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What is This?
The Role of Immediate Postoperative Systemic Corticosteroids When Utilizing a Steroid-eluting Spacer Following Sinus Surgery

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No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. Steroid-eluting spacers can improve local drug delivery immediately following endoscopic sinus surgery and reduce the recurrence of inflammation warranting systemic corticosteroids. For chronic rhinosinusitis with nasal polyps, the need for systemic corticosteroids immediately following endoscopic sinus surgery when using a steroid-eluting spacer has not been studied.

Study Design. A randomized, double-blind, placebo-controlled trial.

Setting. Academic rhinology practice.

Subjects and Methods. Chronic rhinosinusitis patients with nasal polyps who failed medical therapy and elected endoscopic sinus surgery were enrolled. Patients were randomized into either the treatment arm (postoperative prednisone 30 mg daily × 7 days; n = 18) or placebo arm (postoperative placebo pill daily × 7 days; n = 18). Outcomes were evaluated at 1 week, 3 weeks, and 2 months postoperatively. Primary outcome was endoscopic grading at postoperative month 2 using the Lund–Kennedy system. Secondary outcome included disease-specific quality of life using the Sinonasal Outcome Test (SNOT-22) survey. Patient enrolment occurred from January 2012 through February 2013 (NCT01564355).

Results. Both arms received significant improvement in endoscopic grading and disease-specific quality of life from baseline compared to 2-month follow-up (P < .001). There were no significant differences in mean endoscopic scores between the postoperative prednisone and control groups at 1 week (P = .715), 3 weeks (P = .883), or 2 months (P = .343). There were no significant differences in SNOT-22 scores between groups at all follow-up points (all P > .119).

Conclusion. Minimizing systemic corticosteroid use in patients with chronic rhinosinusitis with nasal polyps may avoid adverse events. Results from this study suggest that postoperative systemic corticosteroids immediately following endoscopic sinus surgery may not provide improved outcomes when utilizing a steroid-eluting spacer.

Keywords chronic rhinosinusitis, sinusitis, topical steroid, middle meatal spacer, sinus surgery, corticosteroid

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Introduction

Endoscopic sinus surgery (ESS) is an excellent management option for patients with medically refractory chronic rhinosinusitis (CRS).¹-⁶ An important goal in the early postoperative period is to minimize mucosal inflammation, promote normal ciliary function, and reduce the risk of complications such as synechiae and infection.⁷ To minimize postoperative mucosal inflammation, most experts would recommend high volume saline irrigations and early topical corticosteroid therapy.⁷ However, the early postoperative milieu of sinonasal crusting, retained secretions, and edema significantly impair adequate delivery of topical corticosteroid therapy immediately following ESS. To overcome this challenge, surgeons often consider providing a short course of postoperative systemic corticosteroids, which has been shown to significantly improve postoperative endoscopic outcomes in CRS patients with nasal polyposis.⁸ Although effective, the use of systemic corticosteroids has potential serious adverse effects and identifying strategies to reduce these risks while maintaining the clinical benefit would improve patient care.⁹-¹¹
Drug eluting middle meatal spacers have been developed to deliver topical corticosteroid therapy without the need for spray, drop, or irrigation delivery techniques. In the early postoperative period following ESS, the use of drug-eluting spacers has gained popularity since they can deliver topical corticosteroid to the sinonasal mucosa during a time when the traditional techniques of sprays and irrigations often fail due to impaired access from crusting and edema. Bioabsorbable steroid-eluting stents have also been shown to reduce the recurrence of sinonasal inflammation that would warrant systemic corticosteroid treatment, in the late postoperative period. Since drug-eluting spacers improve topical corticosteroid therapy in the immediate postoperative period, concurrent early postoperative systemic corticosteroid therapy may not be required.

