REVIEW ARTICLE

Efficacy of hypertonic saline versus isotonic saline among children with cystic fibrosis: A systematic review and meta-analysis

Saad Ehsan Ullah[1], Mohammad Munim Zahoor[2], Swatika Gupta[3], Sukhman Boparai[4], Muhammad Muneeb[5], Shahda A.H. Eltieb[6], Abhirami Shankar[7], Harriet Mmaitsi Kidiavai[8], Rimsha Rahim Vohra[9], Anjuli Devi[5], Zainab Asif Bhura[10], Zaid Muhammad Aslam[5], Mudassir Shoaib[11]

SE Ullah, MM Zahoor, S Gupta, S Boparai, M Muneeb, SA.H Eltieb, A Shankar, HM Kidiavai, RR Vohra, A Devi, ZA Bhura, ZM Aslam, M Shoaib. Efficacy of hypertonic saline versus isotonic saline among children with cystic fibrosis: A systematic review and meta-analysis. Can J Respir Ther 2023;59:1–7. doi: 10.29390/cjrt-2022-046.

Background: Inhaled hypertonic saline (HS) reduces pulmonary exacerbations in patients with cystic fibrosis (CF) aged 6 or more years. However, the effectiveness of HS in improving clinical outcomes in younger children aged 6 or less years is not established. This study examines the efficacy of HS in younger CF patients.

Methods: Searches were conducted across three databases (Medline, Cochrane Central and EMBASE) from inception through July 2022. Randomized controlled trials assessing the impact of HS in younger CF patients were included. Trials involving only patients greater than 6 years or control group other than isotonic saline (IS) were excluded. Outcomes measured included lung clearance index (LCI), cystic fibrosis questionnaire (CFQ-R) score, spirometry measures, oxygen saturation, respiratory rate, height and weight. Outcomes were reported as mean differences (MDs) with 95% confidence intervals.

Results: Seven studies (*n* = 390 patients) were included in this review. HS significantly reduced the LCI (MD: -0.67; 95%CI, -1.05 to 0.29, P = 0.0006) compared to IS. In addition, HS was associated with significant improvements in height (MD: 2.23; 95%CI, -0.00 to 4.46, P = 0.05) and CFQ-R (MD: 4.30; 95%CI, 0.65–7.95, P = 0.02), but not in oxygen saturation (MD: -0.15; 95%CI, -0.54 to 0.25, P = 0.47), respiratory rate (MD: -0.21; 95%CI, -2.19 to 1.77, P = 0.83) or weight (MD: 0.70; 95%CI, -0.47 to 1.87, P = 0.24). Furthermore, HS did not significantly improve spirometry measures, including FEV_1 (MD: -0.11; 95%CI, -0.21 to 0.43, P = 0.51) and forced vital capacity (MD: 0.27; 95%CI, -0.49 to 1.04, P = 0.48), but significantly improved FEF_{25-75} (MD: 0.12; 95% CI, 0.05–0.20; P = 0.002).

Discussion: Treatment with HS in younger children with CF improves lung clearance, symptoms and quality of life. FEF_{25-75} may prove a more sensitive measure for assessing intervention related improvements in pediatric CF trials.

Conclusion: The findings support HS as a therapeutic method in CF-affected children.

Key Words: *children; cystic fibrosis questionnaire; hypertonic saline; isotonic saline; lung clearance index; quality of life; spirometry*

INTRODUCTION

Cystic fibrosis (CF) is characterized by early lung disease. Patients with CF have dehydration of their airway secretions because of the absence of CF transmembrane conductance regulator (CFTR) protein activity [1]. Airway secretions from CF gradually restrict airway lumens and serve as the source of persistent airway infection [2, 3]. Hence, strategies that minimize the dehydration of airway secretions and enhance mucus transport may mitigate the development of CF related lung illness.

Hypertonic saline (HS) has been shown to significantly reduce pulmonary exacerbations and moderately improve lung function in CF patients aged 6 years and older. The benefits are believed to be mediated by HS-induced improvements in mucociliary clearance [4]. Accordingly,

[1]*Department of Medicine, Shaikh Zayed Hospital, Lahore, Pakistan*
[2]*Department of Medicine, Lahore Medical and Dental College, Lahore, Pakistan*
[3]*Department of Medicine, Mahatma Gandhi Mission College and Hospital, Navi Mumbai, India*
[4]*Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, India*
[5]*Department of Medicine, Ziauddin University, Karachi, Pakistan*
[6]*Department of Medicine, Al-Shaab Teaching Hospital, Khartoum, Sudan*
[7]*Department of Internal Medicine, West Anaheim Medical Center, Anaheim, CA*
[8]*Department of Family Medicine, Georgina Family Medical Centre, Keswick, ON*
[9]*Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan*
[10]*Department of Internal Medicine, University Health Network, Toronto, ON*
[11]*Department of Medicine, Jinnah Medical and Dental College, Karachi, Pakistan*
Correspondence: Saad Ehsan Ullah, Shaikh Zayed Hospital, University Avenue, New Muslim Town, Lahore, Pakistan. Tel: +0092 335 3506888, E-mail: batrashikari@gmail.com

Published online at https://www.cjrt.ca on 12 January 2023

this intervention is a standard of clinical care in this age group [4, 5]. Recently, however, a study entitled Infant Study of Inhaled Saline trial determined that, in patients aged less than 6 years, HS was not more effective than isotonic in reducing the incidence of pulmonary exacerbations [6]. Hence, the benefits of inhaled HS in younger CF populations are uncertain.

