Systematic Review/Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Effectiveness of hypertonic saline with or without hyaluronic acid among patients with cystic fibrosis: a systematic review and meta-analysis

Zarghuna Khan, MBBS[a], Muhammad O. Naeem, MBBS[b], Dr. Anam Amin, MBBS[c], Laraib Amin, MBBS[d], Abdullah Shah, MBBS[e], Saad Ul. Khaliq, MBBS[c], Aima Azhar, MBBS[f], Sana Naz, MBBS[g], Syed M. Shujauddin, MBBS[g], Muhammad A. Arshad, MBBS[h], Sarosh J. Ali, MBBS[j], Emad U. Sajid, MBBS[j], Sayed Jawad, MBBS[i,*]

Background: The clinical effectiveness of hypertonic saline (HS) in individuals with cystic fibrosis (CF) can be compromised by adverse effects. The objective of this study was to examine the efficacy of hyaluronic acid (HA) in mitigating these negative occurrences.

Methods: A comprehensive review of the literature was carried out using three electronic databases: Medline, Cochrane Central, and Embase. This systematic review and meta-analysis investigate the efficacy of hypertonic saline (HS) with and without hyaluronic acid (HA) in treating cystic fibrosis. Primary outcomes include the incidence of cough, throat irritation, unpleasant taste, and changes in FEV1. Our findings suggest that adding HA to HS significantly reduces adverse effects and enhances patient tolerability, marking a potential improvement in cystic fibrosis therapy. Risk ratios (RRs) and mean differences (MDs) with 95% CI were used to present evaluations. The quality of RCTs was evaluated using the Cochrane Risk of Bias Tool (CRBT). The quality of the observational study was evaluated using the Newcastle–Ottawa Scale.

Results: From the 1960 articles retrieved from the initial search, five relevant studies ($n = 236$ patients) were included in the final analysis. Compared with patients only on HS, patients with HS and HA were significantly less likely to experience cough (RR: 0.45; 95% CI, 0.28–0.72, $P = 0.001$), throat irritation (RR: 0.43; 95% CI, 0.22–0.81, $P = 0.009$), and unpleasant smell (RR: 0.43; 95% CI, 0.23–0.80, $P = 0.09$). In addition, patients with HS with HA had significantly less forced expiratory volume (FEV1) (MD: −2.97; 95% CI, −3.79–−2.15, $P = 0.52$), compared to patients only on HS. Patients on HA + HS had significantly lower rates of cough (RR: 0.45; 95% CI, 0.28–0.72, $P = 0.001$), throat irritation (RR: 0.43; 95% CI, 0.22–0.81, $P = 0.009$), and bad smell (RR: 0.43; 95% CI, 0.23–0.80, $P = 0.09$) when compared to patients on HS alone. Furthermore, compared to patients solely on HS, patients with HS plus HA exhibited a substantially lower forced expiratory volume (FEV1) (MD: −2.97; 95% CI, −3.79 to −2.15, $P = 0.52$) as well.

Conclusion: For CF patients who need ongoing HS therapy and have a history of poor therapy tolerance, adding HA is beneficial.

Keywords: cystic fibrosis, hyaluronic acid, hypertonic saline

Introduction

Cystic fibrosis (CF) is a genetic disorder resulting from mutations in the CFTR gene, which codes for the CF transmembrane conductance regulator. This regulator is responsible for the functioning of an anion channel found in epithelial cells throughout the body. Dysfunction of CFTR leads to uncontrolled absorption of Na+ and a decrease in the volume of airway surface liquid, causing abnormal mucociliary clearance in the lung due to a failure in active Cl- secretion. Mucous retention facilitates

[a]Department of Medicine, Rehman Medical Institute, [b]Department of Pathology, Northwest School of Medicine, [c]Department of Medicine, Northwest General Hospital And Research Centre, [d]Department of Medicine, Northwest School of Medicine, [e]Department of Nephrology and Kidney Transplant Unit, Rehman Medical Institute, Peshawar, [f]Department of Medicine, Fatima Jinnah Medical University, [g]Department of Medicine, Dow University of Health Sciences, [h]Department of Medicine, Bahria University of Medical and Dental College, Karachi, [i]Kabul University of Health Sciences, Kabul, Pakistan and [j]Department of Acute Medicine, Royal Albert Edward Infirmary, Wigan, UK

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Kabul University of Health Sciences, Kabul, Pakistan. Tel.: +92 335 350 6865. E-mail: sayedjawad12345@outlook.com (S. Jawad).

