SYSTEMATIC REVIEW

REVISED The safety and efficacy of spray cryotherapy after endoscopic sinus surgery in chronic rhinosinusitis: A systematic review of randomized controlled trials [version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background

Chronic rhinosinusitis (CRS) is a condition that affects 5–12% of the general population. Endoscopic sinus surgery (ESS) is the preferred treatment because of its few adverse effects and highest success rates. The most common post-operative consequences include synechia, nasal blockage, and disease recurrence. Spray cryotherapy is a novel therapeutic approach with promising outcomes for the treatment of upper airway disorders.

This review aimed to investigate the effects of spray cryotherapy (SCT) following ESS in patients with chronic rhinosinusitis.

Methods

Six electronic databases were searched for randomized clinical trials (RCTs). The selected trials were evaluated for methodological quality, and data were extracted by two independent reviewers. The Cochrane risk-of-bias tool was used to assess the quality of evidence.

Results

Open Peer Review

Approval Status ✔ ? ?

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version 2 (revision) 05 Jun 2024			? view
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Three RCTs with 85 patients were included in the final analysis. SCT was related to -16 and -77 reductions in Lund-McKay and SNOT-22 scores after 36 weeks of follow-up, in contrast to a placebo, which showed -10.4, -65. Regarding the side effects of SCT, no adverse effects were reported, and visual assessments showed no pain, visual field loss, or any other ocular complications.

Conclusions

SCT is a new treatment modality after endoscopic sinus surgery that shows an effective post-operative management strategy with better post-operative scales (Lund-McKay, SNOT-22, POSE, and Lund-Kennedy) and less edema, obstruction, crusting, and inflammation with minimal or no side effects. However, further research with longer follow-ups, a larger sample size, and subjective assessment is needed to assess any possible long-term side effects.

Keywords
chronic rhinosinusitis, functional endoscopic sinus surgery, middle meatus antrostomy, nasal polyposis, spray cryotherapy

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 1**

In this revised version of our article, we have made several key changes to address the feedback from readers and enhance our content's clarity and comprehensiveness. Notably, we have expanded the section on postoperative care of the nasal mucosa after endoscopic sinus surgery (ESS). This new section delves into the challenges and strategies for preventing scarring and synechiae formation, offering practical guidance for clinicians.

We have also corrected terminological inaccuracies noted in the previous version, replacing mentions of 'chronic rhinitis' with 'chronic rhinosinusitis' to more accurately reflect the conditions discussed. Additionally, the description of spray cryotherapy has been expanded in the Introduction to include a detailed discussion of its adverse events and complications, reflecting its growing relevance in the field.

Furthermore, we have refined the language and structure of the Abstract and Conclusions to better communicate ESS's effectiveness and objectives. We move beyond a simple focus on its few adverse effects to emphasize its role in achieving optimal patient outcomes.

These modifications aim to enhance the article's readability, accuracy, and utility for clinical practitioners and researchers in otolaryngology.

Any further responses from the reviewers can be found at the end of the article

Introduction

Chronic rhinosinusitis (CRS) is a name describing a family of clinical conditions that affect 5–12% of the general population, disturbing their quality of life and adding a financial burden to the healthcare system.[1] Chronic rhinosinusitis in adults was defined in the European position paper on rhinosinusitis and nasal polyps 2020 as "the presence of two or more symptoms, one of which should be either nasal blockage, obstruction, congestion, or nasal discharge (anterior or posterior nasal drip), with or without facial pain/pressure, and with or without a reduction or loss of smell; for 12 weeks; with validation by telephone or interview.".[1] CRS can occur with or without polyps, and there appears to be a significant overlap between the two forms of chronic rhinosinusitis in terms of the inflammatory profile, clinical presentation, and treatment effect. Despite these differences in etiology and phenotype, many treatments for chronic rhinosinusitis are initiated in clinical practice without knowledge of a patient's "polyp status," despite the fact that 25–30% of CRS cases present with nasal polyps (NP).[2] CRS has many variations in terms of histology and clinical presentation, making its management controversial. Medically, many options are available, including corticosteroids, antibiotics, antihistamines, anti-leukotrienes, decongestants, saline, and aspirin, while surgical options include primary sinus surgery, revision endoscopic surgery, and many other techniques.[1,3] In the present study, the surgery of interest is endoscopic sinus surgery (ESS) for CRS. Despite being widely utilized with over 250,000 sinus surgeries per year in the US,[4] it is usually associated with synechia, obstruction, and stenosis of the maxillary or frontal ostium, which is caused by the apposition of two mucosal surfaces. Excessive scar formation, adhesions, and sinus osteomeatal stenosis are considered the main causes of disease recurrence and the need for revision surgery.[5]

