Therapeutic effect of nebulized hypertonic saline for muco-obstructive lung diseases: a systematic review and meta-analysis with trial sequential analysis

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ABSTRACT

Overproduction of mucus and impaired clearance play important roles in the pathogenesis of muco-obstructive lung diseases (MOLDs). This study aims to evaluate the therapeutic effect and safety of nebulized hypertonic saline (HS) on MOLDs. Five electronic databases including PubMed, Excerpt Medica Database (EMBASE), Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and International Standard Randomized Controlled Trial Number Register were searched until June 2019. Randomized controlled trials or randomized controlled crossover trials which investigated the therapeutic effect of HS versus non-HS for MOLDs were included. Twenty-one studies met the eligibility criteria. For cystic fibrosis (CF), although the forced expiratory volume in the first second and forced vital capacity did not improve significantly (mean difference (MD) −0.48, 95% CI −3.72 to 2.76), (MD 1.85, 95% CI −4.31 to 8.01), respectively), the clearance capability of lung and quality of life (QOL) improved significantly in the HS group ((standard mean difference 0.44, 95% CI 0.02 to 0.87), (MD −0.64, 95% CI −)1.14, to 0.13), respectively). However, the results of trial sequential analysis showed the evidence needed more researches to support. The effect of nebulized HS on non-CF bronchiectasis, chronic obstructive pulmonary disease, and primary ciliary dyskinesia also need more evidence to conclude, since current studies are limited and results are inconsistent. Most adverse events of nebulized HS were mild and transient. In summary, the current available evidence suggests that nebulized HS may increase the QOL in CF, but there was no significant improvement in lung function. However, it is not possible to draw firm conclusions for other MOLDs due to limited data.

Significance of this study

What is already known about this subject?

- Overproduction of mucus and impaired clearance play important roles in the pathogenesis of muco-obstructive lung diseases (MOLDs).
- Nebulized hypertonic saline (HS) has gathered increasing attention in the treatment of respiratory diseases because it helps to increase the mucociliary clearance.
- The effect of nebulized HS for MOLDs was unclear due to limited data.

What are the new findings?

- For cystic fibrosis (CF), although the forced expiratory volume in the first second and forced vital capacity did not improve significantly, the clearance capability of lung and quality of life improved significantly in the HS group.
- The results of trial sequential analysis showed the evidence of HS for CF needed more research to support.
- The effect of nebulized HS on non-CF bronchiectasis, chronic obstructive pulmonary disease, and primary ciliary dyskinesia also need more evidence to conclude, since current studies are limited and results are inconsistent.

How might these results change the focus of research or clinical practice?

- More studies should be conducted for CF and other MOLDs due to the limited evidence.
- Further studies should pay more attention to clinical endpoints such as quality of life and pulmonary exacerbation.

INTRODUCTION

Mucus, an important component in the airway, can defend the respiratory tract against pathogenic and environmental challenges. Muco-obstructive lung diseases (MOLDs), including chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and non-CF bronchiectasis, have typical pathological changes such as diffuse mucus obstruction, airway-wall ectasia, and chronic inflammation.[1–8] Overproduction of mucus and impaired clearance play important roles in the pathogenesis of MOLDs.[9 10] Mucus accumulates in the small airways and cannot be cleared by cough,

forming the nidus for airflow obstruction, infection, and inflammation.

In the past decades, nebulized hypertonic saline (HS) has gathered increasing attention in the treatment of respiratory diseases because it helps to increase mucociliary clearance. HS may work by rehydrating the surface liquid in the airway, reducing the entanglements, viscosity and elasticity of the mucins, and stimulating cilial beat.[11–13] One systematic review indicated that nebulized HS could help improve the lung function in CF.[14] Another descriptive review showed that nebulized HS could improve the life quality of patients with non-CF bronchiectasis,[15] but the quality of evidence was low because it was not a formal systematic review and meta-analysis.

Although there is one previous meta-analysis performed by Tarrant *et al* investigating the effect of mucoactive agents (including HS) on non-CF bronchiectasis and COPD,[16] the data were insufficient and there is no systematic review and meta-analysis evaluating the effect of mere HS on all kinds of MOLDs to provide comprehensive evidence for treatment guidance. Moreover, no study conducted trial sequential analysis (TSA) to assess whether the current evidence is enough to obtain firm conclusions or further researches on the similar topic are necessary.[17]

Considering the factors above, we have incorporated studies till now and performed a systematic review and meta-analysis to figure out the therapeutic effect and safety of nebulized HS on MOLDs. Besides, TSA was conducted to evaluate the reliability of evidence.

