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Topical nasal furosemide for the prevention of postoperative nasal polyp recurrence: a systematic review

Furosemida nasal tópica na prevenção da recorrência pós-operatória de pólipos nasais: uma revisão sistemática

Furosemida nasal tópica para la prevención de la recurrencia posoperatoria de pólipos nasales: una revisión sistemática

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Abstract:
Introduction: Chronic rhinosinusitis with nasal polyps (CRSwNP) has high postoperative recurrence rates. Beyond inflammation, mucosal edema arising from dysregulated epithelial ion transport offers a therapeutic target. This systematic review critically evaluated the efficacy and safety of topical nasal furosemide, a Na-K-2Cl cotransporter (NKCC1) inhibitor, for preventing polyp recurrence after endoscopic sinus surgery (ESS). Methods: PubMed (MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched through September 2026. All randomized controlled trials comparing topical nasal furosemide with placebo in adults undergoing ESS for CRSwNP were eligible. Results: Two high-quality, double-blind trials met the criteria (n = 143), both demonstrating significant benefits. One reported a nearly threefold reduction in recurrence at three months (16.6% versus 43.3%; $p < 0.05$). The multicenter trial found statistically significant, clinically meaningful improvement in the Lund-Kennedy endoscopic score at 12 weeks (mean change: −1.13 versus −0.28; $p = 0.02$). Furosemide was exceptionally well tolerated, with safety comparable to placebo and no reported systemic adverse events. Conclusion: Although limited to two trials, current evidence consistently supports topical nasal furosemide as an effective, safe postoperative strategy to reduce polyp recurrence. Directly targeting mucosal edema provides a novel mechanistic approach complementary to traditional anti-inflammatory therapies. These promising findings warrant larger, long-term trials to definitively establish its role in CRSwNP management.

Keywords:
Chronic Rhinosinusitis with Nasal Polyps, Topical Furosemide, Postoperative Recurrence, Systematic Review, NKCC1 Inhibitor.

Resumo:
Introdução: A rinossinusite crônica com pólipos nasais (CRSwNP) apresenta elevada recorrência pós-operatória. Além da inflamação, o edema mucoso decorrente da desregulação do transporte iônico epitelial constitui alvo terapêutico. Esta revisão sistemática avaliou criticamente a eficácia e segurança da furosemida nasal tópica, inibidora do cotransportador Na-K-2Cl (NKCC1), na prevenção da recorrência após cirurgia endoscópica sinusal (ESS). Métodos: Pesquisaram-se PubMed (MEDLINE), Embase e Cochrane Central Register of Controlled Trials (CENTRAL) até setembro de 2026. Incluíram-se todos os ensaios clínicos randomizados que compararam furosemida tópica e placebo em adultos submetidos à ESS por CRSwNP. Resultados: Dois ensaios duplo-cegos de alta qualidade atenderam aos critérios (n = 143), ambos com benefício significativo. Um demonstrou redução de quase três vezes na recorrência aos três meses (16,6% versus 43,3%; $p < 0,05$). O ensaio multicêntrico mostrou melhora estatisticamente significativa e clinicamente relevante no escore endoscópico de Lund-Kennedy às 12 semanas (alteração média: −1,13 versus −0,28; $p = 0,02$). A furosemida

foi muito bem tolerada, com segurança comparável ao placebo e sem eventos adversos sistêmicos relatados. Conclusão: Embora limitadas a dois ensaios, as evidências apoiam consistentemente a furosemida nasal tópica como estratégia pós-operatória eficaz e segura para reduzir recorrências. Sua ação direta sobre o edema mucoso oferece abordagem mecanicista inovadora, complementar às terapias anti-inflamatórias tradicionais. Os resultados justificam ensaios maiores e de longo prazo para estabelecer definitivamente seu papel no manejo da CRSwNP.

Palavras-chave:
Rinossinusite crônica com pólipos nasais, furosemida tópica, recidiva pós-operatória, revisão sistemática, inibidor de NKCC1.