Spray cryotherapy (SCT) is a technique that involves treating mucosal lesions with liquid nitrogen at -90°C to freeze cellular water content and impose cellular necrosis for a few minutes to prevent mucosal surface adhesion, resulting in faster healing, less obstruction, and stenosis.[6] It was previously adapted for the treatment of esophageal lesions, including esophageal cancer and Barrett's esophagus.[7–9] In 2010, SCT was first used by Krimsky *et al*. for the treatment of glottic and subglottic stenosis and was the first application of SCT in airway surgery.[10] Subsequently, SCT was successfully used in cases of benign and malignant airway diseases.[11,12] In this systematic review of randomized controlled trials, we summarized and analyzed the available evidence regarding the impact of SCT after ESS for CRS with or without polyps. To our knowledge, this is the first systematic review to address the effects of SCT on healing after ESS surgery. Numerous techniques, such as the use of spacers, nasal packing with absorbent material, such as anti-adhesion packs containing sodium hyaluronate or sodium carboxymethylcellulose, and anatomical barriers, have been demonstrated to prevent these adhesions. These techniques, however, were only somewhat successful in preventing.[7]

Methods

Study design

This systematic review of randomized controlled trials was performed in accordance with the PRISMA checklist.[13,14] The filtration phases were carried out according to the Cochrane criteria.[15]

Inclusion criteria

We included studies that examined the effectiveness of post-operative SCT in patients with chronic rhinosinusitis of either sex, regardless of age, from any healthcare context. The main outcome of interest was investigating the main impact

of SCT after endoscopic sinus surgery for chronic rhinosinusitis with or without nasal polyposis. According to our inclusion criteria, the studies included satisfied the following criteria: 1) randomized control trials (RCT); 2) SCT was used following endoscopic sinus surgery; and 3) Only in English.

Search strategy and study selection

The PubMed, Scopus, ClinicalTrails.gov, Cochrane Library, Web of Science, and Google Scholar databases were used for the searches, which had a date range from inception until 1/8/2023 for all databases. Randomized controlled trials, endoscopic sinus surgery (mesh terms), and spray cryotherapy (mesh terms) were used as search terms. For Google Scholar, Web of Science and ClinicalTrials.gov we used the simplest of keywords "spray cryotherapy and chronic rhinosinusitis" without filter. For PubMed and Scopus "(((spray cryotherapy) or (SCT)) and ((chronic rhinosinusitis) or (chronic rhinitis)) and ((endoscopic sinus surgery) or (endoscopic sinus surgery (MESH)))" were used. We also manually searched the entire text of the recognized systematic reviews that had been published in the area for potentially relevant details. Following the searches, references were located and exported to an Endnote X9 file after duplicates were eliminated. Filtration and extraction were performed by two independent reviewers, and any disagreement was resolved by a third reviewer.

Quality assessment

The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the quality of the retrieved RCTs. The following areas were covered by the Cochrane risk-of-bias assessment tool: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and staff (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other possible sources of bias.

Data acquisition

To prevent bias, each publication was extracted separately by two randomized authors, and any disagreements were resolved by a third reviewer. The study design, participant country, participant age, description of cryotherapy, control groups, outcomes, and time points were among the characteristics extracted from the studies. Each process followed the suggested techniques in Higgins & Cochrane (2020).[15,16]

Data analysis

Because of the small number of included trials, a planned meta-analysis using a random effects model was not possible. Mean differences and 95% confidence intervals are shown. RevMan 5.4 software (Cochrane Collaboration) was used for all analyses. Arguments between the reviewers were handled by a third reviewer (MJJT). We planned subgroup analyses to examine the effects of different types and doses of cryotherapy, as well as the two forms of CRS (one with polyposis and one without). Furthermore, sensitivity analyses were performed to determine whether a significant risk of bias affected the estimates. We aimed to use meta-regression for subgroup and sensitivity analyses if feasible (i.e., at least 10 trials were analyzed); otherwise, qualitative analysis might have been performed in accordance with the guidelines.[17]

Publication bias

For <10 pooled studies, publication bias evaluation is unreliable according to Egger *et al.* As a result, we were unable to use Egger's test for funnel plot asymmetry to evaluate publication bias in the current review.[18,19]

Results

Search results

Our search yielded 322 results; 206 duplicates were eliminated, and the remaining 83 abstracts were reviewed. Three randomized controlled trials were incorporated after 10 prospective full texts were evaluated. Figure 1 in this review provides an illustration of the filtration procedures. According to the Cochrane risk-of-bias tool, all included studies were scored as low risk (Figures 2 and 3).