METHOD

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplemental file).[18] The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD 42019143223).

Search strategy

A comprehensive search for publications was conducted using the following databases from inception to June 2019 without any restriction: PubMed, Excerpt Medica Database (EMBASE), Cochrane Central Register of Controlled Trials, international trial registers (ClinicalTrials.gov and International Standard Randomized Controlled Trial Number Register). The detailed search strategy is shown in online supplemental table S1.

Study selection

The inclusion criteria: (1) Design: randomized controlled trials (RCTs) or randomized controlled crossover studies; (2) Population: patients with COPD, CF, PCD, or non-CF bronchiectasis; (3) Intervention: nebulized HS (>0.9%); (4) Comparison: nebulized saline solution with concentration ≤0.9% or without nebulization; (5) Outcomes: primary outcomes: clearance capacity of lung and lung function; secondary outcomes: quality of life (QOL), pulmonary exacerbations and adverse events (AEs). All of the studies identified were reviewed by two independent investigators. We resolved any disagreement through discussion by all team members.

Data extraction

Study characteristics were extracted independently by two reviewers using a self-designed data extraction sheet. Name of the first author, year of publication, study design, study location, number of participants, age, intervention, control, methods and outcomes were extracted. We resolved any disagreement through discussion by all team members.

Assessment of quality

We used the Cochrane Collaboration risk of bias tool to assess the risk of bias in RCTs and randomized controlled crossover studies.[19] Seven sections including generation of allocation sequence, allocation concealment, blinding of participants and researchers, blinding of outcome assessors, completeness of outcome data, selective outcome reporting, other risk of bias, were evaluated. Each item was marked by low, high or unclear risk of bias. Two reviewers were trained in advance according to the Cochrane Handbook. Any disagreement would be discussed by all team members.

Statistical analysis

Mean difference (MD) was used for continuous variables, and standard mean difference (SMD) was used in continuous data analysis if the criteria or measurement for evaluating the results among different studies were different. Risk ratio (RR) was used for dichotomous variables. We calculated 95% CI for each effect size estimate. We pooled the estimates from each study using a random-effects model. We used the I^2 statistic to assess the statistical heterogeneity within studies. A percentage less than 50% ($I^2 \leq 50$) indicates low statistical heterogeneity.[20] Prespecified subgroup analyses were performed to determine whether the observed associations were modified. To assess the association of different characteristics observed in subgroup analyses and outcomes, univariable meta-regression analyses were conducted. Sensitivity analysis was used to determine the stability of summary risk estimated by omitting one study in turn. Begg's test[21] and Egger's test[22] were conducted to assess the potential publication bias of primary outcomes. Data synthesis and analysis were performed with STATA V.15.0 and Review Manger V.5.2. A value of $p<0.05$ under a two-sided test was considered statistically significant.

Trial sequential analysis

A TSA was performed by TSA V.0.9.5.10 β software.[17 23] Type I error (α) of 5%, a power (1−β) of 80% and heterogeneity (I^2)calculated in the meta-analysis were considered for outcomes. The control event rates were calculated from the control groups, and other required information sizes (RIS) were calculated from studies with low risk of bias. If the items of 'generation of allocation sequence', 'blinding of participants and researchers', 'blinding of outcome assessors' were all assessed as low risk, and none of 'allocation concealment', 'completeness of outcome data', 'selective outcome reporting', 'other risk of bias' was assessed as high risk, the studies will be regarded as low risk. The cumulative Z-curve of each meta-analysis was constructed to assess its crossing of conventional boundary (Z=1.96) and the TSA monitoring boundary.

If the cumulative Z-curve crosses the TSA monitoring boundary, RIS line, or futility boundary, the result reaches a firm conclusion and further trials will not be necessary. Contrarily, if the Z-curve does not cross any boundary or reach RIS line, the evidence is insufficient for drawing a conclusion.

RESULTS

Search results

A total of 11,965 citations was obtained by electronic searching. A total of 11,454 citations remained after removing duplicated reports. Of these remaining citations, 11,356 citations were excluded after reading titles and abstracts. Ninety-eight citations were also excluded after carefully reading the full text. No study was included in manual retrieval by reviewing relevant studies and reviews. Finally, a total of 21 published studies was included in this study (online supplemental figure S1). Ten relevant ongoing studies were obtained in the international trial registers, but the data of these unpublished studies were not used in this study (online supplement table S2).

