Literature Review

Hypertonic saline nasal irrigation for chronic sinusitis: a systematic review and meta-analysis

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is an inflammatory condition of the paranasal sinuses characterized by persistent sinonasal symptoms. It is a prevalent chronic medical ailment worldwide, impacting individuals of all ages and impairs patients' quality of life. Recent findings in otorhinolaryngology reveal that hypertonic saline nasal irrigation is more effective than isotonic saline for addressing this condition. Hypertonic saline with higher osmotic pressure demonstrates superior efficacy in reducing mucosal edema. **Purpose:** To study the efficacy of nasal irrigation with hypertonic saline on chronic rhinosinusitis. **Literature review:** Conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. The search strategy spanned prominent multiple electronic databases (PubMed and SagePub), encompassing publications from 2015 to 2023. Duplicate publications, review articles, and incomplete articles were excluded. A meta-analysis was planned to analyze outcome of Visual Analog Scale (VAS) score. **Result:** The search results from the year 2015-2023 yielded 35 articles from PubMed and 28 articles from SagePub. In the end, 4 eligible studies were obtained. From these, hypertonic saline demonstrated enhanced symptomatic relief. However, only two studies were eligible for meta-analysis, revealing no significant VAS difference between hypertonic and normal saline (mean difference 2.40 [95% CI -2.85 – 7.65]; p 0.37). **Conclusion:** Hypertonic saline nasal irrigation offered moderate side effects, improved nasal symptoms and ciliary activity more than isotonic saline, although there were no significant differences in radiological imaging or sense of smell. However, the meta-analysis did not find a significant difference in VAS scores.

Keywords: chronic rhinosinusitis, ciliary activity, nasal irrigation, hypertonic saline

ABSTRAK

Latar belakang: *Rinosinusitis kronis (RSK) adalah kondisi inflamasi pada sinus paranasal yang ditandai oleh gejala sinonasal persisten. RSK merupakan penyakit kronis yang umum terjadi di seluruh dunia, memengaruhi individu segala usia dan mengganggu kualitas hidup pasien. Temuan terbaru dalam otorhinolaringologi mengungkapkan bahwa irigasi hidung dengan larutan garam hipertonik lebih efektif daripada larutan garam isotonik dalam kondisi ini. Larutan garam hipertonik dengan tekanan osmotik yang lebih tinggi, menunjukkan efikasi unggul dalam mengurangi edema mukosa.* ***Tujuan:*** *Mempelajari efikasi irigasi hidung dengan larutan garam hipertonik pada rinosinusitis kronis.* ***Tinjauan pustaka:*** *Dilakukan sesuai dengan pedoman* Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. *Strategi pencarian melibatkan beberapa basis data elektronik (*PubMed *dan* SagePub*), mencakup publikasi dari tahun 2015 hingga 2023. Publikasi yang duplikat, artikel tinjauan, dan artikel yang tidak lengkap, dieksklusikan. Dilakukan meta-analisis untuk menganalisis hasil skor* Visual Analog Scale (VAS). ***Hasil:*** *Pencarian pada tahun 2015-2023 menghasilkan 35 artikel dari* PubMed *dan 28 artikel dari* SagePub*. Pada akhirnya, didapatkan 4 studi yang memenuhi syarat. Larutan garam hipertonik menunjukkan perbaikan gejala simtomatik yang lebih baik. Namun, hanya 2 studi yang memenuhi syarat untuk meta-analisis, didapatkan tidak ada perbedaan signifikan dalam* VAS *antara larutan garam hipertonik dan normal (selisih rata-rata 2,40 [95% CI -2,85–7,65];*

p 0,37). ***Kesimpulan:*** *Irigasi hidung dengan larutan garam hipertonik memiliki efek samping sedang, memperbaiki gejala hidung dan aktivitas silia lebih baik daripada larutan garam isotonik, meskipun tidak ada perbedaan signifikan dalam pencitraan radiologi atau penciuman. Pada meta-analisis tidak ditemukan perbedaan signifikan dalam skor* VAS.

