Efficacy of 3% hypertonic saline in bronchiolitis: A meta-analysis

ZHI-YONG WANG[1], XIAO-DONG LI[1], AI-LING SUN[1] and XUE-QIN FU[2]

[1]Pediatric Department, Weifang Maternity and Child Care Hospital, Weifang, Shandong 261011;
[2]Pediatric Department, Changyi People's Hospital, Changyi, Shandong 261300, P.R. China

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Abstract. A meta-analysis was performed to analyze the efficacy of 3% hypertonic saline (HS) in bronchiolitis. Pubmed and MEDLINE databases were searched for relevant articles. A total of 2 authors selected the articles according to the inclusion criteria and then data were carefully extracted. Weighted mean difference (WMD) with 95% confidence interval (95% CI) values were used to pool continuous data, including length of stay and clinical severity score (CSS). Relative risk (RR) with 95% CI was calculated to determine the association between 3% HS and re-admission. The pooled data revealed that infants treated with 3% HS exhibited shorter durations of hospitalization compared with those treated with normal saline (NS; WMD=-0.43; 95% CI=-0.70, -0.15). Subgroup analysis examining the combination of HS or NS with additional medication demonstrated that 3% HS with epinephrine significantly decreased the length of hospital stay, with a WMD=-0.62 (95% CI=-0.90, -0.33). The results indicated a lower CSS score in the 3% HS group compared with the NS group (SMD=-0.80; 95% CI=-1.06, -0.54). The pooled outcome indicated a beneficial effect of 3% HS on decreasing re-admission rates compared with NS (RR=0.93; 95% CI=0.70, 1.23). No potential publication bias was observed (Begg's, P=0.133; Egger's, P=0.576). In conclusion, 3% HS was demonstrated to be a more successful therapy compared with NS for infants with bronchiolitis.

Introduction

Bronchiolitis, a common lower respiratory tract infection in infants, is the primary reason of hospitalization of infants in developed and developing countries (1). This disease is characterized by wheezing, cough and tachypnea. Cases mostly present among the infants aged 1-6 months. It usually occurs in early spring and winter seasons (2).

Correspondence to: Dr Zhi-Yong Wang, Pediatric Department, Weifang Maternity and Child Care Hospital, 407 Qingnian Road, Weicheng, Weifang, Shandong 261011, P.R. China
E-mail: zhiyongwf@sohu.com

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It is estimated that 1 in 5 infants each year suffers respiratory infection caused by respiratory syncytial virus (RSV) (3). The mortality rate is 0.5-1.5% among hospitalized infants, but increases to 3-4% for infants with potential pulmonary or cardiac diseases (4). This is a frustrating condition for physicians managing bronchiolitis, as most cases are not responsive to treatment (5). At present, treatment for this disease is primarily supportive with the administration of bronchodilators (6,7), steroids (8,9) and antibiotics (10), which show little benefit.

It has been established that 3% hypertonic solution (3% HS) solution absorbs water from the submucosa, subsequently resolving edema and thereby improving mucociliary function (11). Data from *in vitro* and *in vivo* experiments have indicated that HS accelerates the transport rates of mucus (12,13). It has been demonstrated that inhalation of nebulized 3% HS may improve immediate and long-term clearance of small airways in infants with bronchiolitis (14-16). However, the functional mechanism remains unknown. HS has been suggested to facilitate the removal of inspissated mucus, disruption of mucus strand and reduction of mucosal edema (17,18). HS is usually administered with a bronchodilator to decrease the risk of bronchospasm caused by HS (19). Certain studies have suggested that nebulized 3% HS is useful for infants with bronchiolitis (14,20-24); however, certain studies have reported no beneficial efficacy of HS in bronchiolitis (25-27).

The present meta-analysis was performed to provideadditional insight on this topic. A total of 23 eligible articles were selected. Duration of hospitalization, clinical severity score (CSS) and re-admission rates were analyzed to determine the efficacy of 3% HS compared with NS. The results provided information regarding the clinical application of 3% HS in bronchiolitis.

Materials and methods

Search strategy. Articles were accessed using the Pubmed (from 1966 to March 2018; http://www.ncbi.nlm.nih.gov/PubMed) and MEDLINE (from 1966 to March 2018; https://wwwcf.nlm.nih.gov/serials/journals/index.cfm) databases. The Cochrane Central Register of Controlled Trials (CENTRAL; https://www.cochranelibrary.com/central) was also used. The following terms were used: 'Bronchiolitis' OR 'respiratory syncytial virus' OR 'RSV' OR 'acute wheezing' AND '3% saline'. The search focused on human studies and

had no language restrictions. Concurrently, additional articles were obtained via references of obtained reviews.

Inclusion criteria. The included studies were selected based on the following criteria: i) The studies were designed as randomized controlled trials (RCTs); ii) the studies investigated the efficacy of 3% HS in bronchiolitis; iii) they included a comparison in efficacy between 3% HS and normal saline (NS; 0.9% saline) was performed; and iv) they examined length of stay, CSS score, or re-admission rates.