The purpose of this study is to evaluate the effectiveness of immediate postoperative systemic corticosteroid therapy when utilizing a middle meatal steroid-eluting spacer in CRS patients with nasal polyposis following ESS. The primary outcome was endoscopic grading and the secondary outcome was disease-specific quality of life (QoL). We hypothesized that continuing postoperative systemic corticosteroids would further improve endoscopic grading when utilizing a middle meatal steroid-eluting spacer following ESS for refractory CRS with nasal polyposis.

Methods and Materials

Study Design

This study is a randomized, double-blind, placebo-controlled trial (NCT01564355). Patients were enrolled between January 2012 and February 2013. Inclusion criteria included adults over 18 years of age, a diagnosis of CRS with nasal polyposis according to the 2007 Adult Sinusitis Guidelines, and elected ESS for an indication of refractory CRS. Refractory CRS was defined as persistent symptoms despite a minimum of 3 months topical corticosteroid spray or irrigations, minimum of a 2-week course of systemic corticosteroid (prednisone 30 mg PO once daily) and a minimum 2-week course of broad-spectrum antibiotic in the presence of mucopusulence. Exclusion criteria included patients with suspected systemic inflammatory disease, cystic fibrosis, and any contraindication to systemic corticosteroids. Patients undergoing concurrent septoplasty were not excluded as it has not been shown to be a confounding variable. Study protocol was approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID: 24336), and informed consent was obtained from each study participant.

Patients were randomized into either the intervention or placebo group (Figure 1). Patients in the intervention group received postoperative prednisone therapy (30 mg once daily × 7 days) beginning 1 day after ESS. Patients in the control group received a postoperative placebo (once daily × 7 days) beginning 1 day after ESS. Randomization was performed using a computer generated block-randomization allocation. The block size was 6. The enrolling surgeons (LR and BM) were blinded to the assigned group.

Preoperative Management

In preparation for ESS, all enrolled patients received the same preoperative medications which included 7 days of oral prednisone (30 mg once daily) and 7 days of oral antibiotic. Antibiotic choice was either amoxicillin/clavulanate 875 mg twice daily, trimethoprim/sulfmethoxazole 160/800 mg twice daily (if penicillin allergy) or clarithromycin 500 mg twice daily (if penicillin and sulfa allergy).

Intraoperative Management

All patients underwent ESS which included bilateral maxillary antrostomy, total ethmoidectomy, sphenoidotomy, and frontal sinusotomy. The surgeons were blinded to patient randomization. All patients had 1 Nasopore™ dissolvable spacer soaked with 2 ml of triamcinolone (40 mg/ml) placed into each of the ethmoid cavities at the completion of the ESS procedure. Nasopore is a co-polyetherester urethane foam that fragments within several days in the nasal cavity. Its high absorbency makes it useful as a carrier for fluid substances, as it can hold up to 25 times its weight in topical medication.

Postoperative Management

Postoperative care followed appropriate evidence based recommendations and included the following protocol: high volume nasal saline irrigations (using a Neilmed™ saline sinus rinse bottle) 3 times per day starting 1 day after ESS, continuing the systemic antibiotic for 7 days after ESS, and an endoscopic debridement at 1 and 3 weeks postoperatively. Topical nasal corticosteroid therapy was initiated at the 1 week postoperative visit. Topical steroid therapy following the debridement consisted of high volume budesonide irrigation once daily (1 mg in 240 ml of saline). This was initiated after the patient underwent their first nasal cavity debridement, which allowed for the effective delivery of topical steroid solution into the sinonasal cavity.

Data Collection

Upon patient enrollment, baseline demographic information and preoperative Lund–Mackay computed tomography (CT) score were recorded. The primary outcome was endoscopic grading at postoperative month 2, which was collected using the validated 20-point Lund–Kennedy endoscopic scoring system, which assesses patients on the presence of polyps, edema, discharge, scarring, and crusting. The secondary outcome was disease-specific QoL at postoperative month 2, which was collected using the validated 22-item Sinonasal Outcome Test (SNOT-22) questionnaire. Data were collected in 2 tertiary rhinology clinics at 1 week, 3 weeks, and 2 months postoperatively. The surgeons were blinded to patient randomization throughout this period.