Characteristics of included studies

Three of the articles met the inclusion criteria. Table 1 summarizes the characteristics of the included studies. There were 85 chronic rhinosinusitis patients in the entire study population among all papers that were chosen, with approximately equal representation of men and women (54 males and 57 females). In all studies, the average age of the study population was 42.65±14 years.

Operative techniques

Regarding the operative technique, devices, and post-operative management, the Brymill (Ellington, CT) CRY-AC-3 Cryogenic System was used in all included studies, and all patients received post-operative antibiotics as part of different post-operative protocols. The characteristics of the surgical and post-operative protocols are summarized in Table 2.

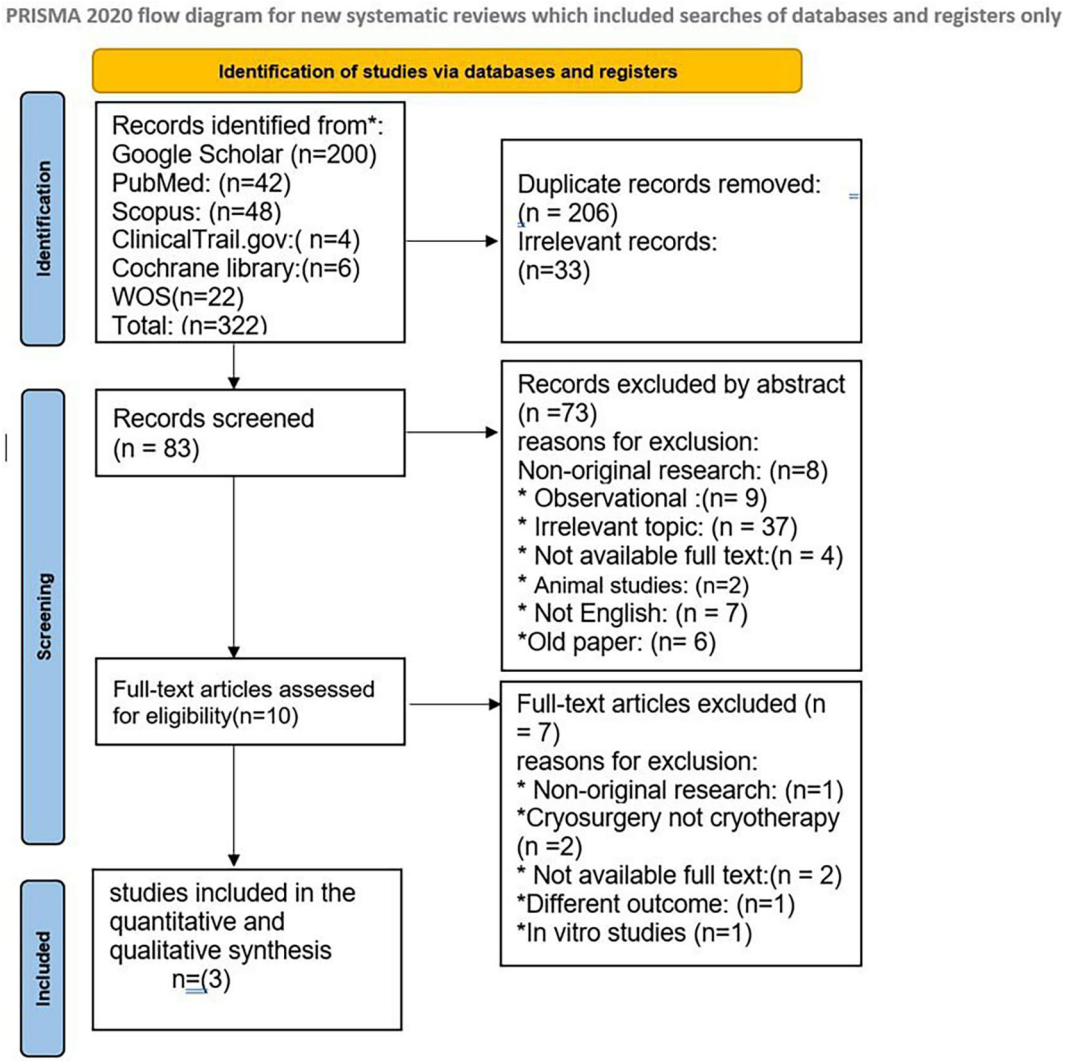

Figure 1. **PRISMA flow chart for included and excluded studies.**

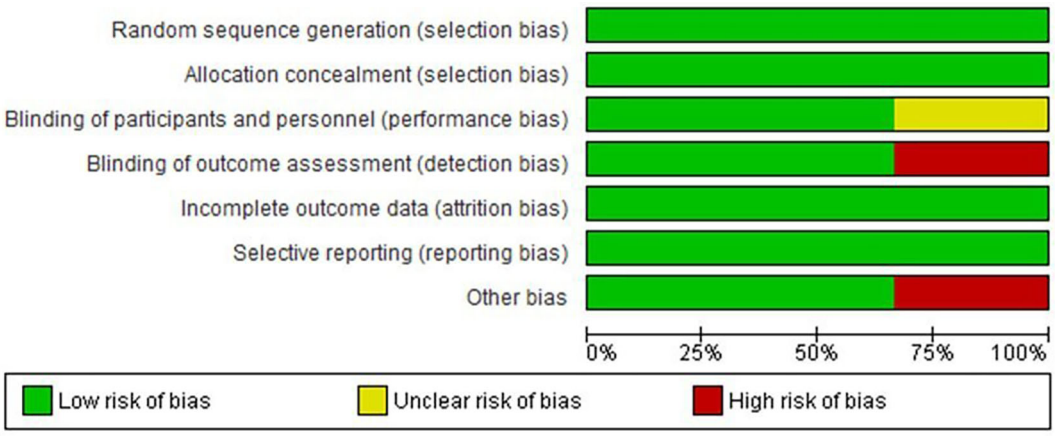

Figure 2. **Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Effect of spray cryotherapy after endoscopic sinus surgery

Owing to the heterogeneity of the data regarding the measurements of post-operative improvement, conducting a meta-analysis was inappropriate. However, spray cryotherapy, according to Rezaeian (2018),[20] was related to -16 and -77 reductions in Lund-McKay and SNOT-22 scores after 36 weeks of follow-up, in contrast to the placebo, which showed -10.4, -65. This outcome was also demonstrated by the POSE and Lund-Kennedy scores. Additionally, adhesions were more frequent on the control side than on the cryotherapy side. One middle meatus with a decreased dimension was reported in an SCT patient, compared to eight middle meatal antrostomies with stenoses in the control group at the final follow-up. In the Trombitaș study, post-operative stenosis is defined as when the MMA diameter is less than 6 mm.

Effect of SCT on post-operative nasal discharge, crustations and histological difference