Inhaled HS is particularly suited as an early intervention technique before the development of substantial lung injury. Exploring the benefits of HS in young patients is challenging however, because of their associated anomalies in measures of standard pulmonary function (eg, forced expiratory volume [FEV]) may not yet be evident [7]. Therefore, conventional outcome measures, such as spirometry, may not be sufficient to establish a possible benefit of HS and other treatments in younger CF patients. To address these challenges the UK Cystic Fibrosis Gene Therapy Consortium has included serial lung clearance index (LCI) measures into the next CFTR gene therapy multidose experiment [8]. The LCI, a measure of ventilation inhomogeneity, shows potential for early lung illness identification in CF [9]. LCI has been demonstrated to be more predictive of future abnormalities in lung function than FEV1 and to correlate with structural changes [9]. In addition, LCI has been shown to detect treatment responses to interventions in children aged 6–18 years with CF whose baseline spirometry was within the normal range (FEV1 > 80%) [10].

Although there are several plausible explanations for the apparent lack of effect of HS on exacerbations in younger CF patients, whether HS promotes a sustained improvement in LCI in these young patients, which is necessary to prevent illness exacerbations in patients with CF, remains unclear. Therefore, in this meta-analysis, our primary objective was to assess the effects of inhaled HS on LCI in young patients with CF. In addition, we seek to define the effect of inhaled HS on the secondary outcome measures: anthropometry, spirometry and health-related quality of life.

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) [11]. Approval from the institutional review board was not required because the data were publicly available.

Search strategy and inclusion criteria

Two reviewers (SEU and SB) independently searched through the Medline, Embase and Cochrane central databases from inception till 18 July 2022. No time or language restrictions were set. The search strategy involved using MeSH terms to determine the keywords for CF and hypertonic solution coupled with the Boolean operators "AND" and "OR". Studies were included if they were 1) randomized controlled trials (RCTs) or post hoc analyses, 2) included patients less than 6 years and with diagnosis of CF, 3) had HS as an intervention and 4) isotonic saline (IS) as a control group. A PRISMA flowchart in Supplementary Figure 1[1] summarizes the systematic literature search. We also reviewed other data sources: bibliographies of editorials and relevant reviews from major medical journals, conference proceedings for indexed abstracts and databases of grey/unpublished literature. The detailed search strategy for databases is provided in Supplementary Table 1.

Data extraction and quality assessment

Data were independently extracted and verified by two reviewers (SB and SEU) using a data extraction form that captured trial characteristics. Any disagreement was resolved by discussion. Summary events and totals were extracted to calculate mean differences with 95% confidence intervals (CIs). Other study characteristics extracted included the number of participants in each arm, publication year, length of follow-up and mean/median ages. The Cochrane Risk of Bias Tool was employed to assess the quality of RCTs across six domains [selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias].

[1]All supplementary materials are available at https://www.cjrt.ca/wp-content/uploads/Supplement-cjrt-2022-046.docx

Outcome measures and statistical analyses

Outcomes of interests included LCI, spirometry measures (FEV_1, forced vital capacity [FVC], FEF_{25-75}), respiratory rate, oxygen saturation, height, weight and quality of life as evaluated by CF questionnaire-revised (CFQ-R) scores [12]. Meta-analysis was performed using RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Outcomes of interest were presented as MDs with 95% CIs and were pooled using an inverse variance weighted random-effects model. When the mean was not available, we used the median for analysis. When the change from the baseline was not reported, we calculated the difference in means between the baseline and the post-treatment measurements. Its standard deviation was derived from the baseline and the follow up by assuming their correlations were 0.5. For crossover trials that did not report the differences between treatment groups, the mean differences were calculated using the reported mean treatment effects of two treatment groups, and the standard errors (SE) of the mean difference were derived by assuming the correlation between the two treatment effects within a trial was 0.25 The pooled analyses were visually represented with forest plots. Higgins I^2 was used to evaluate heterogeneity across studies. A 25% to 50% value was deemed mild, 50% to 75% moderate and greater than 75% severe. Publication bias was assessed using Egger's regression test. A P-value of less than 0.05 was considered significant in all cases.

RESULTS

Characteristics of included studies

After screening 1041 publications identified from the initial search, 7 publications were included in the final analysis (n = 390 patients) (6, 13–18) (Supplementary Figure 1). Study characteristics and baseline demographics are summarized in Table 1. The mean age of patients ranged from 0.26 to 11.10 years. The percentage of males in the included studies ranged from 36% to 60%. Egger's regression was not significant for publication bias (t = 1.67, P = 0.658) as visualized by the funnel plot (Supplementary Figure 2). RCTs were deemed to be of generally low risk of bias according to the Cochrane Risk of Bias Tool (Supplementary Figure 3).