Statistical Analysis and Sample Size Calculation

Completed survey data and scoring scales were collected, transcribed, and manually entered into a database by a trained study coordinator using standardized clinical research forms. Data were deidentified and securely stored during the data collection period (Microsoft Excel; Microsoft Corp, Redmond,
Washington). All statistical analysis was performed using commercially available software (Stata 12.1; StataCorp LP, College Station, Texas). Descriptive statistics were provided for patient demographics including means and frequencies. For the primary and secondary outcomes, differences between the prednisone and placebo groups at 1 week, 3 weeks, and 2 months were analyzed using a 2-sided Student’s t test. Differences between groups from baseline to 2 months postoperatively were analyzed using a paired t test. P < .05 was considered a statistically significant difference.

Based on the data published from the study by Wright et al we assumed a 25% improvement in mean Lund–Kennedy score.68 Using a 2-sample comparison of proportions with a power of 90% and an alpha of 5%, we calculated a sample size of 36 required, 18 in each treatment arm.

**Results**

A total of 36 patients were enrolled. Eighteen patients were randomized into each group: (1) postoperative prednisone group and (2) postoperative placebo group. None of the
patients were lost to follow-up. All patients in each group fully completed the assigned postoperative medical therapy and standardized postoperative care protocols. No patient discontinued therapy due to any reported adverse effect.

As seen in Table 1, both patient groups were similar in terms of demographics and presence of CRS-related comorbid diseases (all \(P > .12\)). There were no significant differences between patient groups in any of the preoperative measures of disease severity, including Lund–Mackay CT scoring (\(P = .696\)), Lund–Kennedy endoscopic grading (\(P = .579\)), and SNOT-22 (\(P = .355\)).

When comparing baseline scores to the final 2-month outcomes, both groups had statistically significant improvements in both endoscopic scoring (\(P < .001\)) and SNOT-22 scores (\(P < .001\)) (Table 2).

When comparing outcomes between the prednisone and placebo groups, there were no significant differences in endoscopic grading or SNOT-22 outcomes at week 1, week 3, or month 2 (all \(P > .119\)) (Figures 2 and 3; Tables 3 and 4).

**Discussion**

This randomized, double-blind, placebo-controlled trial has demonstrated that continuing a short course of postoperative systemic corticosteroids may not provide additional clinical benefit when utilizing a middle meatal steroid-eluting spacer after ESS. It is important to take these results into context of the perioperative medical therapy protocol, which included 7 days of preoperative systemic corticosteroids in preparation for surgery. The findings suggest that the improved topical corticosteroid therapy delivery from the steroid-eluting spacer adequately controls postoperative mucosal inflammation and may preclude the use of continued postoperative systemic corticosteroid therapy. Reducing the duration of systemic corticosteroid therapy in CRS patients with nasal polyposis is important since it may reduce the potential short and long-term adverse effects associated with this therapy.

Following a successful ESS procedure, an open and accessible sinus cavity will allow for continued medical therapy, which is critical for long-term success by minimizing mucosal inflammation. The use of topical sinonasal therapies immediately following ESS can be limited by nasal crusting, retained secretions, and mucosal edema. To overcome this challenge, many surgeons have advocated the use of postoperative systemic corticosteroids to improve surgical outcomes by reducing inflammation of the diseased mucosa in the early postoperative period following ESS. A randomized, double-blind, placebo-controlled study by Wright et al evaluated the effect of perioperative systemic corticosteroids (prednisone 30 mg PO QD for 5 days preoperatively followed by 9 days postoperatively) on surgical outcomes following ESS to determine whether the benefits of this treatment modality are justified given the potential for systemic adverse effects. While patient-reported outcomes did not significantly differ between groups, the patients receiving prednisone received significantly improved endoscopic scores at most time points.
compared to the placebo group. Furthermore, there was improved visualization during ESS in the group of patients receiving preoperative prednisone. These results support the use of perioperative systemic corticosteroids in CRS patients with nasal polyposis.