According to Trombitaș *et al.*,[21] the spray cryotherapy (SC) group significantly outperformed the control group in terms of nasal obstruction and discharge. Furthermore, the placebo side was linked to mononuclear cell infiltration, edema with collagen fiber dislocation, epithelial hyperplasia, goblet cells, and persistent squamous metaplasia on top of the epithelial hyperplasia, whereas the SC side was linked to superior collagen fiber organization. Similarly, according to Albu *et al.*[22] throughout the entire follow-up period, the side that had received cryotherapy showed considerably less edema of the mucosa, polypoid alterations, adhesions, and ostia narrowing. However, both treatments had identical distributions of discharge and crusting.

Table 1. Characteristics of the included studies.

Study ID	Year	Groups	Sample Size	Age (Mean ±SD)	Sex (Male %)	Characteristics of patients	Pre-operative assessment of the patient	Follow up Duration	Conclusion
Rezaeian[20]	2017	SCT	19	42.80 ±16.13	10 (50%)	Adult patients with bilateral nasal polyposis (CRSwNP).	Lund-McKay and SNOT-22 scores	Up to 36 weeks	SCT can consider a good management of NP after functional endoscopic surgery. In addition, there are no serious adverse effects reported from this technique.
		Saline	18	43.65 ±14.27	8 (40%)				
Albu *et al.*[22]	2016	SCT	18	40.23 ±16.45	10 (45%)	Adult patients with CRS.	POSE and Lund-Kennedy	Up to 12 weeks	SCT associated with significant reduction in synechia, edema of the mucosa, polypoid changes, and narrowing of the ostia in the whole follow-up period.
		Saline	18	40.23 6 16.45	10 (45%)				
Trombitaș *et al.*[21]	2019	SCT	23	44.5	11 (42.3%)	Patient with bilateral CRS without polyps (CRSsNP).	Lund-McKay score	Up to 12 months	SCT was associated with better outcome on MMA diameter, histological analysis, nasal obstruction and discharge with no any visual complications.
		Saline	23	44.5	11 (42.3%)				

CRS, Chronic Rhinosinusitis, CRSsNP, Chronic Rhinosinusitis without nasal polyposis; CRSwNP, Chronic Rhinosinusitis with nasal polyposis; LM, Lund-Mackay; MMA, Middle Meatal Antrostomy; POSE, Perioperative Sinus Evaluation; SNOT-22, Sino-nasal Outcome Test-22.

Table 2. Characteristics of the Surgical technique, cryotherapy used and post-operative management.