Study characteristics and quality assessment

Twenty-one published studies on MOLDs including CF (n=14),[24–37] non-CF bronchiectasis (n=4),[38–41] COPD (n=2),[42 43] and PCD (n=1)[44] were included in this study. Eight studies were RCTs, and 13 studies were randomized controlled cross-over studies. Studies were conducted in countries across Asia, Europe and America. A detailed description of these included studies is shown in online supplemental table S3. The quality assessment is presented in online supplemental figure S2. Most included studies were of low or unclear risk of bias. There were only a few discrepancies in quality assessment between reviewers, and all the team members resolved these disagreements through discussion.

Cystic fibrosis

Clearance capability of lung

Three studies compared the Lung Clearance Index (LCI) between HS and non-HS groups.[24 25 37] The pooled data showed there was a significant decrease in LCI in the HS group compared with the non-HS group (MD −0.64, 95% CI −1.14 to 0.13) without substantial heterogeneity (I^2=0.0%, $P_{heterogeneity}$=0.664) (figure 1A). The trial sequential significance boundary for benefit had not been crossed for LCI even though the conventional boundary had been reached (figure 1B). Three studies reported the effect of HS on mucociliary clearance in CF. The pooled data of two studies[34 35] showed that the mucociliary clearance (MCC) in 90 min significantly increased in the HS group compared with the non-HS group (MD 10.48, 95% CI 6.52 to 14.44) without substantial heterogeneity (I^2=0.0%, $P_{heterogeneity}$=0.62) (online supplemental figure S3). But the TSA could not be conducted due to the limited information. Another study,[30] with inappropriate data format, also showed the MCC in 90 min increased significantly (p=0.045).

Lung function

Twelve studies compared the lung function between the HS and non-HS groups.[24–29 31–36] The pooled data showed

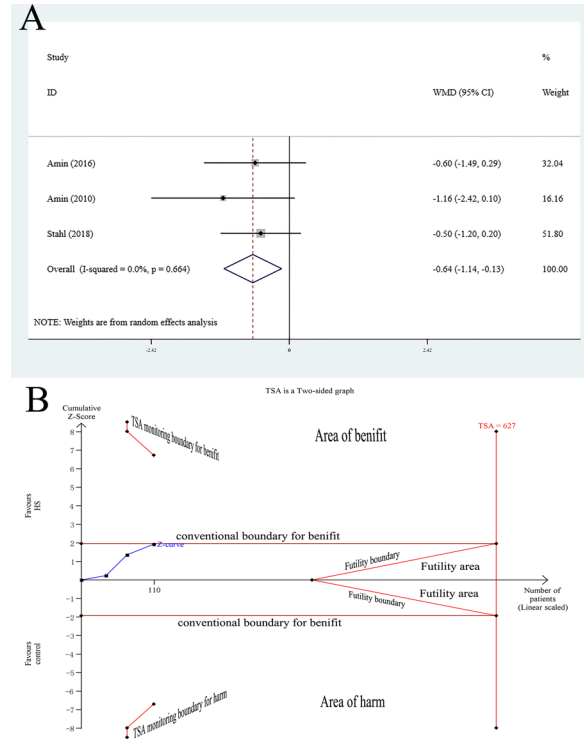

Figure 1 The effects of nebulized hypertonic saline (HS) treatment on the LCI in CF. (A) The forest of LCI. (B) Trial sequential analysis for LCI, α of 5% (two-sided), β of 20%. The cumulative Z-curve (bold solid line) was constructed using a random-effects model. The horizontal line at cumulative Z=−1.96 indicates a conventional level of statistical significance. These trial sequential significance boundary and futility boundary were constructed based on the O'Brien–Fleming method. CF, cystic fibrosis; LCI, Lung Clearance Index; TSA, trial sequential analysis.