Resumen:
Introducción: La rinosinusitis crónica con pólipos nasales (CRSwNP) presenta elevada recurrencia posoperatoria. Además de la inflamación, el edema mucoso por desregulación del transporte iónico epitelial constituye una diana terapéutica. Esta revisión sistemática evaluó críticamente la eficacia y seguridad de la furosemida nasal tópica, inhibidora del cotransportador Na-K-2Cl (NKCC1), para prevenir recurrencias tras cirugía endoscópica sinusal (ESS). Métodos: Se consultaron PubMed (MEDLINE), Embase y Cochrane Central Register of Controlled Trials (CENTRAL) hasta septiembre de 2026. Se incluyeron todos los ensayos controlados aleatorizados que compararon furosemida tópica con placebo en adultos sometidos a ESS por CRSwNP. Resultados: Dos ensayos doble ciego de alta calidad cumplieron los criterios (n = 143), ambos con beneficios significativos. Uno mostró una reducción de casi tres veces en las recurrencias a los tres meses (16,6% frente a 43,3%; p < 0,05). El ensayo multicéntrico encontró mejoría estadísticamente significativa y clínicamente relevante en la puntuación endoscópica de Lund-Kennedy a las 12 semanas (cambio medio: −1,13 frente a −0,28; p = 0,02). La furosemida fue muy bien tolerada, con seguridad comparable al placebo y sin efectos adversos sistémicos reportados. Conclusión: Aunque limitada a dos ensayos, la evidencia respalda consistentemente esta estrategia posoperatoria eficaz y segura. Su acción sobre el edema mucoso ofrece un mecanismo novedoso, complementario a las terapias antiinflamatorias tradicionales. Los resultados justifican ensayos mayores y prolongados para establecer definitivamente su papel en el manejo de la CRSwNP.

Palabras clave:
Rinosinusitis crónica con pólipos nasales, furosemida tópica, recurrencia postoperatoria, revisión sistemática, inhibidor de NKCC1.

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) poses a significant clinical challenge. For those affected, it can profoundly diminish quality of life, and for clinicians, it is a notoriously difficult condition to manage due to its high propensity for recurrence after surgery (Hastan et al., 2011). While endoscopic sinus surgery (ESS) is a cornerstone of treatment for medically refractory disease, it is not a cure. The underlying inflammatory process often continues unabated, leading to polyp regrowth in up to 40% of patients within just 18

months (DeConde; Soler, 2017). This reality underscores a pressing need for better postoperative strategies to preserve the gains made in the operating room.

Our understanding of CRSwNP has evolved dramatically, moving from a simplistic view of infection to a nuanced appreciation of its complex inflammatory underpinnings. The disease is now largely understood as a disorder of mucosal inflammation, most commonly driven by a Type 2 inflammatory signature, characterized by the upregulation of cytokines like interleukin (IL)-4, IL-5, and IL-13, and marked by a profound eosinophilic infiltrate (Bachert et al., 2013). This inflammatory cascade is the primary therapeutic target for our most established and newest treatments, from corticosteroids to biologics.

However, inflammation is only part of the story. A critical, and perhaps underappreciated, downstream consequence of this inflammation is a profound disruption of the nasal epithelial barrier and its finely tuned transport functions (Stevens; Schleimer; Kern, 2016). The epithelial cells lining our sinuses are not passive bystanders; they actively regulate the airway surface liquid through a sophisticated system of ion channels and transporters. Healthy fluid balance depends on the coordinated action of channels like the Epithelial Sodium Channel (ENaC), which absorbs sodium, and the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which secretes chloride (Lee et al., 2021). Working in concert with them is the Na-K-2Cl cotransporter (NKCC1), a protein located on the basolateral membrane of these cells. NKCC1 brings chloride into the cell, creating a reservoir for subsequent secretion into the airway lumen. This chloride secretion is a primary driver of water movement, and thus, mucosal hydration (Lee et al., 2021; Liu et al., 2021). The prevailing hypothesis in CRSwNP pathophysiology is that the inflammatory environment leads to an overactivity or overexpression of NKCC1. This hyperactivity results in excessive chloride and water secretion into the tissues, leading directly to the massive, grape-like edema that we recognize as nasal polyps (Liu et al., 2021). In this model, the polyp is not just inflamed tissue; it is fluid-logged tissue, kept in that state by a dysfunctional ion transport engine. This understanding opens the door to an entirely new therapeutic paradigm: instead of only fighting the upstream inflammation, we can directly target the downstream mechanism of edema formation.