Lung Clearance Index

Four studies compared LCI in children taking HS with children on normal saline. A total of 234 children (117 on HS and 117 on IS) reported data on LCI. Compared with IS, HS significantly reduced the LCI (MD: -0.67; 95% CI, -1.05–0.29, P = 0.0006, I^2 = 0%) (Figure 1).

Spirometry measures

FEV_1 and predicted FEV_1%

Three studies compared FEV_1 in children taking HS with children on normal saline. A total of 66 children (35 on HS and 31 on IS) reported data on FEV_1. There was no significant difference between HS and IS in terms of FEV_1 (MD: -0.11; 95% CI, -0.21 to 0.43, P = 0.51, I^2=0%).

Two studies compared predicted FEV_1% in children taking HS with children on normal saline. A total of 43 children (21 on HS and 22 on IS) reported data on predicted FEV_1%. Likewise, there was no significant difference between HS and IS in predicted FEV_1% (MD: -0.19; 95% CI, -3.36 to 2.98, P = 0.91, I^2 = 0%) (Figure 2A).

FVC and predicted FVC%

Two studies compared FVC in children taking HS with children on normal saline. A total of 43 children (21 on HS and 22 on IS) reported data on FVC. There was no significant difference between HS and IS in terms of FVC (MD: 0.27; 95% CI, -0.49 to 1.04, P = 0.48, I^2 = 83%).

Two studies compared predicted FVC% in children taking HS with children on normal saline. A total of 43 children (21 on HS and 22 on IS) reported data on predicted FVC%. Likewise, there was no significant difference between HS and IS in predicted FVC% (MD: 0.83; 95% CI, -1.67 to 3.33, P = 0.52, I^2 = 0%) (Figure 2B).

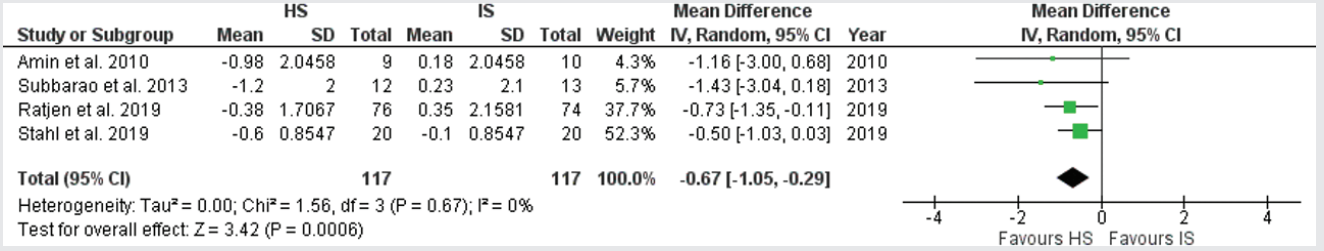
TABLE 1
Baseline demographics and study characteristics of included studies

First author (year)	Study design	Country of study	Total study population	*N* (hypertonic saline)	*N* (isotonic saline)	Male sex (%)	Age (years)	Follow-up (weeks)	Outcomes
Ratjen (2019)	RCT	Canada and USA	150	76	74	46	Mean (SD): 4.50 (1.00)	4, 8, 18, 32 and 40	LCI
Donaldson (2020)	RCT	USA	23	14	9	48	Mean (SD) 11.10 (3.50)	4	FEV; CFQ-R
Stahl (2019)	RCT	Germany	42	21	21	47.6	Mean (SD) 0.26 (0.07)	52	LCI; O_2 Saturation; Respiratory Rate
Nenna (2017)	Cross over RCT	Italy	12	–	–	50	Mean (SD) 5.70 (0.80)	16	FEV; FVC; FEF_{25-75};
Rosenfeld (2012)	RCT	Canada and USA	321	158	163	53.4	Mean (SD) 2.25 (1.45)	12, 24 and 48	O_2 Saturation; Respiratory Rate; Height; Weight
Amin (2010)	Cross over RCT	Canada	19	9	10	36.8	Mean (SD) 10.50 (3.10)	4	LCI; FEV1; FVC; FEF_{25-75}; CFQ-R
Subbarao (2013)	Post-hoc analyses RCT	Canada	25	12	13	60	Median (IQR) 2.60 (1.09–4.10)	48	LCI

CFQ-R Cystic Fibrosis Questionnaire-Revised; FEF_{25-75} forced expiratory flow at 25% to 75% of FVC; FEV forced expiratory volume; FVC forced vital capacity; IQR interquartile range; LCI Lung Clearance Index; RCT randomized controlled trial; SD standard deviation.

FIGURE 1

Forest plot showing changes in Lung Clearance Index (LCI) among children on hypertonic saline (HS) versus children on isotonic saline (IS). CI confidence interval; IV inverse variance; SD standard deviation.