Kata kunci: *rinosinusitis kronis, aktivitas silia, irigasi hidung, larutan garam hipertonik*

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a paranasal sinus inflammatory disorder that most commonly causes chronic sinonasal symptoms. CRS is one of the most common chronic medical conditions worldwide, affecting all age groups. Its estimated incidence is 12.3% in the USA, 10.9% in Europe and 13% in China. CRS is also a condition leading to a significant decrease in the quality of life of patients. It is a curable disease that accounts for billions of dollars in direct and indirect health-care costs each year.[1-3]

CRS is linked to asthma and allergic rhinitis due to its inflammatory causes. Certain inflammatory and immunodeficiency disorders could also induce CRS, but with different symptoms.[3] Granulomatous illnesses including vasculitis and sarcoidosis could also induce CRS, nasal crusting, and epistaxis. Chronic sinonasal symptoms are the most typical manifestation of various vasculitis types, including granulomatosis with polyangiitis and eosinophilic granulomatosis. Immunodeficiency and inadequate mucociliary clearance can cause persistent sinus infections and rhinosinusitis.[4,5]

In the medical practice of nasal irrigation with saline (salty water), sometimes referred to as nasal douching, cleaning, or lavage, the nasal cavity is washed out with isotonic or hypertonic saline solutions.[6] This procedure is also known as nasal douching. Saline solutions can be purchased over-the-counter and can be utilized either on their own or in conjunction with other forms of treatment.[6,7]

Otorhinolaryngologists have recently discovered that using hypertonic saline for nasal irrigation is more effective than using isotonic saline for the same purpose. A hypertonic solution, which has a higher osmotic pressure, is capable of lowering mucosal edema with a greater degree of efficacy.[8] Even though there have been some prospective studies on the effectiveness of different saline concentrations in the treatment of CRS, the clinical effectiveness of nasal irrigation with hypertonic saline remains unclear, and reasonable clinical recommendations cannot be made because there has not been a systematic evaluation of how well it works.[9,10]

The objective of this study is to determine whether CRS could be effectively treated with nasal irrigation using hypertonic saline.

METHOD

"Nasal irrigation", "hypertonic saline" and "chronic rhinosinusitis" were used as keywords. The search for studies to be included in the systematic review was carried out from May 28th, 2023 using the PubMed and SagePub databases by inputting the words: "nasal lavage"[MeSH Terms] OR "nasal irrigation"[All Fields]) AND "hypertonic saline solution"[MeSH Terms], [All Fields] AND "chronic"[All Fields] AND "rhinosinusitis"[All Fields] used in searching the literature.

STUDY SELECTION

To be included in this literature review, the papers must meet the following requirements: 1) The articles must be written in English and its primary focus must be on the efficacy of nasal irrigation with hypertonic saline on chronic rhinosinusitis, and 2) published from 2015 up to May 28th, 2023. Literatures that could not be published includes: editorials, applications without a Digital Object Identifier (DOI), previously published review articles, and entries that were nearly identical to previously published journal articles.

Two authors independently performed the initial search and screened the titles and abstracts. Any discrepancies were resolved through discussion with the third author. Afterward, the studies' full texts were obtained and analyzed further. Studies that met the criteria were included in this review and analysis.

STATISTICAL ANALYSIS

VAS score was applied for analysis. Heterogeneity across studies was evaluated using the inconsistency index (I^2). A random-effect model was used if the significant heterogeneity was found (I^2>40%), otherwise a fixed-effect model was preferred. Outcomes were compared using mean difference and its 95% confidence intervals (CI). Statistical significance was set at $p<0.05$. The Cochrane risk-of-bias was used for evaluating risk of bias of randomized studies; while the Risk of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) was used for non-randomized studies. Publication bias was evaluated using the funnel plot analysis. All analysis was performed using Review Manager version 5.3.