Annals of Medicine & Surgery (2024) 86:6091–6096

Received 3 June 2024; Accepted 31 July 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 30 August 2024

http://dx.doi.org/10.1097/MS9.0000000000002450

bacterial infection and inflammation, ultimately leading to lung damage and respiratory failure[1,2].

Recent trials have suggested that hypertonic saline solution (HS) may be a promising method to enhance mucociliary clearance and improve airway surface liquid hydration in individuals with CF[3,4]. Adding hyaluronic acid (HA) to HS has been pro posed to mitigate adverse effects and further enhance treatment efficacy[3]. However, while most patients tolerate HS treatment well, some experience side effects such as coughing, airway con striction, and an unpleasant salty taste, which can lead to low compliance[4]. These adverse events have prompted limitations in HS usage, despite its potential benefits in reducing pulmonary exacerbations and improving quality of life[4]. Recent acquisitions in understanding the role of matrix components, such as HA, in lung injury have suggested potential protective effects in respira tory disorders[5,6]. Animal studies indicate HA's role in protecting elastin and controlling neutrophil elastase release, highlighting its therapeutic potential[6].

This systematic review and meta-analysis aim to evaluate the efficacy and tolerability of HS with and without HA in CF treatment. While HA's protective function has been demonstrated in animal models, its therapeutic potential in human lung diseases remains to be fully elucidated[6]. To address issues of compliance and tolerability, particularly regarding the taste and side effects of HS, combining it with HA may offer a solution[7,8]. This meta-analysis explores the hypothesis that HS combined with HA could mitigate adverse effects, thereby potentially increasing treatment adherence and efficacy in CF management.

HIGHLIGHTS

- Hypertonic saline, both with and without hyaluronic acid, demonstrates notable efficacy in improving lung function and reducing pulmonary exacerbations among patients with cystic fibrosis, according to a systematic review and meta-analysis.
- The analysis reveals that hypertonic saline significantly enhances mucociliary clearance and decreases the viscosity of mucus, contributing to better respiratory outcomes in cystic fibrosis patients.
- Adding hyaluronic acid to hypertonic saline shows potential in further reducing inflammation and providing additional protective effects on the airway epithelium, as indicated by several included studies.
- Differences in clinical outcomes, such as frequency of hospitalizations and quality of life measures, are observed between treatments with hypertonic saline alone and in combination with hyaluronic acid, suggesting a nuanced approach to therapy selection.
- The study highlights the therapeutic value of hypertonic saline as a cornerstone treatment in cystic fibrosis, with hyaluronic acid potentially enhancing its benefits, thereby offering insights into optimizing respiratory management strategies for these patients.

Methods

This systematic review and meta-analysis have been reported in concordance with guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA)[1]. This study was conducted in accordance with the guidelines provided by the Assessing the Methodological Quality of Systematic Reviews. Ethical approval was not required for this study as it involved publicly available data and did not include any direct patient interaction or data collection.

Search strategy and inclusion criteria

Two reviewers (S.E.U. and M.M.M.) conducted independent searches in the MEDLINE, Embase, and Cochrane central databases from their respective beginnings until 10th March 2024. There were no limitations imposed on time or language. The search method employed MeSH terms to identify the keywords for cystic fibrosis and hypertonic solution, in conjunction with the Boolean operators 'AND' and 'OR'. The inclusion criteria for the studies were as follows: (1) they had to be randomized controlled trials (RCTs) or observational studies, (2) they had to include patients diagnosed with CF, (3) they had to involve the use of hypertonic saline with hyaluronic acid as an intervention, and (4) they had to have a control group that received hypertonic saline only. The literature search process is summarized in full in the PRISMA flowchart, as shown in Supplemental Figure S1, http://links.lww.com/MS9/A592. In addition, we examined other sources of data, including bibliographies of editorials and related reviews from prominent medical journals, conference proceedings containing indexed abstracts, and databases containing grey or unpublished literature. The comprehensive search technique for databases is outlined in Supplemental Table S1, http://links.lww.com/MS9/A592. In addition, we examined other sources of data, including bibliographies of editorials and related reviews from prominent medical journals, conference proceedings containing indexed abstracts, and databases containing grey or unpublished literature. The comprehensive search technique for databases is outlined in Supplemental Table S1, http://links.lww.com/MS9/A592. Studies that met the inclusion criteria were further screened for relevance based on their titles and abstracts. Full-text articles of potentially relevant studies were then retrieved and assessed for eligibility. Disagreements between reviewers regarding study selection were resolved through discussion and consensus, or by consulting a third reviewer (if applicable). The final list of included studies was documented and any reasons for exclusions were recorded.