Data extraction. A total of 2 independent authors reviewed all obtained articles, scanned the full texts, selected eligible articles according to the inclusion criteria and carefully extracted the data. Baseline characteristics of the included trials were identified, including name of first author, publication year, number of patients in each group, the drugs used and their doses. The primary outcomes were the re-admission rates, duration of hospital stay and the CSS score.

Statistical analysis. All statistical analyses were completed with State 12.0 software (Stata Corp LLC, College Station, TX, USA). The weighted mean difference (WMD) with 95% confidence interval (95% CI) was used to pool continuous data of length of stay. Standard mean difference (SMD) with 95% CI was used to pool data of CSS score. Relative risk (RR) with 95% CI was calculated to examine the association between 3% HS and re-admission. Heterogeneity was evaluated by I^2 and P-values. The potential publication bias was assessed with the Begg's funnel plot method and Egger's regression quality of included studies was evaluated according to the modified Jadad scale score (28). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search and study selection. A total of 79 relevant articles were identified from Pubmed and MEDLINE databases. CENTRAL was also used. Of these, 31 articles were excluded, as they were review articles (n=22) or case reports (n=9). Then, the full-texts of the 48 remaining articles were extracted and examined carefully. A total of 15 articles revealed non-relevant outcomes and 10 articles provided no available data; therefore, 23 articles were included. The detailed selection process is demonstrated in Fig. 1. Information concerning the study population, the intervention type, HS dosage, additional medication and outcomes of each study are summarized in Table I. All 23 studies were double-blinded RCTs (14,15,20-25,27,29-42). Jadad scores of each study are presented in Table II.

Effects on the length of stay. A total of 14RCTs were included to analyze the duration of hospitalization (Fig. 2). The pooled data revealed that infants treated with HS nebulizers exhibited shorter periods of hospitalization compared with those treated by NS nebulizers (WMD=-0.43; 95% CI=-0.70, -0.15). Subgroup analysis of additional medications demonstrated that HS nebulizer with epinephrine may significantly decrease the length of hospital stay, with a WMD=-0.62 (95% CI=-0.90, -0.33).

Effects on CSS score. A total of 8RCTs provided data of CSS scores on the first day of treatment (Fig. 3). Compared with the NS nebulizer, HS nebulizers significantly decreased CSS scores on the first day of treatment (SMD=-0.58; 95% CI=-0.85, -0.31). Then, 7RCTs provided data of CSS scores on the second day of treatment. The results demonstrated that there was statistically significant difference in CSS scores between HS and NS nebulizers on the second day (SMD=-0.92; 95% CI=-1.36, -0.49). A total of 7RCTs provided data of CSS scores on the third day of treatment. The pooled results indicated a lower CSS score in the 3% HS group compared with the control group (SMD=-0.93; 95% CI=-1.55, -0.32).

Effects on re-admission. A total of 5RCTs analyzed the effects of HS nebulizers on the re-admission rate. The pooled outcome indicated a beneficial effect of HS nebulizers on decreasing re-admission rate compared with NS nebulizers (RR=0.93; 95% CI=0.70, 1.23; Fig. 4).

Sensitivity analysis and publication bias. A sensitivity analysis was performed to evaluate the effects of the methodological quality of each trial on the pooled results. The results indicated that the pooled results were robust. The funnel plot appeared to be symmetric and no potential publication bias was observed (Fig. 5; Begg's, P=0.133; Egger's, P=0.576, hospital stay).

Discussion

Bronchiolitis is one of the most common lower respiratory tract infections in infants (43,44). The pathophysiology of bronchiolitis is different from that of asthma. It involves infection of the bronchiolar epithelium, characterized by the sloughing and necrosis of epithelial cells, edema, peribronchiolar mononuclear infiltration and secretion of mucus. These changes result in the obstruction of flow in the small and large airways, causing hyperinflation, wheezing and atelectasis (45,46).

Antiviral agents are available for bronchiolitis; however, they are not routinely prescribed due to unconfirmed efficacy. Ribavirin is the only specific drug used to treat RSV infection; however, its efficacy was not been significant (47-50). Studies using glucocorticoids to treat bronchiolitis demonstrated negative effects (51,52). In addition, the application of β_2-agonists may confer short-term improvement in infants with bronchiolitis, in particular the application of epinephrine (53-55). However, no significant effects have been observed in other types of β_2-agonists (46,56).

Previous studies have demonstrated that inhaled HS is a promising therapy (24,26). As stated previously, RSV infection results in edema, necrosis and sloughing of the respiratory epithelium, causing obstruction of the small and large airways. HS may decrease the edema extent of airways through drawing fluid from adventitial and submucosal spaces. This increased fluid may contribute to a loosening of inspissated mucous and improvement of mucociliary clearance. The patients with bronchiectasis demonstrated a significant increase in weight of expectorated sputum and decrease in sputum viscosity (57,58). Concurrently, it has been suggested that nasal HS may alleviate the symptoms of chronic rhinosinusitis. Previously, certain

Table I. Basic information of included studies.