To further improve local drug delivery in the early postoperative period, drug eluting middle meatal spacers have been developed to provide a slow release of continuous topical therapy while removing the need for daily patient dependent delivery techniques and reducing the potential for noncompliance. A variety of off-label middle meatal spacers and corticosteroid variations have been described and evaluated. A randomized trial by Cote and Wright demonstrated a significant improvement in postoperative endoscopic grading when using a Nasopore spacer impregnated with 2 ml of triamcinolone (40 mg/ml) versus a spacer soaked in placebo. A study by More et al compared a triamcinolone impregnated Nasopore spacer to a group treated with postoperative systemic corticosteroids alone and demonstrated no significant difference in the presence of nasal polyps postoperatively. A recent meta-analysis by Zhao et al evaluated steroid-eluting spacers and reported that they may reduce postoperative adhesion rates. FDA-approved bioabsorbable steroid-eluting stents have also been studied with favorable results. In a meta-analysis Han et al examined the effect of the Propel™ mometasone-eluting sinus implant (Intersect ENT; Palo Alto, California) and found a significant decrease in recurrent sinonasal inflammation of a degree that would warrant the use of oral steroid, at postoperative day 30. The authors also found a reduction in postoperative polyp formation, turbinate lateralization and formation of adhesions that would warrant a surgical intervention. This meta-analysis received industry funding from the producer of the stent which was the subject of the study. The study by Cote and Wright used Nasopore dressings that were donated by Stryker Canada. However, this was an investigator-initiated study, and Stryker Canada had no involvement in study design, protocol, methods, or analysis. The authors of the remaining studies discussed above did not describe any industry sponsorship. Overall, the evidence suggests that the use of middle meatal steroid-eluting spacers following ESS provides topical corticosteroid effects and aids in controlling postoperative mucosal inflammation. Since systemic corticosteroids have the potential for both short-term risks and long-term cumulative dose effects, it would be important to identify management strategies to reduce the total duration of systemic corticosteroid use without compromising clinical outcomes. Although the use of preoperative systemic corticosteroids will likely continue, to optimize surgical conditions for patients with nasal polyposis, the use of middle meatal steroid-eluting spacers may represent a novel strategy to preclude the use of continued postoperative systemic corticosteroids. Results from this study suggest that the use of postoperative systemic corticosteroids failed to offer additional clinical benefit when using a middle meatal steroid-eluting spacer following ESS in CRS patients with nasal polyposis. Although all patients received preoperative systemic corticosteroids in preparation for ESS, a reduced treatment course by not continuing pre- dnisone postoperatively may potentially reduce both short- term and long-term adverse effects.

There are certain limitations that should be considered when evaluating the findings from this study. First, a relatively small sample size may incur a risk of committing a type II error (accepting the null when it was false). While the sample size for this study was adequately powered to detect a difference in our primary outcome (ie, endoscopic score), a larger sample size would further reduce the risk of falsely accepting the null hypothesis. A second potential limitation is the relatively short length of follow-up for our final outcome (ie, 2 months). However, since the clinical impact for both the steroid-eluting spacer and postoperative systemic corticosteroid therapy should occur within the first 3 months after ESS, we do not feel a longer follow-up duration would significantly impact the clinical results.

Figure 2. Endoscopic (Lund–Kennedy) grading comparison between prednisone and placebo groups when utilizing a middle meatal steroid eluting spacer.