that no significant difference between the two groups was obtained in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) with substantial heterogeneity ((MD −0.48, 95% CI −3.72 to 2.76; I^2=70.3%, $P_{heterogeneity}$=0.001), (MD 1.85, 95% CI −4.31 to 8.01; I^2=57.0%, $P_{heterogeneity}$=0.098), respectively) (figure 2A and B). The pooled data showed Forced Expiratory Flow (FEF)25-75 was significantly higher in the HS group than the non-HS group without substantial heterogeneity (MD 4.02, 95% CI 0.14 to 7.90; I^2=0.0%, $P_{heterogeneity}$=0.606) (figure 2C). The results of included studies differed in the lung function. Some indicated no significant lung function improvement was found in the HS group, while others indicated there was a significantly higher FEV1 and FVC in the HS group than the non-HS group in the short term.[26] In the subgroup analyses, no evidence of modification effect on FEV1 was found with the change of study location, number of participants, length of HS (months) according to meta-regression analysis (all P interaction >0.05, figure 3). The results of sensitivity analyses by omitting one study in turn and recalculating the pooled MD of FEV1 ranged from (MD −1.71, 95% CI −4.35 to 0.92) to (MD 0.36, 95% CI −2.96 to 3.69) (online supplemental figure S4). The results of Egger's test (p>0.05) and Begg's test (p>0.05) suggested that there was no statistically significant publication bias

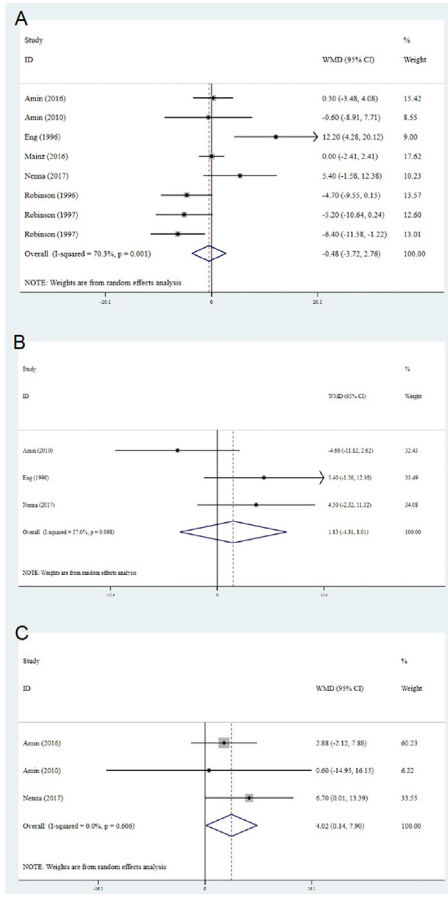

Figure 2 The effects of nebulized hypertonic saline treatment on the lung function in cystic fibrosis (CF); (A) Forced expiratory volume in the first second (FEV1). (B) Forced vital capacity (FVC). (C) Forced Expiratory Flow (FEF)25–75.

of FEV1 in this meta-analysis. TSA showed that the trial sequential significance boundary for benefit had not been crossed for FEF25–75. The evidence of lung function (FEV1, FVC, FEF25–75) was insufficient and further studies are needed (figure 4).

Quality of life

There were seven studies reporting the QOL after HS nebulization.[24 26–29 33 36] Although the measurements of QOL, including the Cystic Fibrosis Questionnaire (CFQ), CFQ-revised and Visual Analog Scale, were different among

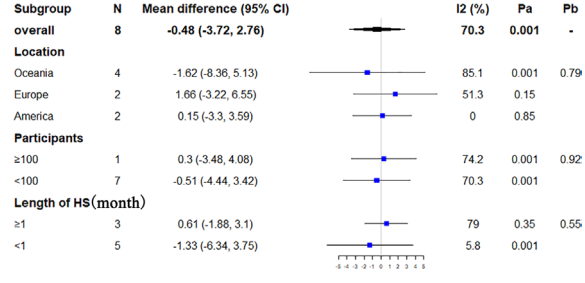

Figure 3 Subgroup analysis of effects of hypertonic saline (HS) for forced expiratory volume in the first second (FEV1) in cystic fibrosis (CF).