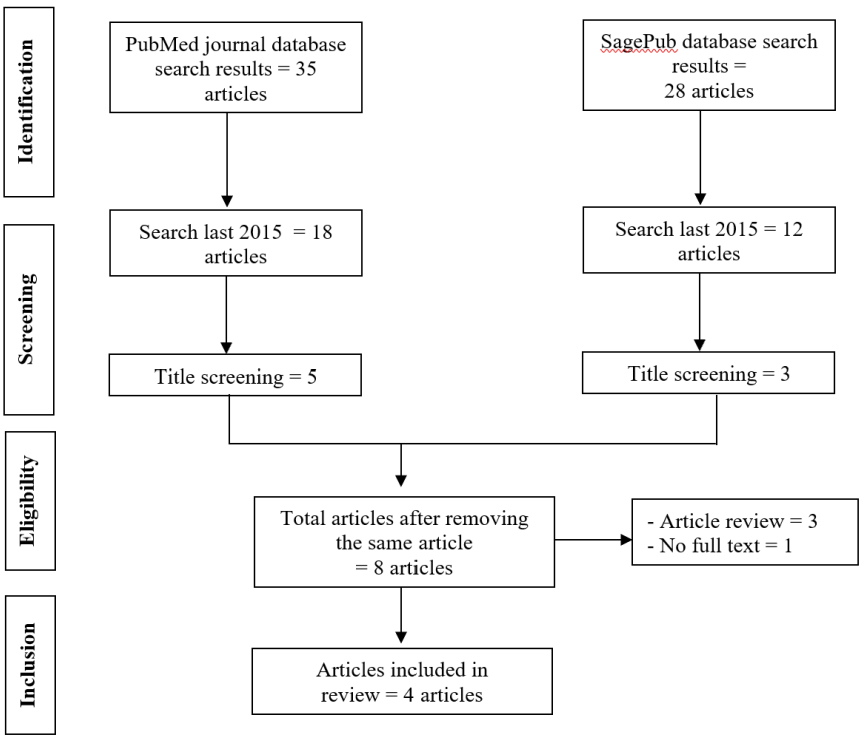

Figure 1. Article search flowchart

RESULT

The search on the PubMed database found 35 articles, while on SagePub found 28 articles. The search results since the year 2015 yielded 18 articles from PubMed and 12 articles from SagePub. Afterwards, a total 8 articles were obtained (5 from PubMed and 3 from SagePub), finally 4 eligible studies were reviewed.

Sudhakaran et al.[11] study included 50 participants. This prospective, randomized study compared the effectiveness of hypertonic versus normal saline in the treatment of CRS patients. Twenty-two patients were treated with normal saline, while 23 patients were with hypertonic saline. They evaluated the outcome using the VAS for nasal blockage, discharge, smell disturbance, headache, facial pain, and overall symptoms. Generally, patients started to experience improvement on the second or third week. By the end of the fourth week, they demonstrated the benefits of hypertonic against normal saline. The mean of VAS was lower for nasal blockage (0.35±0.65 vs. 2.09±1.12; p<0.0005), nasal discharge (0.35±0.65 vs. 2.04±1.26; p<0.0005), headache (0.00±0.00 vs. 1.00±0.80; p<0.0005), smell disturbance (0.17±0.39 vs. 0.83±0.89; p 0.002), and overall symptomatic score (0.57±0.73 vs. 2.0±0.85; p<0.0005). However, they did not find any significant differences in facial pain (0.00±0.00 vs. 0.04±0.21; p 0.323).

Vakil et al. (2022)[12] conducted a study with CRS patients. Patients were examined at 1, 3, and 6 weeks after endoscopic sinus surgery. Their study included 156 patients randomized into two groups. The effectiveness of irrigation with both solutions was evaluated using the 20-item Sino-Nasal Outcome Test (SNOT20), the Visual Analog Scale (VAS), the mucociliary clearance test (MCT), and endoscopic examination. Patients receiving hypertonic saline reported better SNOT20 score after the third week (22.8±5.4 vs. 16.2±4.8; p 0.004) and sixth week (31.3±3.2 vs. 22.2±4.2; p 0.0001). VAS also showed improvement in the third week (13.2±2.8 vs. 8±2.6; p 0.002) and sixth week (17.5±3.4 vs. 12.4±2.4; p 0.0017). However, they did not find any significant differences in the improvement of MCT and crusting found on endoscopic examination.