First author	Year	N (Intervention vs. control)	HS dosage, %	Addition	Outcomes	(Refs.)
Gupta	2016	33 vs. 33	3 vs. 0.9	Salbutamol	LOS, CSS	(29)
Silver	2015	111 vs. 111	3 vs. 0.9	-	LOS, Re-admission	(30)
Ojha	2014	12 vs. 9	3 vs. 0.9	-	LOS, CSS	(31)
Flores	2016	33 vs. 35	3 vs. 0.9	Salbutamol	LOS, CSS	(32)
Angoulvan	2017	385 vs. 387	3 vs. 0.9	-	LOS	(33)
Mandelberg	2003	27 vs. 25	3 vs. 0.9	Epinephrine	LOS, CSS	(20)
Tal	2006	21 vs. 20	3 vs. 0.9	Epinephrine	LOS	(21)
Kuzik	2007	47 vs. 49	3 vs. 0.9	-	LOS	(14)
Miraglia Del Giudice	2012	52 vs. 54	3 vs. 0.9	Epinephrine	LOS, CSS	(24)
Al-Ansari	2010	58 vs. 56	3 vs. 0.9	Epinephrine	LOS, Re-admission	(34)
Luo	2011	57 vs. 55	3 vs. 0.9	-	LOS, CSS	(22)
Sharma	2013	125 vs. 123	3 vs. 0.9	B2 agonist	LOS	(27)
Teunissen	2014	84 vs. 80	3 vs. 0.9	B2 agonist	LOS	(35)
Pandit	2013	51 vs. 49	3 vs. 0.9	Epinephrine	LOS	(36)
Everard	2014	142 vs. 149	3 vs. 0.9	-	LOS, Re-admission	(37)
Mahesh Kumar	2013	20 vs. 20	3 vs. 0.9	B2 agonist	LOS	(38)
Luo	2010	50 vs. 43	3 vs. 0.9	B2 agonist	LOS, CSS	(23)
Wu	2014	211 vs. 197	3 vs. 0.9	-	LOS	(25)
Espelt	2012	37 vs. 45	3 vs. 0.9	B2 agonist	LOS	(41)
Sarrell	2002	33 vs. 32	3 vs. 0.9	Terbutaline	CSS	(15)
Grewal	2009	23 vs. 23	3 vs. 0.9	Epinephrine	Re-admission	(39)
Anil	2010	75 vs. 74	3 vs. 0.9	Epinephrine	Re-admission	(40)
Köse	2016	35 vs. 35	3 vs. 0.9	Salbutamol	CSS	(42)

LOS, length of stay; CSS, clinical severity score; HS, hypertonic saline.

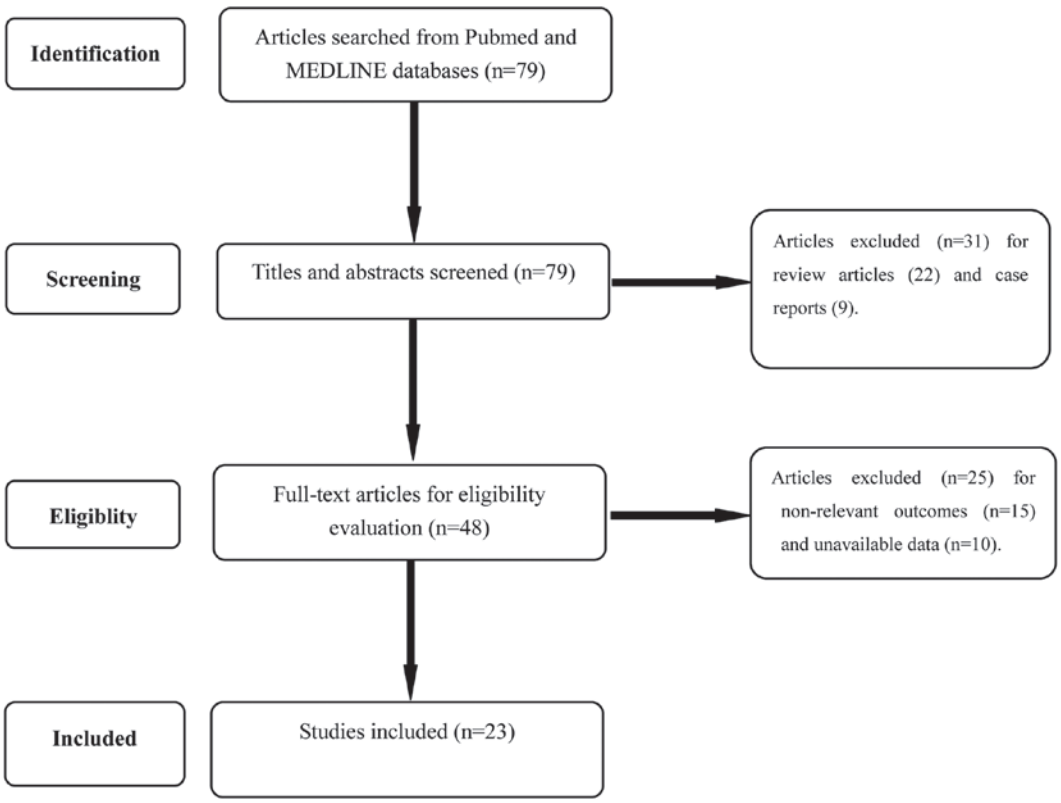

Figure 1. Selection process for articles. A total of 23 eligible articles were included.