Data extraction and quality assessment

The data extraction process involved two reviewers (S.E.U. and M.M.M.) who independently extracted and checked the data using a standardized form. This form included information about the trial's features and identifier. Any inconsistency was resolved by conversation. The original reference papers were examined in case of any inconsistencies. Risk ratios (RRs) and mean differences (MDs) with 95% CIs were calculated using extracted summary events and totals. Additional study attributes were obtained from the overall participant count in each group, publication year, study location, proportion of male participants, duration of follow-up, and average/median ages. The Cochrane Risk of Bias Tool (CRBT) was utilized to evaluate the quality of randomized controlled trials (RCTs) in six areas: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Discrepancies in quality assessment were addressed through discussion, and if unresolved, a third reviewer

was consulted. The number of studies evaluated using the CRBT was 12.

Outcome measures and statistical analyses

The outcomes of interest encompassed cough, throat discomfort, bad taste/saltiness, and changes in FEV1. The meta-analysis was conducted using RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). The results of interest were reported as relative risks (RRs) with 95% CIs. These results were combined using a Mantel–Haenszel weighted random-effects model. Additionally, mean differences (MDs) with 95% CIs were pooled using a generic inverse variance weighted random-effects model. The combined analyses were graphically displayed using forest plots. The Higgins I^2 statistic was employed to assess heterogeneity among the studies[2]. A result ranging from 25 to 49% was considered mild, from 50 to 74% was considered moderate, and any value beyond 75% was con sidered severe. Egger's regression test was employed to evaluate publication bias. In all cases, a *P*-value below 0.05 was deemed statistically significant. Sensitivity analyses were performed to assess the robustness of the results, and subgroup analyses were conducted based on study characteristics to explore potential sources of heterogeneity.

Results

Characteristics of included studies

After reviewing 442 publications obtained from the original search, only five publications[3–7] were selected for the final ana lysis, which comprised a total of 236 patients. The PRISMA flow diagram summarizes the literature search in detail (Fig. 1). Table 1 provides a summary of the study's characteristics and the baseline demographics. The proportion of males exhibited a range of 40.0–53.8% across different studies. The CRBT determined that RCTs generally had a low risk of bias. Based on Egger's regression analysis, there was no statistically significant evidence of publication bias across the studies ($t = 1.57$, $P = 0.12$) (Figure S1, http://links.lww.com/MS9/A592). The risk of bias of included observational study in provided in Figure S2, http://links.lww.com/MS9/A592.

Cough

Five studies conducted a comparison between cough symptoms in patients who were administered hypertonic saline with hyaluronic acid and those who were administered hypertonic saline without hyaluronic acid. There were a total of 236 individuals who provided data on cough, with 138 patients not using hyaluronic acid and 98 patients using hyaluronic acid. Patients who received combination therapy of hypertonic saline with hyaluronic acid experienced a significantly lower incidence of cough compared to patients who did not take hyaluronic acid with hypertonic saline (RR: 0.45; 95% CI, 0.28–0.72, $P = 0.001$). There was moderate heterogeneity between studies ($I^2 = 51\%$) (Fig. 2).

Throat irritation

Five studies conducted a comparison of throat discomfort between patients who took hypertonic saline with hyaluronic acid and those who took hypertonic saline without hyaluronic acid. A total of 236 patients, consisting of 138 patients without hyaluronic acid and patients with hyaluronic acid, provided data on cough. Those who were on combined therapy of hypertonic saline with hyaluronic acid had a significantly lower incidence of throat irritation compared to those who were not taking hyaluronic acid with hypertonic saline (RR: 0.43; 95% CI, 0.22–0.81, $P = 0.009$). There was a minor level of heterogeneity amongst the trials ($I^2 = 46\%$) (Fig. 3).