Article	Used SCT	Surgical technique and procedure	Post-operative management	
			Antibiotics	Others
Rezaeian[20]	Brymill (Ellington, CT) CRY-AC-3 Cryogenic System	Uncinectomy, Infundibulectomy, Middle meatal antrostomy, Frontal sinusotomy, Sphenoidotomy, and Total ethmoidectomy.	Co-Amoxiclav 50 mg/kg TDS for 5 days.	Prednisolone 1 mg/kg/24 h for 5 days. Nasal steroids thrice daily for 1 month.
Albu *et al.*[22]	Brymill (Ellington, CT) CRY-AC-3 Cryogenic System	Endoscopic sinus surgery (details not mentioned).	Oral broad-spectrum antibiotics for about 4 weeks.	Saline nasal irrigation for 4 weeks. Topical steroids for 8 weeks.
Trombitaș *et al.*[21]	Brymill (Ellington, CT) CRY-AC-3 Cryogenic System	Uncinectomy, Middle meatal antrostomy, Anterior ethmoidectomy, and Septoplasty.	Oral broad-spectrum antibiotics for 10 days.	Vaseline gauze. Daily saline nasal irrigation for 4 weeks.

Post-operative complications of spray cryotherapy

According to Albu *et al.*,[22] there were no adverse effects (for example, hemorrhage or infection) in either group during the trial period, and this conclusion was also demonstrated by Rezaeian.[20] Furthermore, Trombitaș *et al.*[21] investigated the visual assessments as SCT was sprayed around the orbit and found no pain, visual field loss, visual acuity, color perception, diplopia, ocular motility, visual acuity, globe displacement, or swelling.

Discussion

The main goal of this study was to investigate the role and impact of SCT in chronic rhinosinusitis with or without nasal polyps following endoscopic sinus surgery. The most obvious finding to emerge from this study was that the overall effects of SCT are favorable, promising, and associated with good outcomes and better healing. SCT is a new post-operative modality that began with Dr. Albu and his team,[22] who used SCT following ESS based on a previous study conducted by Krimsky *et al.*,[23] who used SCT to treat glottic and subglottic narrowing. However, Albu *et al.*[22] reported some limitations, such as a lack of subjective outcomes in the post-operative assessment, a short follow-up period, and the need to divide patients into two groups, with and without polyposis, to evaluate the overall impact of SCT on the healing of different diseases. Following the Albu study, Rezaeian[20] and Trombitaș *et al.*[21] Three studies used the same SCT protocols. However, Rezaeian's study had a 36-week follow-up period and only included patients with CRS with nasal polyposis. In addition, Trombitaș' study showed a longer follow-up period of 12 months (52 weeks), and it also measured mucosal histology pre- and post-operatively, which provided cellular evidence besides the clinical evidence regarding the healing outcome.

The present study investigated chronic rhinosinusitis with and without nasal polyposis. Despite differences in etiology and phenotype, many therapies for chronic rhinosinusitis are initiated in clinical practice without knowing a patient's "polyp status." Determining the type of CRS does not necessarily recommend therapy modifications. Lee-Yee *et al.* examined patients with and without polyps together in the first examination of treatment results, followed by a subgroup analysis, as we did.[24]

The main symptoms of CRS are nasal blockage/obstruction/congestion and nasal discharge (anterior/posterior nasal drip)[25] and SCT shows a great reduction in all rhinosinusitis scores, lesser post-operative adhesions, discharge, side effects, inflammatory cell infiltration, and better collagen fiber arrangements in comparison with placebo, which could be explained by the fact that cryotherapy induces disruption of endothelial damage, thrombosis, and ischemia, and improves mucosal healing and decreases granulation tissue formation.[26] On the histological level, it resulted in better collagen organization and reduced keratinization, and long-term observation documented the absence of scarring and stricture formation.[27]

Greenwald *et al.*[28] studied the safety and efficacy of endoscopic sinus surgery in the treatment of esophageal cancer and found no adverse effects, which is comparable to our findings. Using SCT in airway surgery, on the other hand, has been linked to problems such as barotrauma, pneumomediastinum, nitrogen gas embolism, and pneumothorax.[29] However,

none of these side effects were reported in the trials included in the present study. As a result, SCT as a post-ESS treatment appears to be safe. However, further studies with longer follow-up periods are required to determine the safety of SCT.

One of the main post-operative complications of ESS in CRS is recurrence, which was not reported in any of the included trials for a 12-month follow-up period. However, in a study conducted on the recurrence of nasal polyposis, six-months after ESS recurrence was 35% and after 18-months it was 40%.[30] In other studies, the recurrence rate reached up to 60% after 18 months of follow-up, indicating that the percentage of recurrence increased over time; therefore, longer follow-up is needed to determine the recurrence ratio after SCT.

