Evaluation of the Safety of Low-Dose Topical Imiquimod Cream on Frontal Sinus Ostium Stenosis Following Endoscopic Sinus Surgery: A Pilot Clinical Trial

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Received: 2025-06-04; Received in revised form: 2025-07-23; Accepted: 2025-08-05

Abstract

Background: Frontal sinus ostium stenosis is a common postoperative challenge in endoscopic sinus surgery, potentially leading to disease recurrence. Imiquimod is an immunomodulatory agent with anti-inflammatory and antifibrotic properties, recently gaining attention in experimental studies. To evaluate the safety of low-dose topical imiquimod cream in reducing the rate of frontal sinus ostium stenosis following endoscopic sinus surgery.

Methods: This pilot randomized intra-patient controlled clinical trial was conducted on 20 patients with CRSwNP. Each patient underwent bilateral Draf 2a surgery. One frontal sinus was randomly assigned to receive Gelfoam impregnated with 5% imiquimod cream, with applications repeated in the second and fourth postoperative weeks. The contralateral side served as the control. Patients were assessed at week 4 and month 3 postoperatively via endoscopic and CT imaging. Endoscopic scores were based on the DIP system, and the STDR ratio was evaluated using 3D CT reconstruction. Data analysis was performed using paired t-tests and Wilcoxon tests at a significance level of 0.05.

Results: At three months post-surgery, STDR was significantly lower on the intervention side ($p < 0.05$), indicating reduced soft tissue density and opacification. Endoscopic evaluation also showed a marked improvement in polyp and inflammation scores on the treated side. No significant differences were observed at one month. No major local or systemic adverse effects were reported.

Conclusions: Topical application of low-dose imiquimod cream after endoscopic sinus surgery may effectively reduce inflammation, discharge, polyp formation, and opacification in the frontal sinus, and may be considered a safe preventive option for ostium stenosis. Larger trials are recommended to confirm these findings.

Keywords: Chronic rhinosinusitis, nasal polyps, frontal sinus, imiquimod, endoscopic sinus surgery, STDR

Citation: Mokhtari E. **Evaluation of the Safety of Low-Dose Topical Imiquimod Cream on Frontal Sinus Ostium Stenosis Following Endoscopic Sinus Surgery: A Pilot Clinical Trial.** *Acad J Surg*, 2025; 8(3): 101-105.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory condition of the sinuses, characterized by abnormal mucosal growth and polyp formation. This condition can lead to sinus obstruction, reduced quality of life, and the need for repeated surgical interventions. Standard treatments include topical corticosteroids, antibiotics, and in severe cases, endoscopic sinus surgery. However, the recurrence rate after surgery remains high, indicating the need for adjunct therapies to improve surgical outcomes.

Imiquimod is a topical immunomodulatory agent that acts as an agonist of Toll-like receptor 7 (TLR7), stimulating the immune system to produce antiviral and antitumor cytokines such as interferon-alpha and interleukin-12. It has been used to treat dermatologic conditions such as actinic keratosis and basal cell carcinoma. Studies suggest that imiquimod may reduce inflammation by inhibiting phosphodiesterase (PDE) and increasing intracellular cAMP levels, which in turn boosts anti-inflammatory cytokines such as IL-10.

Given these properties, topical imiquimod may

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help reduce inflammation and prevent frontal sinus ostium stenosis following endoscopic sinus surgery. However, there are limited data on its efficacy and safety in the sinonasal region. This study was designed to assess the safety and efficacy of 5% imiquimod cream in preventing postoperative stenosis of the frontal sinus ostium.

Materials and Methods

Study Design

This study was a pilot intra-patient controlled clinical trial conducted on 20 patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who were resistant to medical therapy and were candidates for bilateral Draf 2a frontal sinus surgery.

Inclusion Criteria

- Male or female patients aged 18 to 65 years
- Presence of bilateral nasal polyps in the frontal sinuses
- Scheduled for primary bilateral Draf 2a endoscopic sinus surgery
- Signed written informed consent for participation

Exclusion Criteria

- Severe cutaneous hypersensitivity or significant underlying diseases (skin, pulmonary, cardiac)
- Unidentified severe drug allergies
- Secondary sinus surgeries or surgeries other than Draf 2a
- Presence of septal cells, turbinoplasty, or other external interventions
- History of rhinoplasty
- Autoimmune disorders, cystic fibrosis, immunodeficiency, cardiovascular, neurological, or renal diseases, or malignancies in the nasal/paranasal regions
- Pregnancy or failure to complete follow-up

Surgical Procedure and Drug Intervention

All patients underwent bilateral Draf 2a endoscopic sinus surgery under general anesthesia. After opening the frontal sinus ostia and before placing nasal packing, a Gelfoam sponge impregnated with one sachet of 5% imiquimod cream (containing 250 mg of cream and 12.5 mg of active drug) was inserted into the randomly assigned intervention side. Randomization was performed using a software program based on the design by Meng et al. (2011).