Table 1. Literatures included in this study

Author	Origin	Method	Sample	Agent	Result
Sudhakaran, 2016[11]	India	Randomized controlled trial	50 patients with CRS	NaCl 3% vs. NaCl 0.9%	Results of the study, hypertonic saline nasal solution at a concentration of 3% was more effective than ordinary saline nasal solution at a concentration of 0.9%.
Vakil, 2022[12]	India	Randomized controlled trial	156 patients, who had CRS	NaCl 3% vs. NaCl 0.9%	Hypertonic saline nasal irrigation post FESS brought greater benefits on symptom improvement and normalization of the sino-nasal mucosa over isotonic saline.

Peric, 2019[13]	Norway, Serbia	Randomized controlled trial	30 patients with aspirin-induced CRS undergoing ESS	Hypertonic (2.3% NaCl) sea water vs isotonic 0.9% NaCl	Patients with aspirin-induced CRS who were given hypertonic saline solution as treatment during the early post-operative period was superior compared to isotonic saline.
Wang, 2020[14]	China	Randomized controlled trial	93 patients with CRS	Buffered hypertonic seawater (BHS) vs physiological seawater (PS)	Both BHS and PS nasal sprays in patients with CRSwNP did not find significant differences in VAS and SNOT-22 scores post-operatively. Despite during the early postoperative care period of CRSwNP, BHS's inhibitory effect on mucosal edema and crusting was superior to those of other treatments. At 8 weeks, participants who did not have ECRSwNP showed the most substantial improvement in LEKS and SCT compared to the other patients.

Peric et al.[13] evaluated the difference in outcome between 2.3% and 0.9% saline in treating patients with aspirin-induced CRS after endoscopic sinus surgery. They randomized 30 patients, and evaluated the outcome using VAS for nasal obstruction, discharge, facial pain, headache, and sleep difficulty on the 1st, 7th, 14th, 21st, and 28th day after nasal packing removal. They also evaluated mucosal edema, nasal secretion, and nasal crusting through endoscopic examination. By the 28th day, patients receiving hypertonic saline reported lower median for nasal obstruction (1[1] vs. 2[1]; p<0.001), headache (1[1] vs. 2[1]; p 0.48), and sleep difficulty (1[0] vs. 2[1]; p 0.041). They also found less mucosal edema (1[0] vs 2[1]; p<0.001), crusting (1[1] vs. 2[1]; p 0.002). Overall, the median for total symptom score (6[2] vs. 9[4]; p 0.001) and total endoscopic score (3[1] vs. 6[2]; p 0.001) were lower for patients receiving hypertonic saline.

Wang et al.[14] compared 2% with 0.9% saline. Their samples included patients with CRS with nasal polyps who underwent endoscopic sinus surgery. Their study included 130 patients randomized into two groups. They evaluated the outcome using SNOT22, VAS, Lund-Kennedy endoscopic score (LKES), and saccharine clearance time (SCT). They did not find significant differences in post-operative VAS and SNOT-22 scores. They only found an improvement in mean difference of LKES (5.11±0.22 vs. 6.06 ±0.26; p 0.01) and SCT (14.84±3.19 vs. 27.81±3.86; p 0.01) on the 8th week. Improvement in LKES component was noted in the mucosal edema and crusting. Interestingly, when the samples were divided into groups with eosinophilic and non-eosinophilic, significant improvement in LKES and SCT was noted only in the non-eosinophilic group.