In accordance with the present results, a previous study conducted by Gorelik *et al*. demonstrated that both cryotherapy and radiofrequency had better outcomes than a placebo.[29] Moreover, SCT has been shown to improve post-operative outcomes in different ENT surgeries, including those for malignant airway disease, as demonstrated by a study conducted by Browning *et al*.[31] Browning *et al*. showed that SCT is safe and demonstrated better outcomes in post-operative respiratory complications from malignancies, such as dyspnea/hypoxia, granulation tissue, and bleeding tissue. Other advantages of using SCT in the management of airway diseases have been reported in many other studies.[23,32,33]

One of the limitations of this study was the lack of data on the clinical history of the included patients, which could alter the patients' results and outcomes. For example, diabetes can slow down the healing process. Furthermore, the Global Allergy and Asthma Network of Excellence epidemiological study found a strong link between asthma and CRS,[34] which raises two concerns: What was the prevalence of asthma in the included studies? How does cryotherapy affect the symptoms of asthma?

Conclusions

The present systematic review was designed to determine the impact of SCT on ESS following chronic rhinitis; the results of this investigation show that SCT is associated with better healing and fewer negative complications such as synechia, edema, obstruction, crusting, and inflammation. Moreover, the findings of this study contribute to existing knowledge on the advantages of using cryotherapy in medicine in general, and specifically in post-operative airway surgery. Nevertheless, more research on this topic needs to be undertaken with osteitis, osteogenesis, and visual side effects, with a suitable assessment to reveal any adverse consequences associated with endoscopic SCT.

Data availability

Underlying data

All underlying data are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'The safety and efficacy of spray cryotherapy after endoscopic sinus surgery in chronic rhinosinusitis: A systematic review of randomized controlled trials', https://www.doi.org/10.6084/m9.figshare.24661968.[14]

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PubMed Abstract | Publisher Full Text

33. Bhora FY, *et al.*: **Treatment of benign tracheal stenosis using endoluminal spray cryotherapy.** *JAMA Otolaryngology–Head & Neck Surgery.* 2016; **142**(11): 1082–1087.
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PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ? ?

Version 2

Reviewer Report 21 October 2024

https://doi.org/10.5256/f1000research.167402.r330039

?

Antonino Maniaci
Department of Medicine and Surgery, University of Enna Kore, Research Committee of Young Otolaryngologists of the International Federation of Otorhinolaryngological Societies, Enna, Italy

Introduction:
- improve the description of spray cryotherapy by expanding on what patients face during recovery and aftercare post-endoscopic sinus surgery.
- Elaborate on spray cryotherapy – how it works, the theoretical mechanisms of action and previous uses in other fields cite doi:10.21037/jtd.2017.01.55.
- Specify more precisely on what the review focus at end of introduction.

Methods:
- justify the decision to include only randomized controlled trials
- This is of course a strength in the evidence, but this may have limited the number of studies that could be included.
- Explanation of how data were extracted from the included studies and their synthesis
- Think about prospectively registering review protocol (e. in PROSPERO).

Results:
- explain why It was not possible to conduct a meta-analysis as there was considerable heterogeneity but one option would be provide more detailed qualitative synthesis of the results across studies.
- Describe the risk of bias assessment in more detail for all included studies;

Discussion:
- Further discuss some of the possible mechanisms by which spray cryotherapy might lead to a better post-operative result.
- Present implications for clinical practice and future directions of research in more depth. describe the useful application of subjective questionnaire to follow-up the response. cite doi:10.1007/s00405-023-07855-8
- Further specify the limitations, especially regarding the low number of studies included and short

periods for follow-up.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: minor revisions

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 29 May 2024

https://doi.org/10.5256/f1000research.156967.r275424

?

Serafín Sánchez-Gómez
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The authors present a systematic review study that evaluated the effects of spray cryotherapy (SCT) following endoscopic surgery for chronic rhinosinusitis. Three randomized clinical trials including a total of 85 patients were selected.

Several decades after the introduction of endonasal endoscopic techniques for the treatment of CRS, adverse events and complications in the surgical field continue to occur despite technical and instrumental improvements. Therefore, it is pertinent to investigate new ways to reduce these events and complications that deteriorate the quality of life of patients, requiring meticulous postoperative care and sometimes leading to reoperations.

The authors present a study that compiles the experience of using spray cryotherapy on the surgical bed after endonasal endoscopic surgery, selecting three clinical trials that met the inclusion and exclusion criteria. The authors applied an extremely rigorous selection criterion for articles, including only those containing randomized and blinded clinical trials. This design is not well-suited for surgical procedures and introduces significant uncertainties about the reliability of the data included in the clinical trials. The inclusion of other well-designed prospective studies would have been acceptable.