Table II. Jadad score of each included study.

First author, year	Study characteristics					
	Generation of allocation sequence	Allocation concealment	Blindness	Withdrawal and drop-out	Jadad score	(Refs.)
Gupta, 2016	1	0	0	0	1	(29)
Silver, 2015	2	2	2	1	7	(30)
Ojha, 2014	2	2	2	1	7	(31)
Flores, 2016	2	2	2	1	7	(32)
Angoulvan, 2017	2	2	2	1	7	(33)
Mandelberg, 2003	1	0	1	1	3	(20)
Tal, 2006	1	0	1	1	3	(21)
Kuzik, 2007	2	2	2	1	7	(14)
Giudice, 2012	2	2	2	0	6	(24)
Al-Ansari, 2010	2	2	2	1	7	(34)
Luo, 2011	2	2	2	1	7	(22)
Sharma, 2013	2	2	2	1	7	(27)
Teunissen, 2014	2	1	2	1	6	(35)
Pandit, 2013	2	2	0	1	5	(36)
Everard, 2014	2	2	2	1	7	(37)
Mahesh Kumar, 2013	2	1	0	1	3	(38)
Luo, 2010	1	2	2	1	6	(23)
Wu, 2014	2	2	1	1	6	(25)
Espelt, 2012	2	2	2	1	7	(41)
Sarrell, 2002	1	0	1	0	2	(15)
Grewal, 2009	2	2	2	1	7	(39)
Anil, 2010	2	2	2	1	7	(40)
Köse, 2016	1	0	1	1	3	(42)

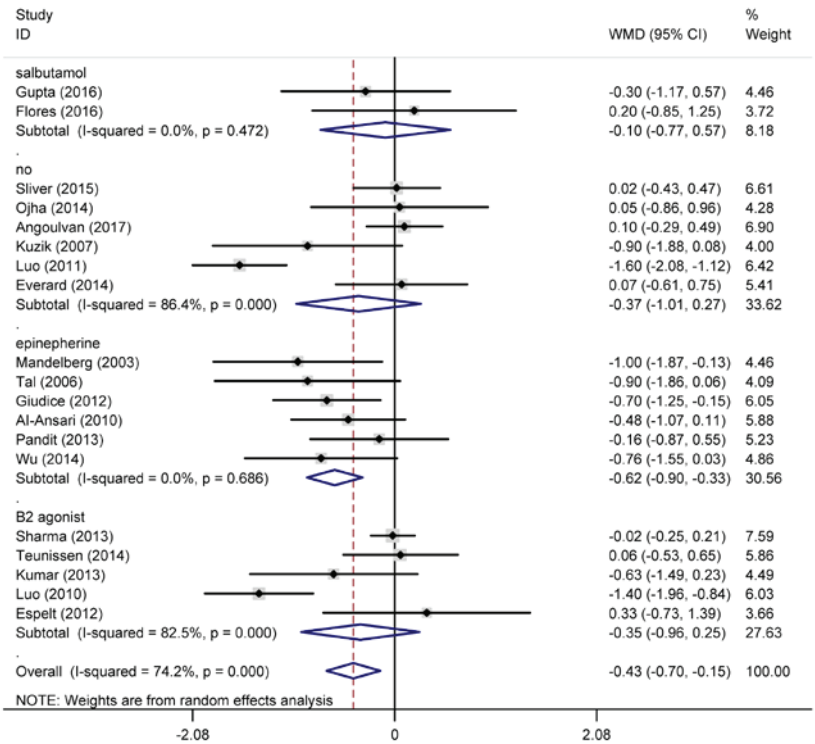

Figure 2. Effects on the length of stay. Infants treated with HS nebulizers exhibited shorter durations of hospitalization compared with those treated by normal saline nebulizers (weighted mean difference=-0.43; 95% CI=-0.70, -0.15). 'Salbutamol', 'epinephrine', 'B2 agonist' and 'no' indicated the addition of salbutamol, epinephrine, B2 agonist and no additional drugs, respectively, in the 3% HS group. HS, hypertonic saline; CI, confidence interval.