META-ANALYSIS

Meta-analysis was feasible only for the study by Vakil et al.[12] and Wang et al.[14] The forest plot diagram can be seen in Figure 2. Study by Sudhakaran et al.[11] was excluded because they reported their VAS score as mean ± SD over a period of time, while the analysis required mean difference before and after treatment. On the other hand, the study by Peric et al.[13] was excluded because they reported their results as median. In the meta-analysis, there was no significant difference in VAS between patients receiving hypertonic and normal saline (mean difference 2.40 [95% CI -2.85–7.65]; p 0.37).

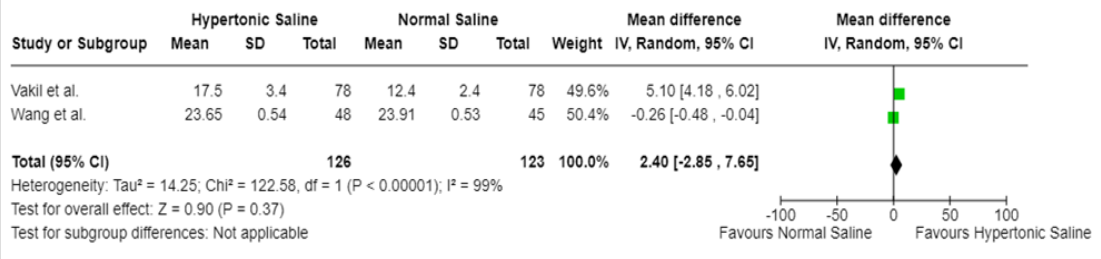

Figure 2. Forest plot diagram

STUDY QUALITY

As all the included studies were randomized controlled trial, the Cochrane Risk of Bias-2 (RoB-2) was used to assess for bias. The summary can be seen in Figure 3. The studies by Sudhakaran et al.[11] and Vakil et al.[12] had been found to have high-risks of bias because they did not employ blinding. Publication bias was not evaluated because funnel plot analysis did not have enough power to detect any bias with only four studies.

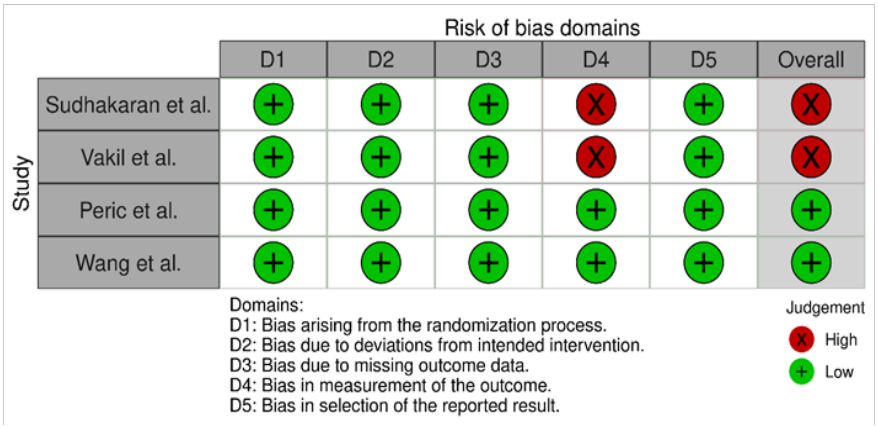

Figure 3. Risk of bias

DISCUSSION

Chronic rhinosinusitis (CRS) is characterized by chronic inflammation of the sinonasal mucosa and is clinically associated with sinus pressure, nasal congestion, rhinorrhea, and a decreased sense of smell persisting for more than 12 weeks. In particular, CRS can be divided into two main subgroups based on the presence or absence of nasal polyps. Patients with chronic sinonasal inflammation have limited clinical treatment options, in part because the underlying mechanisms contributing to disease pathology are heterogeneous and incompletely understood. Changes in mucociliary clearance, abnormalities in the sinonasal epithelial cell barrier, and tissue remodeling are hypothesized to contribute to the chronic inflammatory and tissue-deforming processes characteristic of CRS.[15]