Figure 3. Disease-specific quality of life (SNOT-22) score comparison between prednisone and placebo groups when utilizing a middle meatal steroid eluting spacer.
period would change the outcomes of this study. Nonetheless, this study may have potentially missed a late effect of oral prednisone, beyond the 2-month period. While anecdotally this may seem unlikely, further study with a longer follow-up period may be needed to rule out this possibility. Third, patients in both groups received preoperative systemic corticosteroids (prednisone 30 mg PO QD for 7 days), which will provide residual systemic effects into the postoperative period. However, the preoperative course was very short (7 days) and therefore would be unlikely to provide continued systemic effects up to the 2-month follow-up period. Furthermore, the aim of this study is to specifically evaluate the impact of postoperative systemic corticosteroid when using a middle meatal steroid-eluting spacer following ESS while employing a perioperative treatment strategy that reflects standard practice. Incorporating a research protocol that included preoperative systemic corticosteroids will provide generalizable outcomes to allow surgeons to apply these results to their current practice. Last, our study evaluated an off-label steroid-eluting spacer (Nasopore soaked with 2 ml of 40 mg/ml triamcinolone) and the results from this study may not be generalizable to other steroid-eluting spacers or stents, which may differ in their method of delivery and type of steroid. For example, the Propel sinus implant contains 370 µg mometasone furoate embedded in a polymer matrix that releases the drug over 30 days and does not require debridement following ESS. The off-label Nasopore triamcinolone method differs from the Propel method since it releases a very short burst of topical steroid over the first couple days until the remnant spacer is debrided in-office. The Nasopore-Triamcinolone method also differs in that triamcinolone is a potent topical steroid, with the local effect being observed even 2 months after placement of the absorbable spacer.

Despite these limitations, we feel the randomized, double-blind, placebo-controlled study design strengthens the results and contributes to the literature by evaluating the need for postoperative systemic corticosteroids in the era of drug-eluting spacers and stents.

**Conclusion**

To reduce the risk of adverse effects, it is important to identify treatment strategies that minimize and reduce the duration of systemic corticosteroids in the management of CRS patients with nasal polyposis. Results from this study suggest that continuing a short course of postoperative systemic corticosteroids immediately following ESS for CRS with nasal polyposis may not provide additional clinical benefit when utilizing a middle meatal steroid-eluting spacer.

**Author Contributions**

Jon F. Dautremont, data analysis, manuscript writing, literature review, editing; Brad Mechor, patient enrollment, data collection, editing; Luke Rudmik, patient enrollment and evaluation, data collection and analysis, manuscript editing.

**Disclosures**

Compelling interests: None.
Sponsorships: None.
Funding source: None.

**References**

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**Table 3.** Endoscopic (Lund–Kennedy) Grading Comparison between Prednisone and Placebo Groups When Utilizing a Middle Meatal Steroid-eluting Spacer.

<table>
<thead>
<tr>
<th></th>
<th>Prednisone group (mean ± SD)</th>
<th>Placebo group (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>6.5 ± 1.4</td>
<td>6.3 ± 1.2</td>
<td>.715</td>
</tr>
<tr>
<td>Week 3</td>
<td>5.1 ± 2.3</td>
<td>5.0 ± 2.2</td>
<td>.883</td>
</tr>
<tr>
<td>Month 2</td>
<td>2.2 ± 1.6</td>
<td>1.7 ± 1.5</td>
<td>.343</td>
</tr>
</tbody>
</table>

**Table 4.** Disease-specific Quality of Life (SNOT-22) Score Comparison between Prednisone and Placebo Groups When Utilizing a Middle Meatal Steroid-eluting Spacer.

<table>
<thead>
<tr>
<th></th>
<th>Prednisone group (mean ± SD)</th>
<th>Placebo group (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>17.7 ± 9.5</td>
<td>25.2 ± 17.2</td>
<td>.119</td>
</tr>
<tr>
<td>Week 3</td>
<td>17.5 ± 10.1</td>
<td>16.8 ± 13.8</td>
<td>.859</td>
</tr>
<tr>
<td>Month 2</td>
<td>11.5 ± 7.3</td>
<td>10.4 ± 10.1</td>
<td>.722</td>
</tr>
</tbody>
</table>

Abbreviation: SNOT-22, Sinonasal Outcome Test.