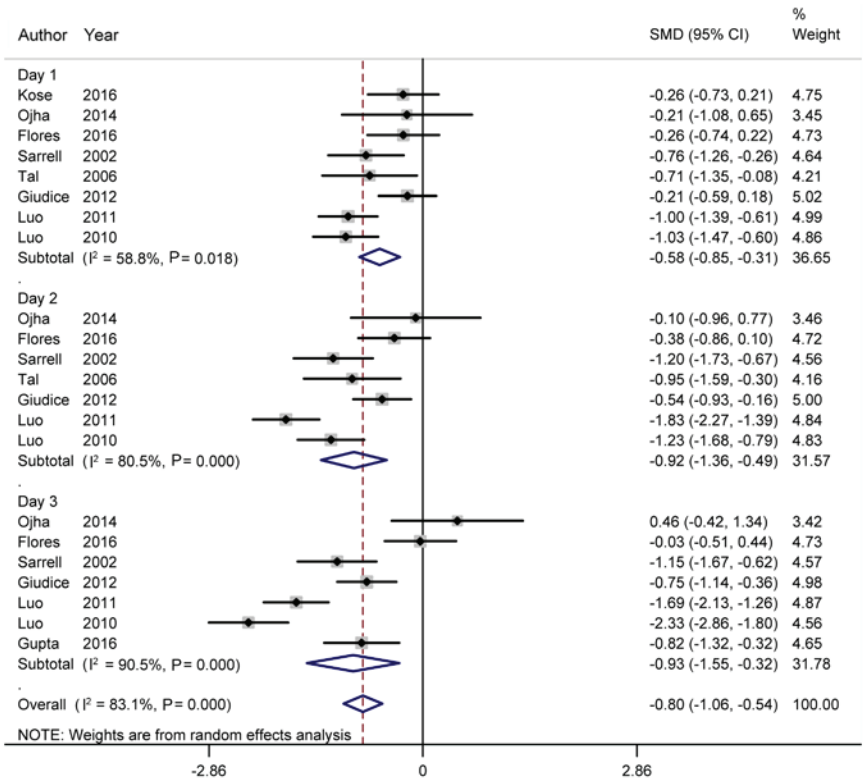

Figure 3. Effects of HS use on the CSS score. Compared with normal saline, HS treatment significantly decreased the CSS score on the first (SMD=-0.58; 95% CI=-0.85, -0.31), second (SMD=-0.92; 95% CI=-1.36, -0.49) and third (SMD=-0.93; 95% CI=-1.55, -0.32) days. CSS, clinical severity score; HS, hypertonic saline; SMD, standard mean difference; CI, confidence interval.

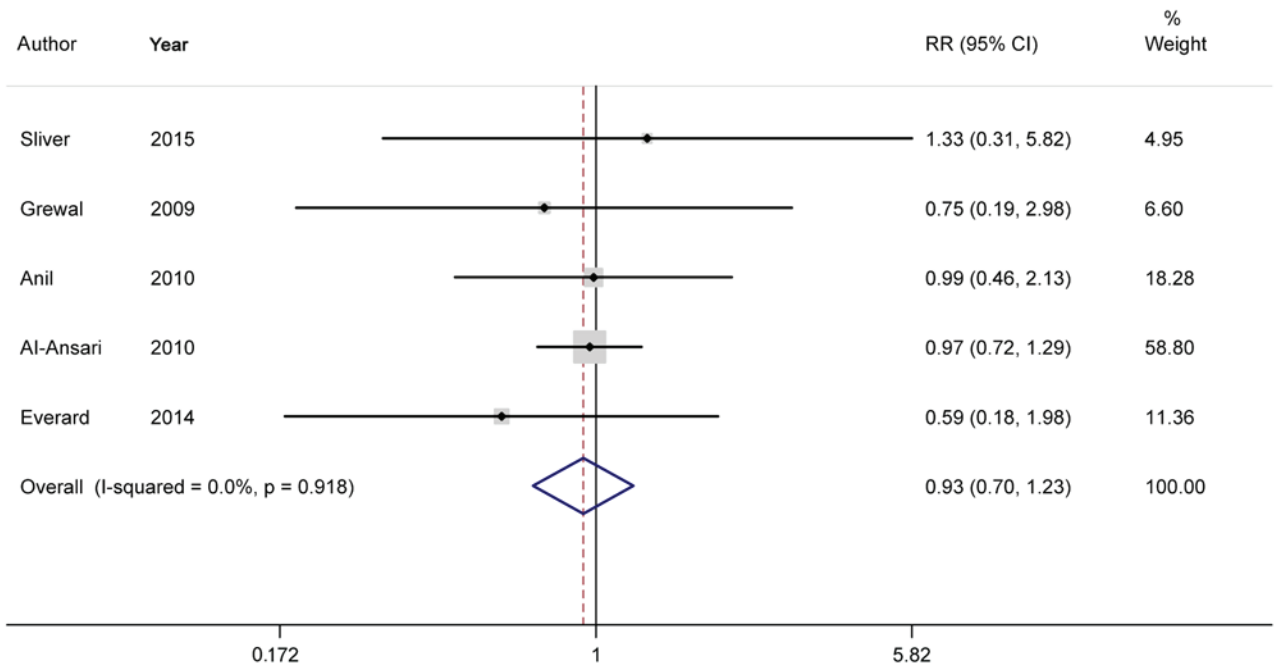

Figure 4. Effects on re-admission. Pooled outcomes indicated a beneficial effect of hypertonic saline nebulizers on decreasing re-admission rates compared with the normal saline nebulizer (RR=0.93; 95% CI=0.70-1.23). RR, relative risk; CI, confidence interval.

studies revealed the benefit of HS in decreasing respiratory distress (15,20,34,59) and length of stay (21,22-24) among infants with bronchiolitis.