The methodology of the systematic review is pertinent and correct. It would have been desirable for the authors to submit their project to be included in the PROSPERO database of systematic reviews. Nevertheless, the use of the PRISMA statement and Cochrane methodology ensures that the authors have used the best methods to adequately conduct a systematic literature review. The presentation of results in the PRISMA flowchart and tables is appropriate and sufficient.

Given the novelty of spray cryotherapy in the field of ESS, the authors could have provided more information about this therapy in the Introduction, as adverse events and complications are well-known.

The results of their systematic review showed that SCT was associated with better outcomes in Lund-McKay, SNOT-22, POSE, and Lund-Kennedy scales compared to placebo. It was also associated with less edema, obstruction, crusting, and inflammation. No adverse effects of SCT were reported. These are perfectly suitable outcome variables for the review's objective.

The authors have identified the main five weaknesses of the study:

1. The sample size was small (only 3 studies with a total of 85 patients). Larger studies are needed.

2. Follow-up periods were relatively short, up to a maximum of 12 months. Longer follow-up studies are needed.

3. No information was provided on the clinical history of the included patients, which could have affected the results.

4. Potential long-term side effects of SCT, such as osteitis or other ocular complications, were not evaluated.

5. Only English articles were included, which could have introduced language bias. Studies in other languages should also be considered.

Throughout the draft, a series of errors have been detected that should be resolved:

a. In the Abstract, a consideration needs improvement: The phrase "Endoscopic sinus

surgery (ESS) is the preferred treatment because of its few adverse effects" significantly limits the objective of the surgery if it is not stated that the reason for choosing this technique is due to achieving the best results, not only due to adverse effects.
b. In the 6th line of the Introduction, in the phrase "...with validation by telephone or interview.", there is an unnecessary period at the end of the phrase.
c. The third inclusion criterion in the Methodology section has "Only in English" capitalized, whereas the first criterion is in lowercase. The decision on capitalization should be consistent.
d. In the first paragraph of the Discussion, the phrase is incomplete or has punctuation errors: "Following the Albu study, Rezaeian22 and Trombitas et al.20 Three studies..."
e. The phrase in the Conclusion column of Table 1 contains English writing errors: "SCT was associated with better outcomes in MMA diameter, histological analysis, nasal obstruction, and discharge, with no visual complications."
f. The phrase in the paragraph starting with Greenwald et al. should be corrected as the surgical technique does not correspond to the disease.
g. In the phrase "Other advantages of using SCT in the management of airway diseases have been reported in many other studies," the word "many" is excessively emphatic and should be omitted.
h. The first sentence of the Conclusions, "The present systematic review..." could be better expressed as "The present systematic review was designed to determine the impact of SCT on ESS in patients with chronic rhinosinusitis" or "...following endoscopic surgery for chronic rhinosinusitis"

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rhinology, cochlear implants

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 01 Jun 2024

Abdulqadir Nashwan

Comment (Lines 90-95): At the same time, general information about chronic rhinosinusitis seems somewhat redundant. It may be worth adding information about the difficulties and challenges of postoperative care of the nasal mucosa after ESS, postoperative access to prevent scarring and synechiae formation.
Response: We appreciate the suggestion to provide more details on postoperative care. We will add information focusing on these challenges and how they can be managed effectively, as highlighted in references 5 and 6.

Comment (Resolved Line 239): The paragraph beginning "Greenwald et al." is most likely a misspell: replace endoscopic sinus surgery with spray cryotherapy.
Given the researchers' stated goal, it seems rational to replace chronic rhinitis with chronic rhinosinusitis in the conclusion section.
Response: The corrections have been made to accurately reflect the treatment discussed and the condition being addressed in the conclusion.

Comment: The authors applied an extremely rigorous selection criterion for articles, including only those containing randomized and blinded clinical trials. This design is not well-suited for surgical procedures and introduces significant uncertainties about the reliability of the data included in the clinical trials. The inclusion of other well-designed prospective studies would have been acceptable.
Response: We use randomized control trials as our inclusion criterion to ensure the highest quality data. Despite an extensive search for additional relevant studies, none met our rigorous standards, not even non-randomized clinical studies.

Comment (Lines 99-101): Given the novelty of spray cryotherapy in the field of ESS, the authors could have provided more information about this therapy in the Introduction, as adverse events and complications are well-known.
Response: We acknowledge this oversight and will revise the Introduction to include more comprehensive details about spray cryotherapy, especially regarding its adverse events and complications.

Comment (Line 36): In the Abstract, a consideration needs improvement: The phrase "Endoscopic sinus surgery (ESS) is the preferred treatment because of its few adverse effects" significantly limits the objective of the surgery if it is not stated that the reason for choosing this technique is due to achieving the best results, not only due to adverse effects.
Response: We will adjust the wording to clarify that the choice of ESS is based on its effectiveness in achieving the best outcomes, not merely its few adverse effects.