FEF_{25-75} and predicted FEF_{25-75}%

Two studies compared forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}) in children taking HS with children on normal saline. A total of 364 children (179 on HS and 185 on IS) reported data on FEF_{25-75}. There was no significant difference noted between HS and IS in terms of FEF_{25-75} (MD: 0.12; 95% CI, 0.05–0.20, P = v0.002, I^2 = 0%).

Three studies compared predicted FEF_{25-75}% in children taking HS with children on normal saline. A total of 43 children (21 on HS and 22 on IS) reported data on predicted FEF_{25-75}%. Likewise, there was no significant difference between HS and IS in predicted FEF_{25-75}% (MD: 6.63; 95% CI, 1.95–11.31, P = 0.006, I^2 = 0%) (Figure 2C).

Oxygen saturation

Two studies compared LCI in children taking HS with children on normal saline. A total of 361 children (178 on HS and 183 on IS) reported data on oxygen saturation. Compared with IS, HS did not significantly improve oxygen saturation (MD: -0.15; 95% CI, -0.54 to 0.25, P = 0.47, I^2 = 0%) (Figure 3A).

Respiratory rate

Two studies compared respiratory rate in children taking HS with children on normal saline. A total of 361 children (178 on HS and 183 on IS) reported data on respiratory rate. Compared with IS, HS did not significantly reduce the respiratory rate (MD: -0.21; 95% CI, -2.19 to 1.77, P = 0.83, I^2 = 0%) (Figure 3B).

Height

Two studies compared height in children taking HS with children on normal saline. A total of 361 children (178 on HS and 183 on IS) reported data on height. Compared with IS, HS did not significantly reduce the height (MD: 2.23; 95% CI, -0.00 to 4.46, P = 0.05, I^2 = 0%) (Figure 4A).

Weight

Four studies compared weight in children taking HS with children on normal saline. A total of 361 children (178 on HS and 183 on IS) reported data on weight. Compared with IS, HS did not significantly reduce the weight (MD: 0.70; 95% CI, -0.47 to 1.87, P = 0.24, I^2 = 13%) (Figure 4B).

Cystic Fibrosis Questionnaire-Revised

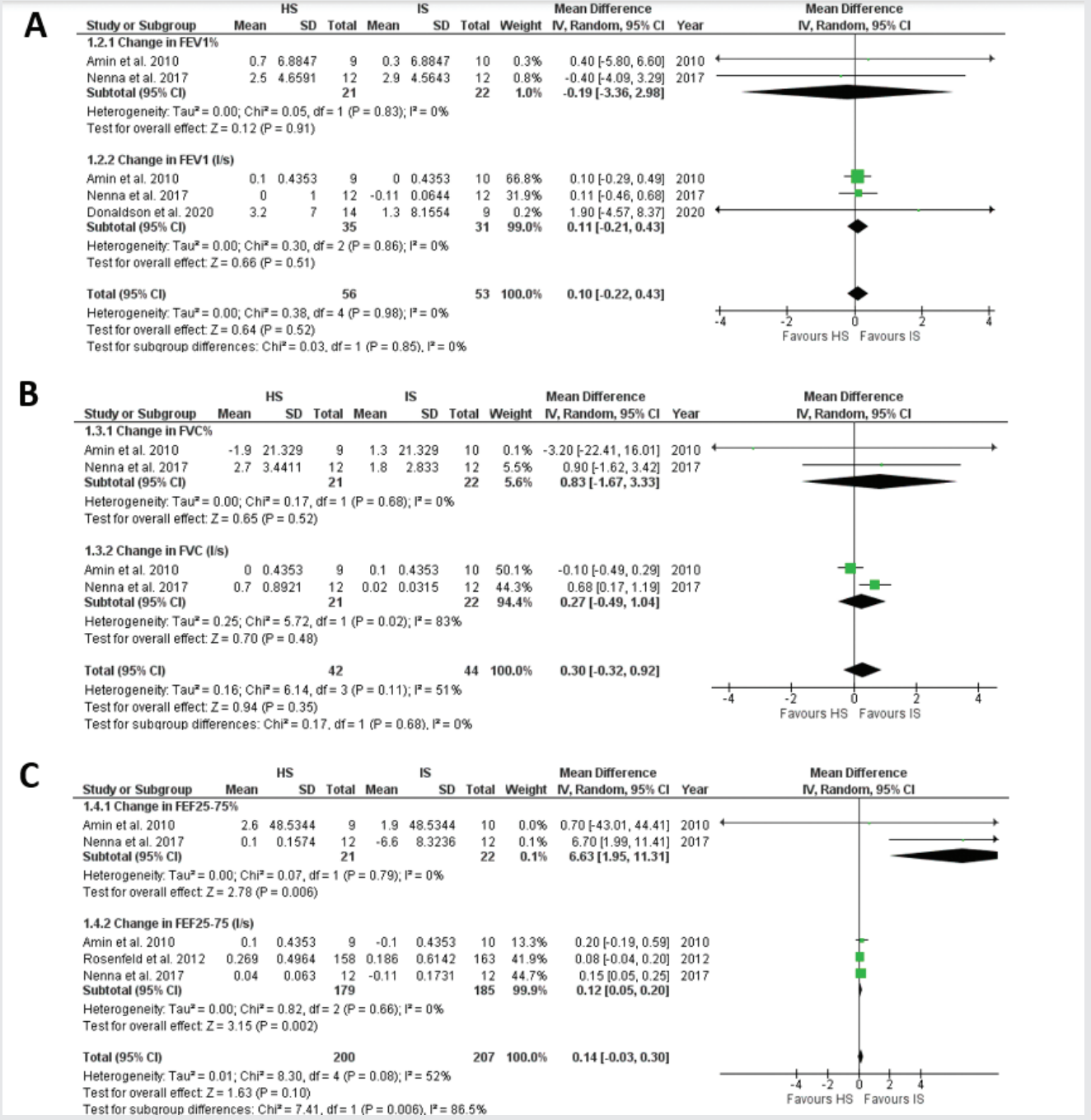
Three studies compared CFQ-R scores in children taking HS with children on normal saline. A total of 363 children (181 on HS and 182 on IS) reported data on CFQ-R. Compared with IS, HS significantly improved CFQ-R scores (MD: 4.30; 95% CI, 0.65–7.95, P = 0.02, I^2 = 0%) (Figure 5).