Unpleasant taste

Five studies conducted a comparison of throat discomfort in patients who were administered hypertonic saline with hyaluronic acid against those who were administered hypertonic saline without hyaluronic acid. A total of 236 individuals, consisting of 138 who did not get hyaluronic acid and 98 who did receive hyaluronic acid, provided information on disagreeable taste. Patients who received combined therapy of hypertonic saline with hyaluronic acid experienced a significantly lower incidence of unpleasant taste compared to patients who did not take hyaluronic acid with hypertonic saline. The reduction in incidence was statistically significant (RR: 0.43; 95% CI, 0.23–0.80, $P = 0.008$), although there was moderate heterogeneity between studies ($I^2 = 51\%$). Invalid input. Please provide a valid text (Fig. 4).

FEV1

Two studies conducted a comparison of the forced expiratory volume in one second (FEV1) in individuals who were administered hypertonic saline with hyaluronic acid vs those who were administered hypertonic saline without hyaluronic acid. Sixty-three patients in all, with 31 not receiving hyaluronic acid and 32 receiving hyaluronic acid, provided data on FEV1. In comparison to patients who did not receive hyaluronic acid with hypertonic saline, individuals who received a combination therapy of hypertonic saline with hyaluronic acid saw a significant decrease in FEV1 (mean difference: –2.97; 95% CI, –3.79 to –2.15, $P > 0.001$) with no variation among the studies ($I^2 = 0\%$) (Fig. 5).

Discussion

Our meta-analysis of five randomized controlled trials (RCTs) demonstrates that adding hyaluronic acid (HA) to hypertonic saline (HS) significantly improves symptoms such as cough, throat irritation, disagreeable taste, and forced expiratory volume in 1 s (FEV1) in cystic fibrosis (CF) patients. These findings are crucial because they suggest that this combination could reduce treatment nonadherence and premature discontinuation of medication. Previous research has consistently shown that HS enhances mucociliary clearance in CF patients by improving airway surface hydration. It has proven effective in both short-term and long-term studies, enhancing lung function and reducing exacerbations. However, its practical application has been limited by adverse effects such as cough, throat irritation, and disagreeable taste, which often lead patients to discontinue treatment.

HA, known for its specific physiochemical properties, has been suggested as a potential solution to these challenges when used alongside HS. Patient preference for the combination over HS alone in single-dose studies supports this notion, suggesting additive or synergistic benefits. Our study specifically evaluated