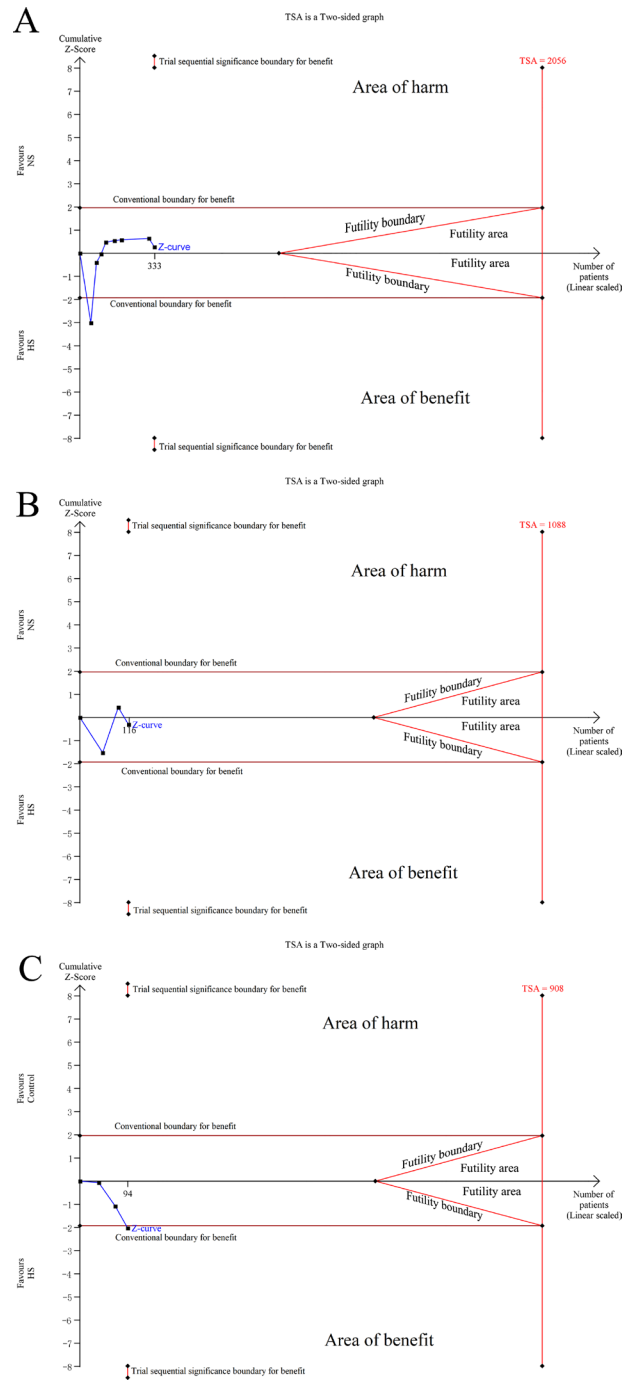

Figure 4 Trial sequential analysis (TSA) for lung function in cystic fibrosis (CF), α of 5% (two sided), β of 20%; the cumulative Z-curve (bold solid line) was constructed using a random-effects model. The horizontal line at cumulative Z=−1.96 indicates a conventional level of statistical significance. These trial sequential significance boundary and futility boundary were constructed based on the O'Brien–Fleming method. (A) Forced expiratory volume in the first second (FEV1). (B) Forced vital capacity (FVC). (C) Forced Expiratory Flow (FEF)25–75. HS, hypertonic saline.

studies, the higher scores of these instruments in the HS group indicated the improvement of QOL. The pooled data showed QOL was significantly improved in the HS group than the non-HS group with significant heterogeneity (SMD

0.44, 95% CI 0.02 to 0.87, I^2=76.2%, $P_{heterogeneity}$=0.002) (online supplemental figure S5). Two studies could not be pooled due to the missing necessary values. The result of one study[27] showed that the QOL was improved significantly (p=0.02). The result of another study[28] showed that the QOL was not improved significantly.

Pulmonary exacerbations

One included study indicated that fewer pulmonary exacerbations were obtained in the HS group compared with the non-HS group (p=0.02),[27] while another study did not find any significant differences in the pulmonary exacerbation rate between the two groups (RR 0.98, 95% CI, 0.84 to 1.15).[36] It was interesting that the two studies showed different results of the effect of HS on pulmonary exacerbation. We could not draw a conclusion due to the discrepancy in the two included studies. Maybe the age of the participants affected the results. One of them was conducted in adults with a mean age of around 18.5 years, whereas the other study was conducted in children with the average age of 2.2 years.