DISCUSSION

In this meta-analysis evaluating the efficacy of HS in patients with CF, we report several key findings. First, there was a significant reduction in the LCI in patients inhaling HS. Second, HS significantly reduced the FEF and predicted FEF% in children with CF. Third, the CFQ-R score

FIGURE 2

Forest plot showing changes in* A *forced expiratory volume (FEV)$_1$ and predicted FEV$_1$%,* B *forced vital capacity (FVC) and predicted FVC%,* C forced expiratory flow at 25%–75% of FVC *(FEF$_{25-75}$) and FEF$_{25-75}$% among children on hypertonic saline (HS) versus children on isotonic saline (IS). CI confidence Interval; IV inverse variance; SD standard deviation.



was significantly higher in children inhaling HS than in children on IS. However, no distinct benefit of HS was noted on spirometry measures, including FEV$_1$, FVC, oxygen saturation, respiratory rate and weight.

Because of the paucity of data regarding treatment options in children with CF, efficacy information is frequently derived from trials conducted on older children and adults. Small studies have established associations between the use of HS and improvements in LCI. For example, in the inhaled HS in preschool children with CF trial, a strong correlation was seen between HS and improvements in LCI$_{2.5}$ in children aged 3–6 years [13]. Likewise, in a study of infants younger than 6 months, preventive treatment with HS was associated with a significantly better LCI$_{2.5}$ trajectory compared to IS over 52 weeks [14]. Consistent with these findings, our meta-analysis revealed significant improvement in LCI among patients on HS. Inhaled HS has a beneficial effect on the

FIGURE 3

Forest plot showing changes in A oxygen saturation and B respiratory rate among children on hypertonic saline (HS) versus children on isotonic saline (IS). IV inverse variance; CI confidence interval; SD standard deviation.

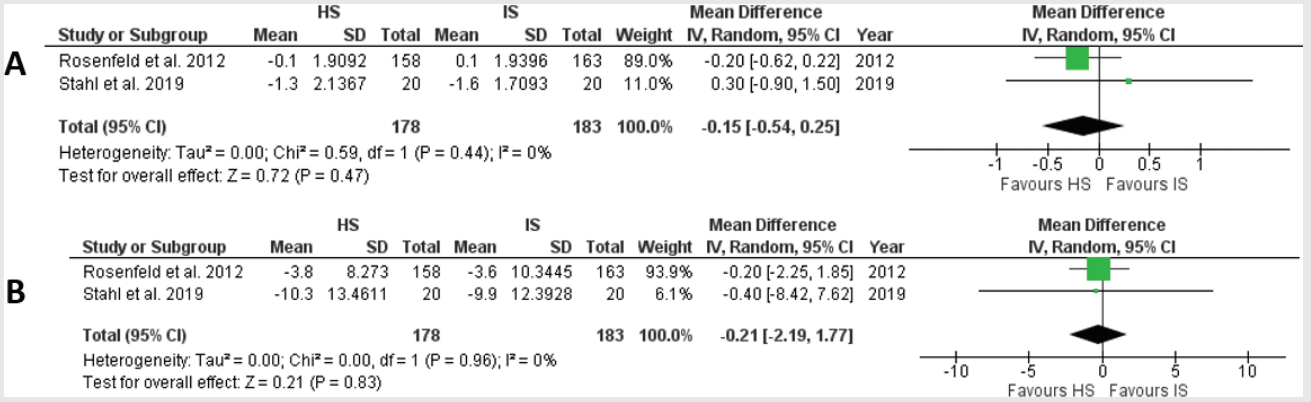
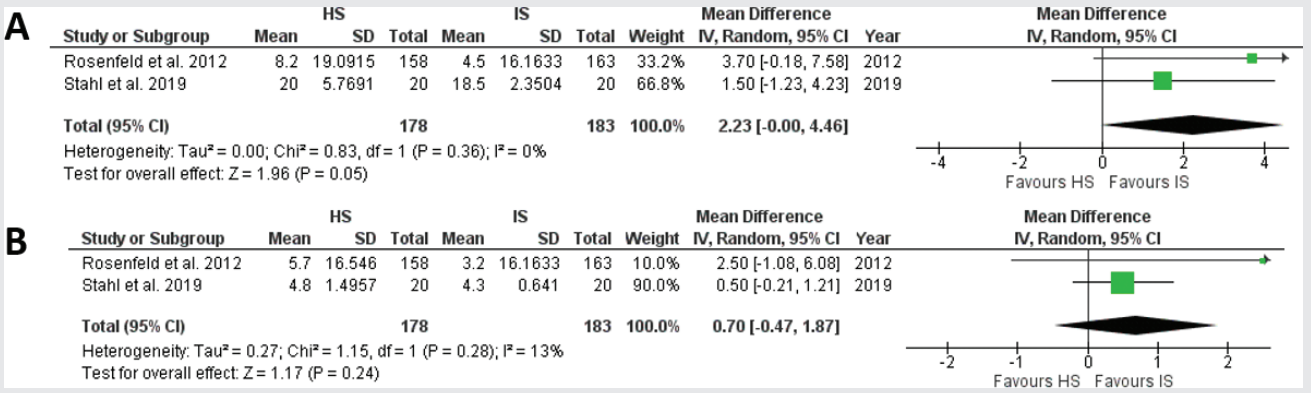