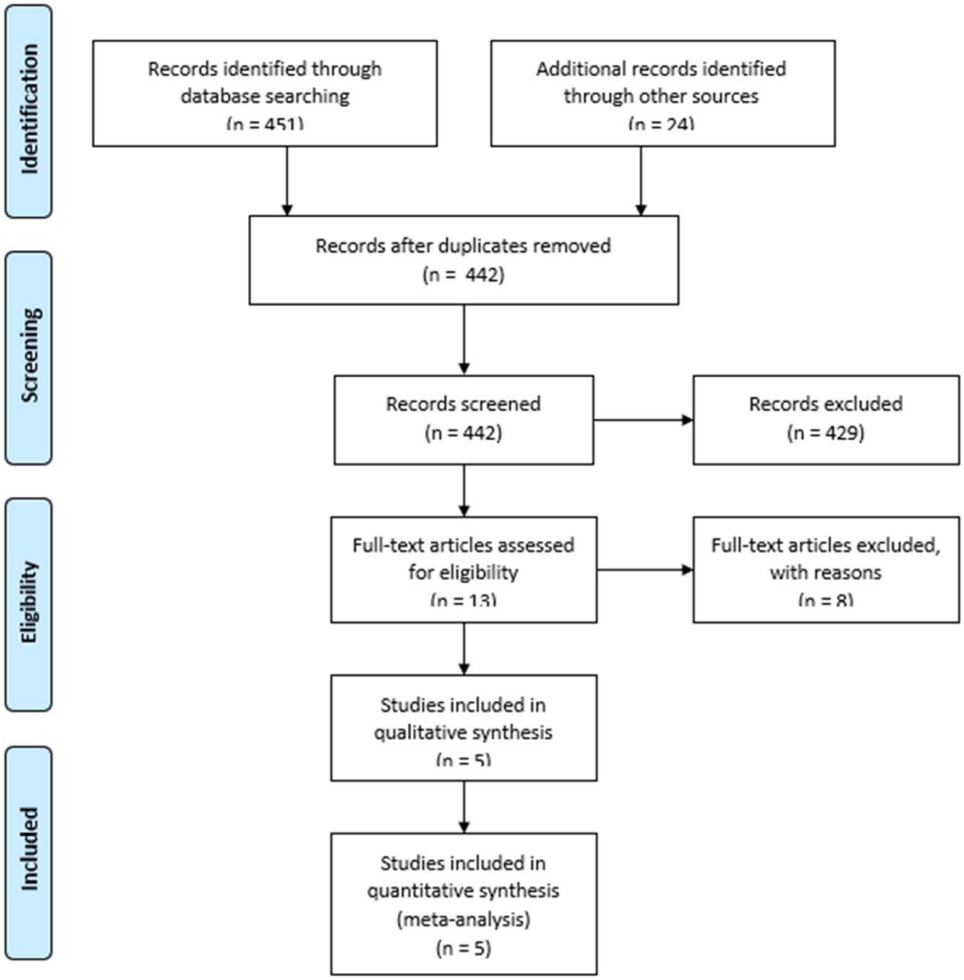

Figure 1. Prisma flowchart.

the tolerability of HS combined with HA compared to HS alone in CF patients. Our meta-analysis indicates that adding HA to HS significantly improves the tolerability profile. The combination consistently reduced saltiness, throat irritation, and irritative cough. Notably, while coughing is a mechanism through which HS enhances mucociliary clearance, HA altered this effect by reducing cough severity, potentially affecting sputum clearance differently.

Experimental models suggest that HA's effects on chronic respiratory diseases involve inhibiting human neutrophil elastase, protecting elastin, preventing bronchoconstriction mediated by tissue kallikrein, enhancing airway epithelial barrier integrity, and stimulating ciliary beating. These effects vary depending on HA's molecular weight: low-molecular-weight HA promotes blood vessel growth and inflammation, whereas high-molecular-weight HA inhibits inflammatory responses. Our findings suggest that HA enhances the effectiveness of HS treatment in CF patients, improving medication tolerance and compliance with inhalation therapy. However, the precise mechanisms by which HA mitigates adverse effects of HS inhalation remain unclear and warrant further investigation.

It is important to acknowledge limitations in our study, including the lack of dose data from clinical trials, which precluded determining the optimal HS dosage. Additionally, insufficient data hindered the evaluation of HS's effects on anthropometric parameters. Future research should address these gaps and explore specific

Table 1

Baseline demographics and study characteristics of included studies.

First author (years)	Study design	Country of study	Total study population	N (HS)	N (HA/HS)	Male sex (%)	Follow-up (days)
Ros[3] (2014)	RCT	Italy	40	20	20	40	28
Buonpensiero[4] (2010)	RCT	Italy	20	10	10	45	2
Brivio[5] (2016)	Pilot RCT	Italy	39	20	19	41	28
Furnari[6] (2012)	RCT	Italy	30	15	15	53.3	28
Cazzarolli[7] (2017)	Comparative Study	Italy	104	63	24	53.8	N/A

IQR, interquartile range; RCT, randomized controlled trial.

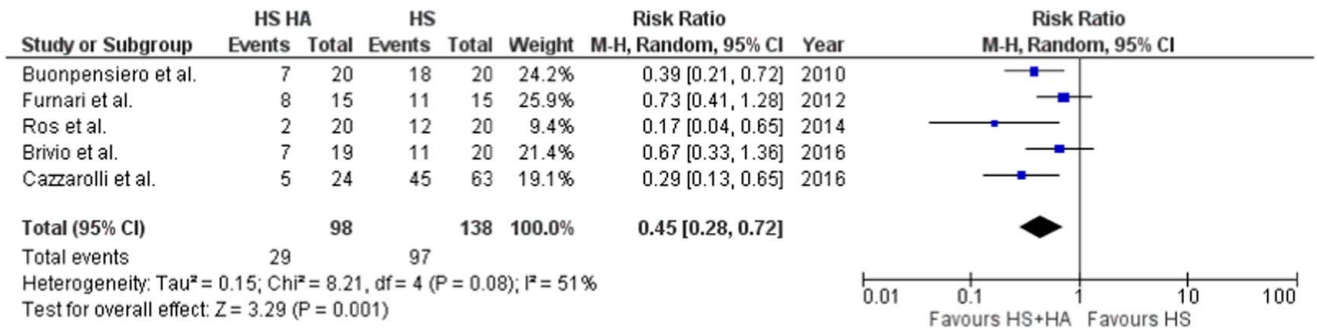

Figure 2. Forest plot showing the incidence of cough among patients on hypertonic saline with and without hyaluronic acid. HS, hypertonic saline; IS, isotonic saline; IV, inverse variance.