However, there are inconsistent data concerning the efficacy of 3% HS in bronchiolitis. The study by Teunissen *et al* (35) demonstrated that 3% HS was safe for bronchiolitis; however, it did not decrease the length of stay orduration of supplemental oxygen required in infant hospitalization due to bronchiolitis. Sharma *et al* (27) revealed that the CSS in 3 and 0.9% saline groups were not significantly different. The mean length of

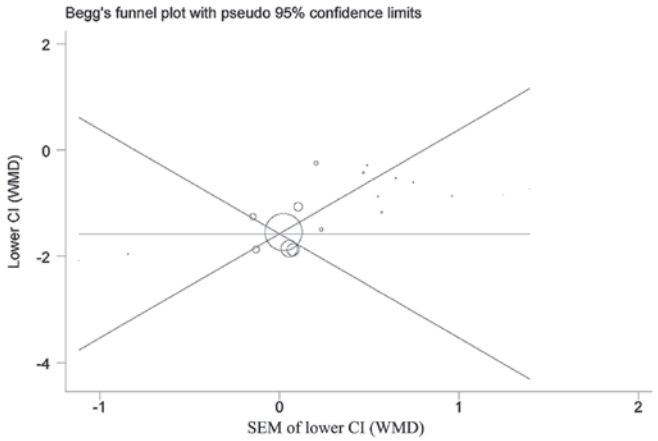

Figure 5. Publication bias detection using Begg's funnel plot. The funnel plot appears to be symmetric and no potential publication bias was observed (P=0.133). CI, confidence interval, WMD, weighted mean difference. SEM, standard error of the mean, pseudo confidence interval, an approximate value of confidence interval.

hospital stay was 63.93±22.43 h in the 3% saline group and 63.51±21.27 h in 0.9% saline group (P=0.878). Therefore, nebulized 3% HS was not superior to 0.9% saline in infants with diagnosed bronchiolitis. Pandit *et al* (36) reached a similar conclusion: Nebulization with HS + adrenaline and normal saline +adrenaline were equally effective in the treatment of bronchiolitis in infants. Our analysis, based on 23 studies, demonstrated that 3% HS was more effective compared with 0.9% NS in decreasing the length of hospitalization, CSS score and rate of re-admission. Compared with individual articles, the pooled results were much more credible.

However, there were limitations in the present study. Firstly, significant heterogeneity was observed in the analysis of length of stay. Although subgroup analysis of supplemental medication was performed, heterogeneity was observed in subgroup analysis of β_2 agonists (P<0.001) and 3% HS-only treatment (P<0.001). This may be due to the differences in patient characteristics, severity of bronchiolitis and performance of individual physicians. Secondly, only 3% HS was analyzed and other concentrations of HS were not considered; comprehensive analysis should therefore be preformed to confirm the efficacy of HS.

In conclusion, 3% HS is superior to normal saline (0.9% saline) in decreasing length of stay, CSS score and rate of re-admission in cases of infant bronchiolitis.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ZYW designed the study. ZYW and XDL screened the literature. ZYW and ALS extracted the data from the literature. ZYW and XQF conducted the meta-analysis and wrote the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Klassen TP: Recent advances in the treatment of bronchiolitis and laryngitis. Pediatr Clin North Am 44: 249-261, 1997.
2. Kabra SK and Ghai OP: Respiratory disorders. In: Ghai Essentials Pediatrics. 6th edition. CBS Publishers and Distributors, New Delhi, pp352-354, 2004.
3. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, Auinger P, Griffin MR, Poehling KA, Erdman D, *et al*: The burden of respiratory syncytial virus infection in young children. N Engl J Med 360: 588-598, 2009.
4. Dennis MM: Bonchiolitis. Arch Dis Child Educ Pract 90: 81-86, 2005.
5. Mathew JL: Hypertonic saline nebulization for bronchiolitis. Indian Pediatr 45: 987-989, 2008.
6. Gadomski AM and Scribani MB: Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 6: CD001266, 2014.
7. Skjerven HO, Hunderi JO, Brügmann-Pieper SK, Brun AC, Engen H, Eskedal L, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, *et al*: Racemic adrenaline and inhalation strategies in acute bronchiolitis. N Engl J Med 368: 2286-2293, 2013.
8. Farley R, Spurling GK, Eriksson L and Del Mar CB: Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 10: CD005189, 2014.
9. Hartling L, Fernandes RM, Bialy L, Milne A, Johnson D, Plint A, Klassen TP and Vandermeer B: Steroids and bronchodilators for acute bronchiolitis in the first two years of life: Systematic review and meta-analysis. BMJ 342: d1714, 2011.
10. Fernandes RM and Hartling L: Glucocorticoids for acute viralbronchiolitis in infants and young children. JAMA 311: 87-88, 2014.
11. Wabnitz DA and Wormald PJ: A blind, randomized, controlled study on the effect of buffered 0.9 and 3% sodium chloride intranasal sprays on ciliary beat frequency. Laryngoscope 115: 803-805, 2005.
12. Wills PJ, Hall RL, Chan W and Cole PJ: Sodium chloride increases the ciliary transportability of cystic fibrosis and bronchiectasis sputum on the mucusdepleted bovine trachea. J Clin Invest 99: 9-13, 1997.
13. Sood N, Bennett WD, Zeman K, Brown J, Foy C, Boucher RC and Knowles MR: Increasing concentration of inhaled saline with or without amiloride: Effect on mucociliary clearence in normal subjects. Am J Respir Crit Care Med 167: 158-163, 2003.
14. Kuzik BA, Al-Qadhi SA, Kent S, Flavin MP, Hopman W, Hotte S and Gander S: Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. J Pediatr 151: 266-270, 270.e1, 2007.
15. Sarrell EM, Tal G, Witzling M, Someck E, Houri S, Cohen HA and Mandelberg A: Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. Chest 122: 2015-2020, 2002.
16. Zhang L, Mendoza-Sassi RA, Wainwright C and Klassen TP: Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 4: CD006458, 2008.
17. Robinson M, Hemming AL, Regnis JA, Wong AG, Bailey DL, Bautovich GJ, King M and Bye PT: Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax 52: 900-903, 1997.