FIGURE 4

Forest plot showing changes in A height and B weight among children on hypertonic saline (HS) versus children on isotonic saline (IS). CI confidence interval; IV inverse variance; SD standard deviation.



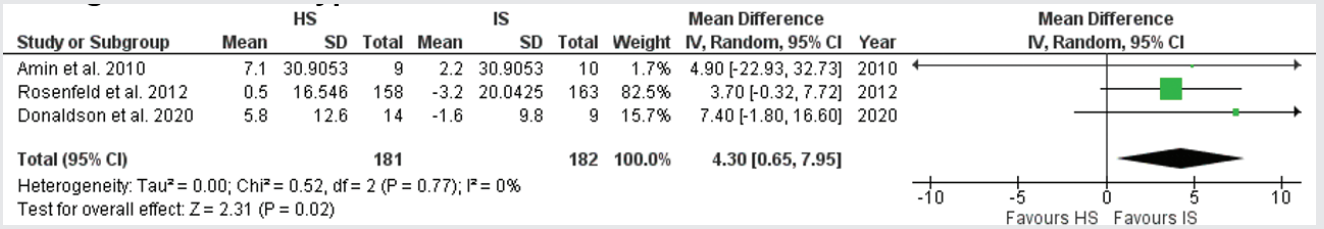
airways through several postulated molecular mechanisms: it rehydrates the airway surface, which improves mucus rheology; it induces coughing; and it disrupts ionic interactions within the mucus and shields the negative charges, reducing the viscosity of secretions [4, 19]. Additionally, by lowering the airway's inflammatory edema, HS helps promote both expiratory and inspiratory decrease of airway resistance [20, 21]. Nonetheless, these findings provide evidence for the beneficial effects of early initiation of HS on physiological parameters and demonstrate that HS is an effective early intervention treatment for children.

Our meta-analysis revealed that HS has no significant impact on FEV_1 and FVC in children compared to IS. In contrast, in the subgroup analysis of the Infant Study of Inhaled Saline trial, children treated with HS had beneficial effects on $FEV_{0.5}$ as determined by sedated infant lung function tests [6]. Importantly, children under the age of 6 years may not always have the same sensitivity of spirometry measurements to diagnose disease or capture treatment benefits as they do in adults and children over the age of 6 years [22]. Numerous observational studies on spirometry in preschool children with CF have reported baseline $FEV_{0.75}$ (an equivalent of FEV_1 in children under 6 years) to be in the healthy range [23]. Moreover, spirometry has restricted applications because it necessitates a patient's full knowledge and cooperation, whereas young children cannot actively participate in many of the physiological tasks necessary for pulmonary function tests. Compared to FEV_1, FEF_{25-75} is considered a more sensitive marker for reflecting hyperresponsiveness, inflammation and disease severity [24]. Our findings revealed significant improvements in FEF_{25-75}% and FEF_{25-75}, indicating that FEF_{25-75} may be a more sensitive spirometric measurement in this age range in a clinical trial setting where sites receive standardized training certification and feedback on all lung function tests.