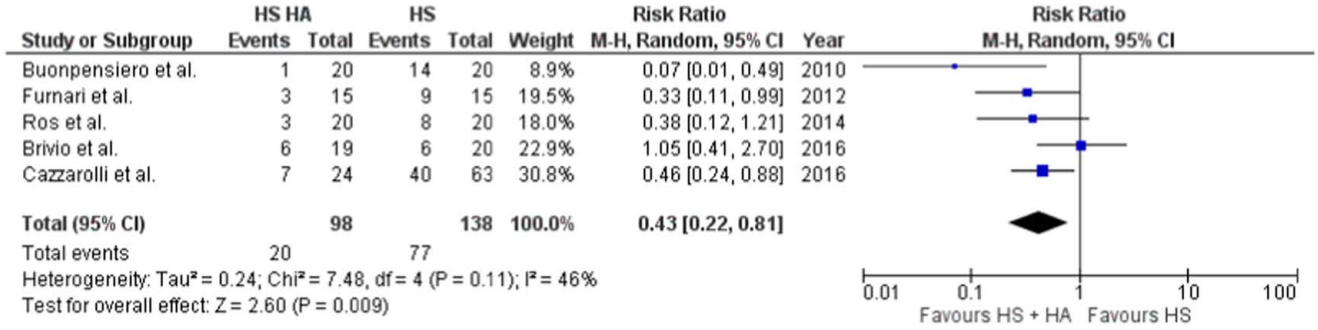

Figure 3. Forest plot showing the incidence of throat irritation among patients on hypertonic saline with and without hyaluronic acid. HS, hypertonic saline; IS, isotonic saline; IV, inverse variance.

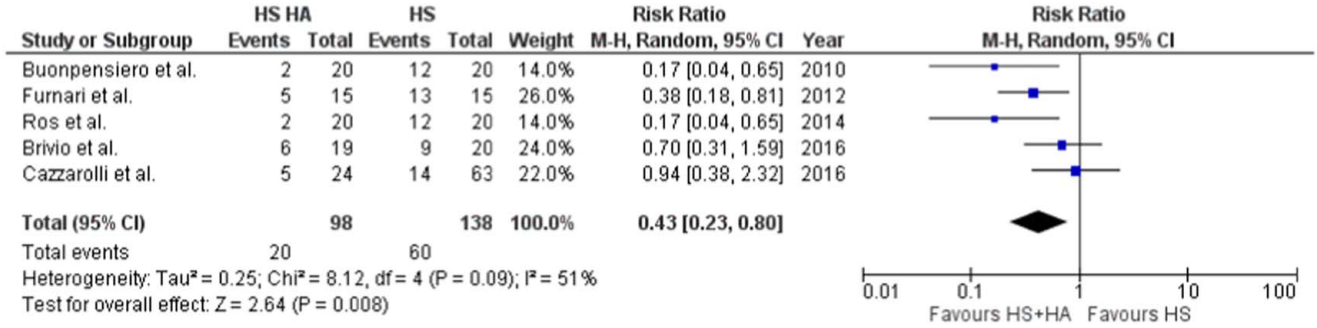

Figure 4. Forest plot showing incidence of unpleasant taste among patients on hypertonic saline with and without hyaluronic acid. HS, hypertonic saline; IS, isotonic saline; IV, inverse variance.

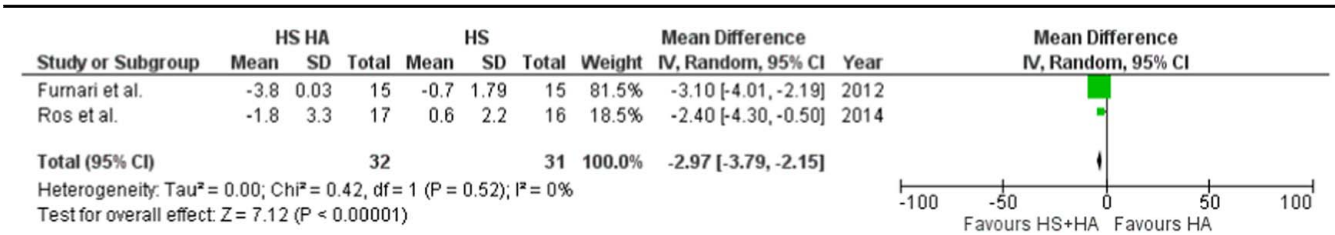

Figure 5. Forest plot showing changes in fev1 among patients on hypertonic saline with or without hyaluronic acid. HS, hypertonic saline; IS, isotonic saline; IV, inverse variance.