18. Tomooka LT, Murphy C and Davidson TM: Clinical study and literature review of nasal irrigation. Laryngoscope 110: 1189-1193, 2000.
19. Delvaux M, Henket M, Lau L, Kange P, Bartsch P, Djukanovic R and Louis R: Nebulised salbutamol administered during sputum induction improves bronchoprotection in patients with asthma. Thorax 59: 111-116, 2004.
20. Mandelberg A, Tal G, Witzling M, Someck E, Houri S, Balin A and Priel IE: Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. Chest 123: 484-487, 2003.
21. Tal G, Cesar K, Oron A, Houri S, Ballin A and Mandelberg A: Hypertonic saline epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. Isr Med Assoc J 8: 169-173, 2006.
22. Luo Z, Fu Z, Liu E, Xu X, Fu X, Peng D, Liu Y, Li S, Zeng F and Yang X: Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis. Clin Microbiol Infect 17: 1829-1833, 2011.
23. Luo Z, Liu E, Luo J, Li S, Zeng F, Yang X and Fu Z: Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. Pediatr Int 52: 199-202, 2010.
24. Miraglia Del Giudice M, Saitta F, Leonardi S, Capasso M, Niglio B, Chinellato I, Decimo F, Maiello N, Capristo C, Perrone L and Peroni D: Effectiveness of nebulized hypertonic saline and epinephrine in hospitalized infants with bronchiolitis. Int J Immunopathol Pharmacol 25: 485-491, 2012.
25. Wu S, Baker C, Lang ME, Schrager SM, Liley FF, Papa C, Mira V, Balkian A and Mason WH: Nebulized hypertonic saline for bronchiolitis: A randomized clinical trial. JAMA Pediatr 168: 657-663, 2014.
26. Florin TA, Shaw KN, Kittick M, Yakscoe S and Zorc JJ: Nebulized hypertonic saline for bronchiolitis in the emergency department: A randomized clinical trial. JAMA Pediatr 168: 664-670, 2014.
27. Sharma BS, Gupta MK and Rafik SP: Hypertonic (3%) saline vs. 0.93% saline nebulization for acute viral bronchiolitis: A randomized controlled trial. Indian Pediatr 50: 743-747, 2013.
28. Zhang Y, Ding S, Li C, Wang Y, Chen Z and Wang Z: Effects of N-acetylcysteine treatment in acute respiratory distress syndrome: A meta-analysis. Exp Ther Med 14: 2863-2868, 2017.
29. Gupta HV, Gupta VV, Kaur G, Baidwan AS, George PP, Shah JC, Shinde K, Malik R, Chitkara N and Bajaj KV: Effectiveness of 3% hypertonic saline nebulization in acute bronchiolitis among Indian children: A quasiexperimental study. Perspect Clin Res 7: 88-93, 2016.
30. Silver AH, Esteban-Cruciani N, Azzarone G, Douglas LC, Lee DS, Liewehr S, Nazif JM, Agalliu I, Villegas S, Rhim HJ, *et al*: 3% hypertonic saline versus normal saline in inpatient bronchiolitis: A randomized controlled trial. Pediatrics 136: 1036-1043, 2015.
31. Ojha AR, Mathema S, Sah S and Aryal UR: A comparative study on use of 3% saline versus 0.9% saline nebulization in children with bronchiolitis. J Nepal Health Res Counc 12: 39-43, 2014.
32. Flores P, Mendes AL and Neto AS: A randomized trial of nebulized 3% hypertonic saline with salbutamol in the treatment of acute bronchiolitis in hospitalized infants. Pediatr Pulmonol 51: 418-425, 2016.
33. Angoulvant F, Bellêttre X, Milcent K, Teglas JP, Claudet I, Le Guen CG, de Pontual L, Minodier P, Dubos F, Brouard J, *et al*: Effect of nebulized hypertonic saline treatment in emergency departments on the hospitalization rate for acute bronchiolitis: A randomized clinical trial. JAMA Pediatr 171: e171333: 2017.
34. Al-Ansari K, Sakran M, Davidson BL, El Sayyed R, Mahjoub H and Ibrahim K: Nebulized 5 or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. J Pediatr 157: 630-634, 634.e1, 2010.
35. Teunissen J, Hochs AH, Vaessen-Verberne A, Boehmer AL, Smeets CC, Brackel H, van Gent R, Wesseling J, Logtens-Stevens D, de Moor R, *et al*: The effect of 3 and 6% hypertonic saline in viral bronchiolitis: A randomised controlled trial. Eur Respir J 44: 913-921, 2014.
36. Pandit S, Dhawana N and Thakur D: Utility of hypertonic saline in the management of acute bronchiolitis in infants: A randomised controlled study. Int J Clin Pediatr 2: 24-29, 2013.