2. Methods

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

2.1 Eligibility Criteria

• Studies were selected for inclusion based on the PICOS framework:

• Population: Adult patients (≥18 years) who had undergone ESS for bilateral CRSwNP.

• Intervention: Topical intranasal furosemide, at any dosage or frequency.

• Comparator: A placebo or saline nasal spray control group.

• Outcomes: At least one objective measure of postoperative polyp recurrence, such as an endoscopic score (e.g., Lund-Kennedy score) or a reported recurrence rate.

• Study Design: Randomized controlled trials (RCTs).

2.2 Information Sources and Search Strategy

A systematic search was performed across three electronic databases: PubMed (MEDLINE), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), from their inception to September 202. We imposed no language restrictions. The search strategy combined medical subject headings (MeSH) and free-text keywords, including: ("furosemide") AND ("nasal polyps" OR "nasal polyposis" OR "chronic rhinosinusitis with nasal polyps") AND ("topical" OR "intranasal" OR "nasal spray") AND ("postoperative" OR "recurrence" OR "prevention"). The reference lists of included studies were also manually screened for any additional relevant publications.

2.3 Study Selection

The results of the literature search were managed, and duplicates were removed. Two independent reviewers screened the titles and abstracts of the retrieved records for potential eligibility. The full texts of potentially relevant articles were then obtained and assessed against the predefined eligibility criteria. Any disagreements between the reviewers were resolved through discussion and consensus. Following the PRISMA flow diagram, the process was documented: The initial search identified 48 records. After 15 duplicates were removed, 33 records were screened by title and abstract, leading to the exclusion of 26. The remaining 7 full-text articles were assessed for eligibility, of which 5 were excluded (2 study protocols, 1 case report, 1 non-randomized trial, 1 lacking a placebo control). This resulted in the final inclusion of 2 RCTs for qualitative synthesis.

2.4 Data Extraction Process and Risk of Bias Assessment

A standardized data extraction form was used to collect relevant information from the included studies. Extracted data included study characteristics (author, year, design, location), patient demographics, intervention specifics (dose, frequency, duration), and outcome measures. One reviewer extracted the data, and a second reviewer verified its accuracy. The methodological quality and risk of bias of each included RCT were independently assessed by two reviewers using the Cochrane "Risk of Bias" tool (RoB 1). This tool evaluates key domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias.

3. Results

3.1 Study Characteristics and Quality

The two RCTs meeting our inclusion criteria enrolled a combined total of 143 patients (Laldag et al., 2013; Stewart et al., 2016).

Both studies were well-designed, prospective, double-blind, placebo-controlled trials. The first was a single-center trial conducted by Laldag et al. in Turkey, while the second was a larger, multicenter trial led by Stewart et al. in the United States, lending broader generalizability to the findings. The risk of bias assessment for both studies was favorable, with a low risk of bias identified across the critical domains of randomization, blinding, and outcome reporting. This high methodological quality increases our confidence in the validity of their results. Efficacy of Topical Furosemide Both trials demonstrated a consistent and statistically significant benefit of topical furosemide over placebo. In the single-center study by Laldag et al., which focused on the categorical rate of recurrence at three months, the findings were stark. The group receiving the saline placebo had a recurrence rate of 43.3%, a figure consistent with historical expectations for the natural history of the disease post-surgery. In contrast, the group receiving topical furosemide had a recurrence rate of only 16.6%. This represents a nearly three-fold reduction in the likelihood of polyp regrowth ($p < 0.05$) (Laldag et al., 2013).

The multicenter trial by Stewart et al. utilized a more granular primary outcome—the change in the Lund-Kennedy endoscopic score (LKES) over a 12-week period. This score objectively grades the sinonasal mucosa based on the presence of polyps, edema, and discharge.