CRS is clinically diagnosed with a physical examination and focused sinonasal history, which includes chronic rhinosinusitis–associated comorbidities and relevant family history. Clinical consensus guidelines from the American Academy of Otolaryngology–Head and Neck Surgery define chronic rhinosinusitis as the presence of at least two of four cardinal symptoms (i.e., facial pain/pressure, hyposmia/anosmia, nasal obstruction, and nasal drainage) for at least 12 weeks, along with objective evidence on physical examination (anterior rhinoscopy or endoscopy) or radiography, such as computed tomography.[16–18]

Multiple studies had shown that patients with chronic rhinosinusitis got benefit from at least once daily saline irrigations by experiencing a reduction in their symptoms and an improvement in their quality of life. However, sinonasal irrigation protocols vary widely in terms of the volume, frequency and duration of treatment, and nasal devices used.[6]

Although randomized controlled trials (RCTs) demonstrated that isotonic and hypertonic saline irrigations were equally beneficial, at least one study found that hypertonic saline irrigations led to more burning sensation or patient's pain. This is despite the fact that both types of irrigations were shown to be equally effective. Isotonic saline irrigations are currently recommended as a component of standard medical therapy for CRS because of their efficacy and safety. In order to achieve the best results, saline irrigations should ideally be used in conjunction with an intranasal corticosteroid spray.[17]

Numerous individuals who suffer from CRS use this medication either alone or in conjunction with other treatments. The exact way that saline nose irrigation works is not known. Saline nasal irrigation may improve the function of the nasal mucosa in a number of ways, including directly cleaning out mucus, removing antigens, biofilm, or inflammatory mediators (which reduces inflammation), and improving mucociliary function (as shown by more frequent ciliary beats). The success of irrigation may depend on both how it is done and what the percentage of the salt solution is.[6,19,20]

A study disclosed significantly improved effectiveness of hypertonic saline nasal irrigation in management of CRS patients' nasal symptoms and MCT scores, as compared to isotonic saline. Both hypertonic saline and isotonic saline did not lead to significant improvement when evaluated through radiologic imaging. In various studies different concentrations of hypertonic saline solutions had been used. Hypertonic saline nasal irrigation can significantly improve mucociliary clearance rate. Buffering hypertonic saline could increase the thickness of the mucus layer and reduced the viscosity of the mucus, which was more conducive to improve movement of the cilia.[8,20]

The literature search was looking for studies by using RCT methods to investigate efficacy of nasal irrigation with hypertonic

saline on chronic rhinosinusitis. This literature search revealed 4 studies that matched the search criteria: Sudhakaran et al.[11], Vakil et al.[12], Peric et al.[13] and Wang et al.[14]

According to Sudhakaran et al.[11], hypertonic saline nasal solution (3%) was more effective than ordinary saline nasal solution (0.9%). They evaluated the symptoms of the patients using VAS of 0 to 10 (0=none and 10=most severe) for nasal blockage, nasal discharge, headache, facial pain, smell disturbance and overall symptomatic improvement. They obtained significant improvement results in almost all of the symptoms they evaluated. However, they did not find any significant differences in facial pain.

Another study conducted in India by Vakil et al.[12] stated that hypertonic saline solution provided a greater benefit on symptom improvement and normalization of the sino-nasal mucosa over isotonic saline. This was evident in their findings on CRS patients who underwent Endoscopic Sinus Surgery (ESS) and were administered hypertonic saline solution (3%) and isotonic saline solution (0.9%). Assessment was performed using the 20-item Sino-Nasal Outcome Test (SNOT20) score, Visual Analogue Scale (VAS) scores to evaluate symptom severity, mucociliary clearance (MCC) using the saccharine clearance test, and endoscopic assessment using a 0^{o} nasal endoscope. However, they did not find any significant differences in the improvement of MCT and crusting found on endoscopic examination.