37. Everard ML, Hind D, Ugonna K, Freeman J, Bradburn M, Cooper CL, Cross E, Maguire C, Cantrill H, Alexander J and McNamara PS: SABRE: A multicentrerandomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. Thorax 69: 1105-1112, 2014.
38. Mahesh Kumar KB, Karunakara BP, Manjunath MN and Mallikarjuna HB: Aerosolised hypertonic saline in hospitalized young children with acute bronchiolitis: A randomized controlled clinical trial. J Pediatr Sci 5: e174, 2013.
39. Grewal S, Ali S, McConnell DW, Vandermeer B and Klassen TP: A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. Arch Pediatr Adolesc Med 163: 1007-1012, 2009.
40. Anil AB, Anil M, Saglam AB, Cetin N, Bal A and Aksu N: High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. Pediatr Pulmonol 45: 41-47, 2010.
41. Espelt MI; Hospital General de Niños Pedro de Elizalde: Efficacy of nebulized hypertonic saline in the treatment of acute bronchiolitis (Hypertonic). ClinicalTrials.gov Identifier: NCT01238848. http://www.clinicaltrials.gov/ct2/show/NCT01238848?term=espelt+bronchiolitis&rank=1. Accessed November 11, 2010.
42. Köse S, Şehriyaroğlu A, Esen F, Özdemir A, Kardaş Z, Altuğ U, Karakuş E, Özcan A, Kısaarslan AF, Elmalı F, *et al*: Comparing the efficacy of 7, 3 and 0.9% saline in moderate to severe bronchiolitis in infants. Balkan Med J 33: 193-197, 2016.
43. Coffen SE: Bronchiolitis: Inpatient focus. Pediatr Clin North Am 52: 1047-1057, 2005.
44. Hall CB: Respiratory syncytial virus. In: Textbook of Pediatric Infectious Diseases. 3rd edition. Philadelphia, Saunders; pp1633-1656, 1991.
45. Hall CB: Respiratory syncytial virus and parainfluenza virus. N Engl J Med 344: 1917-1928, 2001.
46. Darville T and Yamauchi T: Respiratory syncytial virus. Pediatr Rev 19: 55-61, 1998.
47. Meert KL, Sarnaik AP, Gelmini MJ and Lieh-Lai MW: Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: A prospective double-blind, randomized trial. Crit Care Med 22: 566-572, 1994.
48. Moler FW, Steinhart CM, Ohmit SE and Stidham GL: Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. J Pediatr 128: 442-448, 1996.
49. Guerguerian AM, Gauthier M, Lebel MH, Farrell CA and Lacroix J: Ribavirin in ventilated respiratory syncytial virus bronchiolitis: A randomized, placebo-controlled trial. Am J Respir Crit Care Med 160: 829-834, 1999.
50. Wheeler JG, Wofford J and Turner RB: Historical cohort evaluation of ribavirin efficacy in respiratory syncytial virus infection. Pediatr Infect Dis J 12: 209-213, 1993.
51. van Woensel JB, Wolfs TF, van Aalderen WM, Brand PL and Kimpen JL: Randomized double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. Thorax 52: 634-637, 1997.
52. Cade A, Brownlee KG, Conway SP, Haigh D, Short A, Brown J, Dassu D, Mason SA, Phillips A, Eglin R, *et al*: Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis. Arch Dis Child 82: 126-130, 2000.
53. Menon K, Sutcliffe T and Klassen TP: A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. J Pediatr 126: 1004-1007, 1995.
54. Barr FE, Patel NR and Newth CJ: The pharmacologic mechanism by which inhaled epinephrine reduces airway obstruction in respiratory syncytial virus associated bronchiolitis. J Pediatr 136: 699-700, 2000.
55. Bertrand P, Araníbar H, Castro E and Sánchez I: Efficacy of nebulized epinephrine vs salbutamol in hospitalized infants with bronchiolitis. Pediatr Pulmonol 31: 384-288, 2001.
56. Flores G and Horwitz RI: Efficacy of 2-agonists in bronchiolitis: A reappraisal and meta-analysis. Pediatrics 100: 233-239, 1997.
57. Patterson JE, Bradley JM and Elborn JS: Airway clearance in bronchiectasis: A randomized crossover trial of active cycle of breathing techniques (incorporating postural drainage and vibration) versus test of incremental respiratory endurance. Chron Respir Dis 1: 127-130, 2004.
58. Charman J and Reid L: Sputum viscosity in chronic bronchitis, bronchiectasis, asthma and cystic fibrosis. Biorheology 9: 185-199, 1972.
59. Ipek IO, Yalcin EU, Sezer RG and Bozaykut A: The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. Pulm Pharmacol Ther 24: 633-637, 2011.