Postoperative Treatment

After nasal packing removal (day 3), all patients used topical corticosteroid sprays and saline irrigation bilaterally. At weeks 2 and 4, Gelfoam soaked in imiquimod cream was reinserted into the intervention side under 30-degree endoscopic visualization.

Follow-up and Evaluation

Endoscopic evaluations were performed at weeks 2, 4, and month 3 postoperatively by the primary surgeon using a 30-degree endoscope. The DIP score system (Discharge, Inflammation, Polyps/edema) was used to grade findings. Additionally, a CT scan was conducted at month 3 and reviewed by a second blinded surgeon. The STDR (Soft Tissue Density Ratio) was calculated by comparing pre- and postoperative CT scans using 3D reconstructions on a PACS system.

DIP Scoring Criteria

Discharge

0 = No discharge
5 = Thick mucus
10 = Purulent discharge

Inflammation

0 = No inflammation
5 = Moderate inflammation
10 = Severe inflammation

Polyp/Edema

0 = Normal mucosa
5 = Significant edema without polyps
10 = Polyps filling the nasal cavity

STDR Measurement

To assess sinus opacification, the Soft Tissue Density Ratio (STDR) was calculated using 3D CT image reconstruction. The volume of soft tissue opacification was compared to the bony volume of the frontal sinus pre- and postoperatively using PACS software.

Results

This study evaluated 20 patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who underwent bilateral Draf 2a functional endoscopic sinus surgery. The mean age of the patients was 46.66 years, with a range of 30 to 60 years. Of the total, 12 patients (60%) were female and 8 (40%) were male. Four patients (20%) had a history of asthma.

In each patient, one frontal sinus was randomly designated as the intervention side and treated with 5% imiquimod cream, while the opposite side served as the control. The intervention was applied at the end of surgery and repeated at weeks 2 and 4 postoperatively.

Table 1: Caption

Outcome Variable	Timepoint	Median (Intervention)	Median (Control)	z-value	p-value	Interpretation
Polyp Score	4 weeks	2	3	0.552	0.5807	⟶ No significant difference
Polyp Score	3 months	1	3	–3.785	0.0002	↓ Strong long-term effect
Inflammation Score	4 weeks	2	3	0.552	0.5807	⟶ No significant early effect
Inflammation Score	3 months	1	3	–3.789	0.0002	↓ Significant sustained reduction
Discharge Score	4 weeks	2	3	–0.333	0.7389	⟶ No early effect
Discharge Score	3 months	1	3	–2.988	0.0028	↓ Significant delayed reduction

Outcome Variables and Results

At month 3 postoperatively, the STDR index on the intervention side was significantly lower than that of the control side ($t = –15.07$, $p < 0.0001$), indicating reduced soft tissue density and opacification in the frontal sinus. This finding aligns with improved mucosal condition and sinus ventilation on the treated side.

Throughout the 3-month follow-up period, no notable local side effects such as erythema, blistering, or ulceration were observed. There were also no reports of fever or systemic side effects.

Discussion and Interpretation of Results

The findings of the present study demonstrate that topical application of 5% imiquimod cream after functional endoscopic sinus surgery (FESS) may positively influence the reduction of inflammatory indicators and improve clinical outcomes in patients with CRSwNP. Significant reductions in polyp, inflammation, and mucosal discharge scores on the intervention side over three months postoperatively confirm the drug's potential efficacy. These results are consistent with the known mechanism of imiquimod, which stimulates innate immunity and promotes anti-inflammatory cytokines such as IFN-α and IL-12, while suppressing IL-4 and IL-5 [7,8].

1. Polyp Score

In this study, the regrowth of nasal polyps on the imiquimod-treated side was significantly lower at three months postoperatively (median: 1 vs. 3; $p = 0.0002$). This suggests that imiquimod may play a key role in suppressing mucosal hyperplasia by inhibiting Th2-mediated inflammatory pathways. Similar findings were reported by Lee et al. (2020), who demonstrated that TLR7 activation by imiquimod reduced nasal epithelial cell growth and IL-5 secretion in a murine model of CRSwNP [9]. However, the absence of significant differences at 4 weeks ($p = 0.5807$) could be attributed to the delayed onset of the drug's effects, as noted in earlier studies [10].

2. Inflammation Score

The marked reduction in mucosal inflammation on the intervention side at three months ($p = 0.0002$) indicates the anti-inflammatory effect of imiquimod on sinus mucosa. By activating macrophages and dendritic cells, imiquimod upregulates anti-inflammatory mediators such as IL-10 and modulates the Th2 response, contributing to inflammation control [11]. Although the difference was not statistically significant at 4 weeks, a downward trend in inflammation was still observed.