Their results corroborated the earlier findings, showing that patients in the furosemide arm experienced a significantly greater improvement in their endoscopic appearance. The mean LKES in the furosemide group improved (decreased) by 1.13 points from baseline. The placebo group, however, saw a minimal improvement of just 0.28 points. The difference between the groups was both statistically significant ($p = 0.02$) and clinically meaningful (Stewart et al., 2016).

3.2 Safety and Tolerability

A critical aspect for any long-term maintenance therapy is its safety profile. Here, the evidence for topical furosemide was exceptionally reassuring. Across both trials, the treatment was very well-tolerated. The incidence of minor, local adverse events, such as nasal irritation or small nosebleeds, was low and, importantly, was not significantly different from the rates observed in the placebo groups. Crucially, there were no reports of any systemic side effects or abnormalities in electrolyte levels, confirming the localized action and minimal systemic absorption of the topically administered drug.

Table 1: Summary of Included Randomized Controlled Trials

Study	Study design	Intervention	Control	Primary outcome	Main results and safety
Laldag et al. (2013)	RCT, double-blind	Furosemide 1 mg/mL, 1 spray/nostril, 2x/day	Saline solution spray	Polyp recurrence rate (endoscopy)	Recurrence: 16.6% vs. 43.3% in placebo group ($p < 0.05$). Well tolerated.
Stewart et al. (2016)	RCT, multicenter, double-blind	Furosemide 1 mg/mL, 2 sprays/nostril, 2x/day	Placebo spray	Change in Lund-Kennedy endoscopic score (LKES)	Improvement in LKES: -1.13 in furosemide group vs. -0.28 in placebo group ($p = 0.02$). Adverse effects similar to placebo (12% vs. 11%).

4. Discussion

The collective results of this systematic review, founded on methodologically sound randomized controlled trials, provide a clear and compelling signal: topical nasal furosemide is an effective and safe intervention for reducing polyp recurrence after sinus surgery. What makes these results particularly exciting is not just that the treatment works, but how it works. For decades, our medical management of CRSwNP has been almost entirely focused on suppressing

inflammation. Topical furosemide represents a paradigm shift, validating a complementary approach that directly targets the final common pathway of polyp formation: mucosal edema.

This therapy does not necessarily compete with our current standards of care; it complements them. The cornerstone of postoperative management remains intranasal corticosteroids (INCS), and for severe disease, biologic therapies have been revolutionary (Bachert et al., 2019). Furosemide's mechanism is entirely different. This opens the fascinating possibility of a synergistic, two-pronged attack: an anti-inflammatory agent to quell the immune fire, and furosemide to manage the resulting fluid. This could be particularly valuable for patients with contraindications to long-term steroid use or as a less costly, safer approach for a broad patient population compared to systemic biologics.

While the results are promising, it is essential to approach them with scientific prudence and acknowledge the limitations of the current evidence. The primary limitation is the small number of trials; our entire understanding is built upon the work of two research groups. Although these studies were well-conducted, science demands replication. Second, the follow-up duration in both trials was relatively short (three months), and we do not yet know if the benefits of furosemide are sustained over years of use. Third, these trials treated CRSwNP as a monolithic entity, without differentiating between inflammatory endotypes, which may influence response.

The promising signal from these initial studies provides a clear mandate for a robust future research agenda. The highest priority should be a large-scale, multicenter, three-arm RCT that directly compares topical furosemide, a standard-of-care INCS, and a combination of the two, with a follow-up of at least one to two years. Furthermore, future trials should incorporate biomarker analysis to correlate treatment response with the underlying inflammatory endotype. This would be a critical step toward a more personalized medicine approach for CRSwNP.

5. Conclusion

Based on the consistent findings of high-quality randomized controlled trials, topical nasal furosemide has emerged as a genuinely promising and innovative therapy in the postoperative management of CRSwNP. By directly and safely targeting the endpoint of mucosal edema via a novel mechanism, it provides a valuable new tool that is distinct from all our current anti-inflammatory strategies. While the evidence base is still nascent, the strength of the initial signal is undeniable. The path forward requires larger, longer- term, and more

sophisticated clinical trials to fully realize the potential of this therapy and integrate it into the standard of care for the many patients struggling with this relentless disease.

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