Our results are consistent with previous studies demonstrating that the LCI is more sensitive than spirometry for identifying lung disease in people with CF. The LCI has been demonstrated to correlate with FEV_1 and represent disease progression, despite being aberrant at an earlier stage of the illness [25, 26]. By combining high-resolution CT (HRCT) scans with LCI and spirometry, Gustafsson et al. connected structural and physiological indicators of CF lung disease [27]. LCI was shown to be the most sensitive measure, and a normal LCI nearly ruled out an abnormal HRCT; spirometry, on the other hand, was found to be the least sensitive, frequently looking normal despite illness as verified using HRCT. Previous studies have established that the LCI is a responsive

FIGURE 5

Forest plot showing changes in Cystic Fibrosis Questionnaire-Revised (CFQ-R) among children on hypertonic saline (HS) versus children on isotonic saline (IS). IV inverse variance; CI confidence interval; SD standard deviation.



outcome that can be used for CF patients with normal pulmonary function [27]. The current meta-analysis is the first to establish that this is true for pediatric population as well. These findings and the LCI's applicability to children of all ages make it a suitable endpoint for future early intervention trials in CF.

Moreover, we also noted that changes in health status in response to HS, as manifested by improved LCI and FEF_{25-75}, are associated with significant improvements in health-related quality of life (HRQoL) in children with CF, as there was a significant increase in CFQ-R scores in these patients. However, we could not assess the changes in HRQoL using the more reliable Sino Nasal Outcome Test (SNOT-22) score because of the unavailability of data. To our knowledge, this is the first meta-analysis of improvements in HRQoL in CF-affected children treated with HS.

This study's findings would support the usefulness of LCI in interventional investigations. The LCI has not yet been linked to mortality; therefore, it is uncertain whether the LCI's sensitivity is a true reflection of early CF lung disease or a secondary effect that is present but unrelated to disease progression and survival. Although we have demonstrated that LCI correlates with FEF_{25-75} and quality-of-life scores, more longitudinal studies in patients with more severe lung disease are necessary to confirm its relationship to survival in patients with CF. This presents a clinical conundrum, as death in people with moderate illness is uncommon, and the LCI values may differ between patients with mild and severe disease. Moreover, although the current findings support the use of the LCI as a surrogate outcome measure for measuring pulmonary alterations in moderate CF lung disease, more longitudinal studies are necessary to evaluate the accuracy of the LCI in comparison to spirometry. Additionally, it is plausible that outcomes may vary according to patient characteristics, such as gender. Therefore, future studies should evaluate the potential differences in efficacy of HS in CF patients stratified by patient characteristics. Although the LCI in our meta-analysis improved with HS therapy, the minimal clinically significant difference for the LCI is not yet established. Future studies should aim to establish the minimal clinically significant difference for both children and adults separately.

Several limitations in this study should be noted. First, we could not establish the optimum dosage of HS because of the lack of data regarding dosages in the included clinical trials. Second, we could not properly assess the impact of HS on anthropometric measurements because of a lack of data. Third, we could not control for different nebulization methods in our analysis. However, there was a trend toward improvement in children's height when using HS compared with IS. Future studies should evaluate the use of HS anthropometry in children.

CONCLUSION

In conclusion, this meta-analysis revealed that HS treatment significantly improves LCI, symptoms, pulmonary function and quality of life in CF-affected children compared to IS. This study supports using HS as an early therapeutic method in CF-affected children.

DISCLOSURES

Contributors

SEU, MMZ and SG contributed to the conception and design of work. SB, MM and AS contributed to the analysis and interpretation of data. All authors drafted the manuscript. ZMA and MS critically revised the manuscript. All authors gave the approval for the final version of the manuscript.

Funding

None to declare.

Competing Interests

All authors declare no conflict of interest.

Ethical Approval

Ethical approval was not required because of the use of publicly available data.

REFERENCES

1. Puchelle E, De Bentzmann S, Zahm JM. Physical and functional properties of airway secretions in cystic fibrosis – Therapeutic approaches. *Respiration* 1995;62(Suppl 1):2–12. https://doi.org/10.1159/000196486
2. Elizur A, Cannon CL, Ferkol TW. Airway inflammation in cystic fibrosis. Chest 2008;133(2):489–95. https://doi.org/10.1378/CHEST.07-1631
3. Henderson AG, Ehre C, Button B, et al. Cystic fibrosis airway secretions exhibit mucin hyperconcentration andincreased osmotic pressure. J Clin Invest 2014;124(7):3047. https://doi.org/10.1172/JCI73469
4. Taylor LM, Kuhn RJ. Hypertonic saline treatment of cystic fibrosis. Ann Pharmacother. 2007;41(3):481–4. https://doi.org/10.1345/APH.1H425
5. Pezzulo AA, Stoltz DA, Hornick DB, Durairaj L. Inhaled hypertonic saline in adults hospitalised for exacerbation of cystic fibrosis lung disease: A retrospective study. BMJ Open 2012;2(2):e000407. https://doi.org/10.1136/BMJOPEN-2011-000407
6. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: The ISIS randomized controlled trial. JAMA 2012;307(21):2269–77. https://doi.org/10.1001/JAMA.2012.5214
7. Szczesniak R, Heltshe SL, Stanojevic S, Mayer-Hamblett N. Use of FEV1 in cystic fibrosis epidemiologic studies and clinical trials: A statistical perspective for the clinical researcher. J Cyst Fibros 2017;16(3):318–26. https://doi.org/10.1016/J.JCF.2017.01.002
8. Alton EW, Armstrong DK, Ashby D, et al. A randomised, double-blind, placebo-controlled trial of repeated nebulisation of non-viral cystic fibrosis transmembrane conductance regulator (CFTR) gene therapy in patients with cystic fibrosis. Effic Mech Eval 2016;3(5):1–210. https://doi.org/10.3310/EME03050
9. Perrem L, Rayment JH, Ratjen F. The lung clearance index as a monitoring tool in cystic fibrosis: Ready for the clinic? Curr Opin Pulm Med 2018;24(6):579–85. https://doi.org/10.1097/MCP.0000000000000515
10. Welsh L, Nesci C, Tran H, Tomai M, Ranganathan S. Lung clearance index during hospital admission in school-age children with cystic fibrosis. J Cyst Fibros 2014;13(6):687–91. https://doi.org/10.1016/J.JCF.2014.05.012