mechanisms underlying HA's effects when combined with HS in CF treatment. Addressing these challenges will improve the accuracy and applicability of study findings in clinical practice. Our findings align with previous studies that highlight the benefits of adding HA to HS in CF treatment. The significant reduction in adverse effects such as cough, throat irritation, and unpleasant taste supports the use of HA+HS as a more tolerable alternative. However, limitations include variability in study designs and small sample sizes. Future research should focus on larger, multicenter trials to validate these findings and explore the long-term benefits of HA+HS therapy. Nevertheless, this study has limitations that warrant consideration. The absence of dose-specific data in the included clinical trials limits our ability to determine the optimal HS dosage. Additionally, the lack of data on anthropometric parameters prevents a comprehensive evaluation of HS's broader effects. Future research should focus on elucidating the specific mechanisms by which HA enhances the tolerability of HS in CF patients. Investigating optimal dosages, long-term effects, and comparative effectiveness against alternative treatments would provide further insights into improving CF management. Addressing these areas will not only enhance treatment outcomes but also contribute to reducing healthcare costs and improving the quality of life for CF patients. In conclusion, while this meta-analysis underscores the potential of combining HA with HS in CF treatment, ongoing research is essential to refine therapeutic approaches and address current study limitations effectively.

Conclusion

Given the presence of the investigated symptoms and the pleasantness of the inhalation, we may conclude that HA improves the effectiveness of HS treatment in CF patients as evidenced by statistically significant advantages. Specifically, HA was associated with improved tolerance to HS, leading to better patient compliance with frequent inhalations. Consequently, this would enhance treatment outcomes. Future clinical trials are warranted to further investigate the appropriate dosages of HA.

Ethical approval

Since all the data used in this study is publicly available in the trials referenced within the manuscript, ethical approval was not required.

Consent

Since all the data used in this study is publicly available in the trials referenced within the manuscript, no patient was directly involved in this study. Hence, there was no need to obtain consent from patients. However, the trials included in this study did obtain patients' consent prior to their enrollment.

Source of funding

None to declare.

Author contribution

Z.K. and M.O.N.: conceived the idea and designed the study; A.A. and L.A.: collected the data and analyzed it; A.S. and S.J.A.: drafted the manuscript; S.U.K., S.M.S., and M.A.A.: conducted literature search and created the illustrations; A.A., S.N., and E. U.S.: revised the manuscript critically.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: National Institute for Health Research (NIHR) International Prospective Register of Systematic Reviews (PROSPERO).
2. Unique identifying number or registration ID: CRD42024553908.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=553908

Guarantor

Sayed Jawad, Department of Medicine, Kabul University of Medical Sciences, Kabul, Pakistan.

Data availability statement

All the data used in this study is publicly available in the trials, which are referenced in the bibliography.

Provenance and peer review

It was not invited but rather not commissioned and externally peer-reviewed.

References

[1] Schmidt BZ, Haaf JB, Leal T, *et al*. Cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis: current perspectives. Clin Pharmacol 2016;8:127.
[2] Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med 2010;363:2233–47.
[3] Moreno RMG, García-Clemente M, Diab-Cáceres L, *et al*. Treatment of pulmonary disease of cystic fibrosis: A comprehensive review. Antibiotics (Basel) 2021;10:486.
[4] Gennari-Felipe M, Borges L, Dermargos A, *et al*. Hypertonic solution in severe COVID-19 patient: A potential adjuvant therapy. Front Med 2022;9:917008.
[5] Yasin A, Ren Y, Li J, *et al*. Advances in hyaluronic acid for biomedical applications. Front Bioeng Biotechnol 2022;10:910290.
[6] Tanner L, Single AB. Animal models reflecting chronic obstructive pulmonary disease and related respiratory disorders: translating pre-clinical data into clinical relevance. J Innate Immunity 2020;12:203–25.
[7] Restrepo RD, Alvarez MT, Wittnebel LD, *et al*. Medication adherence issues in patients treated for COPD. Int J Chr Obstruct Pulmon Dis 2008;3:371–84.
[8] Nevitt SJ, Thornton J, Murray CS, *et al*. Inhaled mannitol for cystic fibrosis. Cochr Database Syste Rev 2020;5:CD008649.