebulized MgSO4 had a duration of hospitalization that was not significantly shorter than the group with standard care. The BSS of both groups from hours 1, 2, 4, 8, 12, 16, and 24 decreased, but the difference between the two groups was not significant (Debbarma et al., 2021).

CONCLUSION

In conclusion, based on guidelines, the use of nebulized fluids and medications is still not recommended in children with bronchiolitis. Meanwhile, based on the previous studies, administering nebulized saline and medication to children with bronchiolitis provides more clinical benefits than without nebulization. Therefore, further research is needed that is able to objectively show the effectiveness of nebulized fluids and drugs, such as systematic review studies and meta-analyses. Other supporting research such as randomized clinical and observational research is still needed so that it can strengthen the basis of clinical practice of saline nebulization and medication in children with bronchiolitis.

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