3. Mucosal Discharge Score

Sinus discharge, a bothersome symptom post-surgery, significantly decreased on the imiquimod-treated side ($p = 0.0028$). This may result from reduced inflammatory cell infiltration and decreased secretion of inflammatory mediators. The reduction in discharge also likely lowers the risk of re-obstruction and secondary infection in the frontal ostium [12].

4. STDR Index

The STDR, a radiologic measure for evaluating soft tissue opacification in the sinuses, significantly declined on the intervention side ($t = –15.07$, $p < 0.0001$). This reduction suggests a decrease in inflammatory or fibrotic tissue in the frontal recess and supports the drug's effectiveness in enhancing sinus clearance.

5. Drug Safety

During the three-month follow-up, no notable local side effects such as erythema, blistering, or ulceration were observed. Furthermore, no systemic complications such as fever were reported. Prior dermatologic studies have also shown that low-dose imiquimod has a high safety profile, with most side effects limited to local application areas [13].

6. Intra-Patient Design Analysis

The intra-patient (split-body) design used in this study improved control over confounding variables such as age, immune status, disease severity, and

inflammatory response. This design minimized inter-subject variability and enhanced statistical power an approach supported in dermatologic drug trials as well [14].

Conclusion

The findings from this pilot study suggest that low-dose 5% topical imiquimod cream after Draf 2a frontal sinus surgery may effectively reduce clinical symptom recurrence, including inflammation, mucosal discharge, and polyp regrowth, over a three-month period. Furthermore, a significant reduction in the STDR index on postoperative CT scans of the intervention side compared to the control indicates the drug's potential in preventing restenosis and improving frontal sinus ventilation.

Although no significant differences were observed in the first month postoperatively, improvements in both clinical and radiologic indices by month three demonstrate a delayed and progressive therapeutic effect, likely due to the drug's immune-modulating properties through TLR7 activation and enhanced secretion of cytokines such as IFN-α and TNF-α.

Previous studies, including those by Casado et al. (2009) in HIV-positive patients and Clejan (2005) in animal models, support the effectiveness of imiquimod in reducing infections and inflammatory lesions in nasal tissues. However, clinical trials specifically targeting the sinus region are scarce, and this study represents one of the first matched-intervention investigations in this area.

The intra-patient comparison approach provided better control over individual confounders and improved the precision of statistical analyses. In addition, the use of STDR and 3D reconstruction of the frontal sinus enhanced the accuracy of outcome evaluation. Most importantly, no serious local or systemic side effects were observed during the follow-up period, indicating a relatively safe profile for the drug at the applied dose. Based on these findings, topical imiquimod cream may serve as a promising adjunct therapy after FESS in patients with CRS and frontal polyposis. However, validation through larger, more advanced clinical trials is necessary.

Study Limitations

As a pilot study, several limitations must be acknowledged:

1. **Small Sample Size:** With only 20 participants, the statistical power to detect subtle differences was limited.
2. **Short Follow-up Duration:** A three-month follow-up may be insufficient to assess the long-term effectiveness of imiquimod, especially in chronic and recurrent diseases such as CRS.
3. **Design Constraints:** Although the intra-patient design reduces variability, it does not replace double-blind, placebo-controlled trials with independent control groups.
4. **Potential Observation Bias:** While CT and endoscopic assessments were performed by a blinded secondary examiner, the possibility of observation bias cannot be fully excluded.

Recommendations for Future Studies

Given the promising results and limitations of this pilot study, future research should consider the following:

- **Larger Sample Sizes & Advanced Trial Phases:** Expanding the study population and conducting phase 2 and 3 trials across multiple centers to improve statistical reliability and generalizability.
- **Longer Follow-up Periods:** Extending follow-up to at least 6–12 months to better evaluate long-term efficacy, recurrence of polyps, and ostium restenosis.
- **Dose Comparison Studies:** Evaluating different concentrations of imiquimod to determine the optimal therapeutic dose with minimal adverse effects.
- **Immunologic Profiling:** Assessing changes in local cytokine expression (e.g., IFN-α, TNF-α, IL-6) via biopsy or lavage analysis to elucidate the exact mechanisms of imiquimod action in the sinus mucosa.
- **Comparative Studies with Other Topical Agents:** Comparing imiquimod with other postoperative therapies such as topical budesonide, mitomycin-C, or dexamethasone.
- **Patient-Reported Outcomes:** Including validated questionnaires such as SNOT-22 to evaluate treatment impact on patient quality of life in addition to clinical parameters.

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