11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009;339:b2700. https://doi.org/10.1136/BMJ.B2700
12. Alpern AN, Brumback LC, Ratjen F, Rosenfeld M, Davis SD, Quittner AL. Initial evaluation of the parent cystic fibrosis questionnaire–Revised (CFQ-R) in infants and young children. J Cyst Fibros 2015;14(3):403–11. https://doi.org/10.1016/J.JCF.2014.11.002
13. Ratjen F, Davis SD, Stanojevic S, et al. Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2019;7(9):802–9. https://doi.org/10.1016/S2213-2600(19)30187-0
14. Stahl M, Wielpütz MO, Ricklefs I, et al. Preventive inhalation of hypertonic saline in infants with cystic fibrosis (PRESIS) a randomized, double-blind, controlled study. Am J Respir Crit Care Med 2019;199(10):1238–48. https://doi.org/10.1164/RCCM.201807-1203OC/SUPPL_FILE/DISCLOSURES.PDF
15. Donaldson SH, Danielle Samulski T, LaFave C, et al. A four week trial of hypertonic saline in children with mild cystic fibrosis lung disease: Effect on mucociliary clearance and clinical outcomes. J Cyst Fibros 2020;19(6):942–8. https://doi.org/10.1016/J.JCF.2020.07.009
16. Subbarao P, Stanojevic S, Brown M, et al. Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis. A pilot study using inhaled hypertonic saline. Am J Respir Crit Care Med 2013;188(4):456–60. https://doi.org/10.1164/RCCM.201302-0219OC
17. Amin R, Subbarao P, Jabar A, et al. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. Thorax 2010;65(5):379–83. https://doi.org/10.1136/THX.2009.125831
18. Nenna R, Midulla F, Lambiase C, et al. Effects of inhaled hypertonic (7%) saline on lung function test in preschool children with cystic fibrosis: Results of a crossover, randomized clinical trial. Ital J Pediatr. 2017;43(1). https://doi.org/10.1186/S13052-017-0376-6
19. Reeves EP, Molloy K, Pohl K, McElvaney NG. Hypertonic saline in treatment of pulmonary disease in cystic fibrosis. Sci World J. 2012;2012:465230. https://doi.org/10.1100/2012/465230
20. Reeves EP, Williamson M, O'Neill SJ, Greally P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis 2012;183(11):1517–23. https://doi.org/10.1164/RCCM.201101-0072OC
21. Liu XC, Wang Q, She YS, et al. Hypertonic saline inhibits airway smooth muscle contraction by inhibiting Ca2+ sensitization. Clin Exp Pharmacol Physiol 2017;44(10):1053–1059. https://doi.org/10.1111/1440-1681.12807
22. Jones MH, Howard J, Davis S, Kisling J, Tepper RS. Sensitivity of spirometric measurements to detect airway obstruction in infants 2012;167(9):1283–86. https://doi.org/10.1164/RCCM.200204-339OC
23. Ramsey KA, Ranganathan S, Park J, et al. Early respiratory infection is associated with reduced spirometry in children with cystic fibrosis. Am J Respir Crit Care Med 2014;190(10):1111–6. https://doi.org/10.1164/RCCM.201407-1277OC
24. Lukic KZ, Coates AL. Does the FEF25-75 or the FEF75 have any value in assessing lung disease in children with cystic fibrosis or asthma? Pediatr Pulmonol 2015;50(9):863–8. https://doi.org/10.1002/PPUL.23234
25. O'Neill K, Bradley JM, Tunney M, Elborn JS. S44 Lung clearance index (LCI) and FEV1 correlate equally with treatment burden as measured by cystic fibrosis questionnaire-revised (CFQ-R). Thorax 2011;66(Suppl 4):A23. https://doi.org/10.1136/THORAXJNL-2011-201054B.44
26. Nyilas S, Schlegtendal A, Yammine S, Casaulta C, Latzin P, Koerner-Rettberg C. Further evidence for an association between LCI and FEV1 in patients with PCD. Thorax 2015;70(9):896.https://doi.org/10.1136/THORAXJNL-2015-207206
27. Gustafsson PM, De Jong PA, Tiddens HAWM, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax 2008;63(2):129–34. https://doi.org/10.1136/THX.2007.077784