Peric et al.[13] conducted a study to compare the effects of hypertonic sea water (2.3% NaCl) and isotonic (0.9% NaCl) on symptoms and endoscopic findings in patients with aspirin-induced CRS during the period of 1 month after ESS. This study found that hypertonic saline solution yielded superior results compared to isotonic saline solution.

One study in China by Wang et al.[14] compared 2% saline with 0.9% saline. Their samples included CRS patients with nasal polyps (CRSwNP) who underwent endoscopic sinus surgery. They also divided the samples into two subgroups: eosinophilic CRSwNP (ECRSwNP) and non-eosinophilic CRSwNP (nonECRSwNP) for evaluation. They assessed the outcomes using SNOT22, VAS, Lund-Kennedy endoscopic score (LKES), and saccharine clearance time (SCT). In this study, they did not find significant differences in post-operative VAS and SNOT-22 scores. They only found an improvement in the mean difference of the LKES score. This study yielded non-significant results, possibly due to a single-center trial involving only CRSwNP patients, the lack of exploration into nasal irrigation methods, and the reliance on self-reported compliance data, which could introduce potential bias.

From the result of our review, it was found that hypertonic saline irrigation gave several benefits in treating CRS. All of the included RCT, except the study by Wang et al.[14], reported better clinical improvement in patients who received hypertonic saline irrigation. Moreover, two RCTs also found improvement in endoscopic result. However, the meta-analysis study was only could be performed in the study by Vakil et al.[12] and Wang et al.[14], because the results reported by the rest of the studies were not compatible.

In the meta-analysis, there was no significant differences between those who received hypertonic and isotonic saline. Vakil et al.[12] found significant improvement, while contrastingly Wang et al.[14] did not. One possible reason was the difference of nasal saline concentration. Vakil et al.[12] used 3% nasal saline, while Wang et al.[14] used 2%. However, it was still too hasty to deduce that 3% nasal saline is more effective.

The absence of standardized protocols, and variations in the concentration and frequency of hypertonic saline usage, could contribute to the observed diversity in meta-analyses. Consequently, the symptom improvement seen in CRS patients using hypertonic saline nasal irrigation, while promising, might not consistently achieve statistical significance in these comprehensive analyses.

Hypertonic saline can cause an increase in intracellular Ca2+ release, while Ca2+ increases tile rate of ciliary oscillation. They also found that hypertonic saline nasal irrigation was more effective in improving symptoms and did not increase the incidence of side effects. The nasal irrigation procedure was found to have few adverse effects, making it a safe treatment option. There is no one universally accepted norm for the practice of clinical nasal irrigation, and people have varying opinions regarding the practice. It is tough to steer clear of particular adverse consequences.[8,11]

Recognizing the importance of individual patient responses (subjective assessments by patients) to hypertonic saline nasal irrigation was crucial. Personalized treatment plans that consider the unique characteristics and needs of each CRS patient could enhance the effectiveness of this intervention. Therefore, even though the results of meta-analyses might not always reveal statistically significant symptom improvement in all studies, the practical value of hypertonic saline nasal irrigation remained evident in CRS management, and could be felt by patients.

This review and analysis had several limitations. Although all of the included studies were RCT, each of them only studies of a small number of participants. This small number of samples could reduce the confidence in the result. Another limitation was that three out of four the included studies were done in Asia. This could limit the generalizability to other populations. Nevertheless, the review found that most RCTs showed the benefits of hypertonic over isotonic saline. This could serve as the foundation for larger RCTs to be conducted in the future.

In conclusion, nasal irrigation using hypertonic saline presented moderate adverse effects, enhanced relief for nasal symptoms, and better ciliary activity compared to isotonic saline, although there were no significant differences in radiological imaging or sense of smell. However, this literature review did not find a significant difference in VAS scores. This occurred despite the fact that certain cases indicated that hypertonic saline had mild side effects that made patients uncomfortable compared to isotonic saline. Further studies with larger sample size and broader population are needed. Additionally, further studies are required to consider the methods and concentrations in nasal irrigation administration.

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