Non-CF bronchiectasis

There were four studies reporting the effect of HS on non-CF bronchiectasis,[38–41] three of which[38–40] were for adults and one[41] was for children. We did not pool these data due to the inappropriate format. Among those four studies, one study[38] showed that 7% HS significantly improved the ease of expectoration (p<0.0001), FEV1 (p=0.043) and FVC (p=0.011). Another study[39] also showed that nebulized 7% HS significantly improved the QOL (St. George's Respiratory Questionnaire, p<0.01), FEV1 (p<0.01) and FVC (p<0.01) after 3 months. One study[40] held the negative opinion that inhalation of 6% HS and non-HS has similar effects on exacerbations, QOL, sputum colonisation and respiratory function over 12 months in bronchiectasis. One study[41] showed that 7% HS was proved to be more effective on sputum expectoration than NS in children with bronchiectasis with no significant change in lung function.

Chronic obstructive pulmonary disease

Two studies reported the effects of nebulized HS on COPD.[42 43] One study[42] indicated the mean radioaerosol retention was significantly higher in the control group than the HS group, while no significant difference was obtained between the HS group and the control group for FEV1, FVC, FEV1/FVC, peak flow rate. Another study[43] indicated there was no significant difference in QOL between the two groups.

Primary ciliary dyskinesia

One study reported the effect of nebulized HS on PCD.[44] This study indicated no significant effect of HS in adult patients with PCD on QOL (p=0.38), but significant improvement was found in expectoration measured by the modified lower respiratory tract infection visual analogue scale (p=0.03).

Adverse events

Some included studies reported the AEs of nebulized HS in MOLDs. Studies reported many potential AEs including respiratory exacerbations, chest pain, gastrointestinal symptoms, and headache. Although there is higher frequency of AEs in the HS group, there were no significant differences between the two groups. None of these AEs was considered to be related to the trial medication. Nobody died related to the nebulized HS directly.

DISCUSSION

This is a comprehensive systematic review and meta-analysis evaluating the effect of HS on MOLDs. The main finding of this systematic review and meta-analysis was that nebulized HS may increase clearance capability of lung and improve QOL in CF. Besides, the evidence about the effect of HS on non-CF bronchiectasis, COPD and PCD was not sufficient. HS nebulization is a safe therapy since no obvious AEs occurred due to HS nebulization.

Previous systematic reviews[14 45] about CF and non-CF bronchiectasis were conducted in recent years. The main view of one review[14] suggested that nebulized HS could improve lung function in CF, and another review[45] indicated that the effect of nebulized HS for non-CF bronchiectasis was unclear due to limited data. One previous systematic review with meta-analysis[16] showed that HS could not improve lung function, QOL and sputum burden significantly in non-CF bronchiectasis. However, we did not pool these data in the two included studies[39 40] of the meta-analysis due to the different meaning of FEV1 and FEV1% and objective description might be more suitable. The meta-analysis of our study showed that QOL and LCI were improved significantly, but TSA indicated that the evidence was insufficient. The main finding of our meta-analysis further extends the finding of previous meta-analyses in several important ways such as the clinical end points. Moreover, our systematic review included more studies evaluating the effects of HS on other MOLDs, such as PCD and COPD.

There are several strengths that should be noted. First, all included studies were RCTs or randomized control crossover studies with high quality, which provided stronger evidence. Furthermore, this is the first review to evaluate the effect of nebulized HS on the treatment of MOLDs. Moreover, TSA helps us to judge the reliability of pooled results and decide whether further researches are necessary.

This systematic review has several potential limitations that should be taken into account. First, great heterogeneity existed among studies and it could not be eliminated completely by conducting subgroup analyses. Some data could not be pooled due to limited data and inappropriate form of data. Furthermore, meta-regression and dose-response analysis were not accessible in some cases due to limited numbers of studies or substantial heterogeneity among studies.

Further studies should focus on the following points. The results of TSA showed that the evidence of HS for CF was insufficient, therefore, more studies should be conducted for CF and other MOLDs. Further studies should pay more attention to clinical end points such as QOL and pulmonary exacerbation. Besides, our study found that HS may not be effective for PCD, therefore, more experimental and clinical studies should be performed to investigate the mechanisms of HS in clearance of mucus in different diseases.

In summary, the current available evidence suggests that nebulized HS is a safe treatment and may improve the clearance capability of lung and QOL, but there was no significant improvement in lung function in patients with CF. The results of TSA showed that the evidence was insufficient and more studies need to be conducted to confirm the conclusion. Moreover, the results for MOLDs should be interpreted cautiously due to the limited evidence and heterogeneity among the studies.

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