Comment (Line 121): The third inclusion criterion in the Methodology section has "Only in English" capitalized, whereas the first criterion is in lowercase. The decision on capitalization should be consistent.
Response: The capitalization will be corrected to maintain consistency throughout the document.

Comment (Line 223): In the first paragraph of the Discussion, the phrase is incomplete or has punctuation errors: "Following the Albu study, Rezaeian22 and Trombitas et al.20 Three studies..."
Response: This error will be rectified to ensure the sentence is complete and clear.

Comment (Line 261): In the phrase "Other advantages of using SCT in the management of airway diseases have been reported in many other studies," the word "many" is excessively emphatic and should be omitted.
Response: The word "many" will be removed to avoid undue emphasis and maintain a neutral tone.

Comment (Lines 270-271): The first sentence of the Conclusions, "The present systematic review..." could be better expressed as "The present systematic review was designed to determine the impact of SCT on ESS in patients with chronic rhinosinusitis" or "...following endoscopic surgery for chronic rhinosinusitis"
Response: We will revise the conclusion to reflect these suggestions for greater clarity and precision in presenting the study's objectives and outcomes.

Competing Interests: No competing interests were disclosed.

Reviewer Report 18 April 2024

https://doi.org/10.5256/f1000research.156967.r261156

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Ekaterina Savchenko
Polyclinic of the St. Petersburg Metropoliten, Saint Petersburg, Russian Federation

Mohammad J. J. Taha et al. present an important and interesting systematic review to analyse data from randomised clinical trials on the outcomes of spray cryotherapy (SCT) after endoscopic sinus surgery (ESS) in patients with chronic rhinosinusitis with and without polyps.
Functional endoscopic surgery of the nasal cavity and paranasal sinuses is currently the leading method of surgical treatment of chronic rhinosinusitis. In the postoperative period it is necessary to correct inflammatory and regenerative processes to reduce postoperative reactive phenomena, prompt healing, reduce the risk of complications. The accumulated clinical and scientific data show that despite the diversified preventive measures after ESS local complications in the nasal cavity remain an urgent problem.
Spray cryotherapy is a possible treatment method that can reduce complications after ESS.
Abstract
Covers the aims, methodology, overall results and conclusions.

Introduction
Aspects of endoscopic sinus surgery and the relevance of adjunctive postoperative care are covered in detail and convincingly. The authors provide information on the place of the problem in otorhinolaryngology and the health care system, and recall the impact of chronic rhinosinusitis on quality of life. At the same time, general information about chronic rhinosinusitis seems somewhat redundant. It may be worth adding information about the difficulties and challenges of postoperative care of the nasal mucosa after ESS, postoperative access to prevent scarring and synechiae formation. It is probably worth presenting information about the existing possible solutions to these problems, emphasising that this issue has no unambiguous solution.
Methodology
A systematic review of randomised controlled trials was conducted according to the PRISMA checklist. The filtering stages of the studies were carried out according to Cochrane criteria. Which indicates the compliance of the publication with international standards. The inclusion criteria are relevant to the research objectives. The process of material collection is described in an accessible and consistent manner and provides insight into the sample obtained. Each publication was extracted separately by two independent authors and any disagreements were resolved by a third reviewer. The size of the sample obtained influenced the planned statistical processing methods, which did not affect the quality of the article or its informative value in any way.
Results
As a first figure, a PRISMA flow chart of included and excluded studies is presented, which allows to assess the amount of work undertaken in the process of selecting studies for the systematic review.
Subsequently, the risks of bias for each included study are given graphically.
A table of studies provides a comprehensive overview of the patient groups, participant characteristics, outcomes and time periods of follow-up.
The effects of cryotherapy administered after endoscopic sinus surgery are systematically analysed based on the SNOT-22, Lund-McKay, POSE and Lund-Kennedy scoring scales.
Discussion
An extended review of the literature on the above topic was performed and references to similar studies are provided.
The paragraph beginning "Greenwald et al." is most likely a misspell: replace endoscopic sinus surgery with spray cryotherapy.
Given the researchers' stated goal, it seems rational to replace chronic rhinitis with chronic rhinosinusitis in the conclusion section.
In summary, this is a systematic review that is an important addition to the literature. As the authors correctly note, cryotherapy after endoscopic sinus surgery is a promising method that requires follow-up RCTs.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical and scientific interests: endoscopic sinus sugery, laser surgery in otorhinolaryngology, laryngeal and tracheal microsurgery, otosurgery, oncology, dacryology.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.