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Lack of Additive Benefit of Oral Steroids on Short-Term Postoperative Outcomes in Nasal Polyposis

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INTRODUCTION
Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common health problem, affecting 2% to 5% of the general population. The European position paper on rhinosinusitis and nasal polyps (EPOS) consensus defines CRSwNP as the presence of two or more nasal symptoms, one of which should be either nasal blockage or nasal discharge, and/or reduction/loss of smell, and/or facial pain for more than 12 weeks, and the presence of either nasal polyps by nasal endoscopy or mucosal changes within the ostiomeatal complex and/or paranasal sinuses by computed tomography (CT) scan.

Intranasal corticosteroids (CSs) are the first-line treatment for CRSwNP, and oral corticosteroid (OCS) therapy is reserved for patients with severe symptoms. CSs exert their anti-inflammatory effect by acting on specific receptors present in all human cells, including polyp tissue. The reason why some nasal polyp phenotypes are resistant to intranasal CSs is not well understood. However, some investigators have postulated that, among others, abnormal glucocorticoid receptor expression or a reduced effect of CSs on nasal polyp fibroblast proliferation may explain resistance to topical therapy.

Glucocorticoid receptor (GR) has functional (GRα) and nonfunctional (GRβ) isoforms. It is believed that a reduction in the expression of GRα and an increase in GRβ found in sinonasal tissue has a role in the lack of response to medical treatment found in chronic rhinosinusitis (CRS). Furthermore, a recent study has also detected a decrease of GRα in peripheral blood mononuclear leukocytes of patients with CRS. This new evidence suggests that there is also a different systemic GR isoform expression in these patients. Mucins have different functions depending on whether they are secreted or membrane-bound. Membrane-tethered mucins such as mucin 1 (MUC1) and mucin 4 (MUC4) are also implied in the airway inflammatory response. Low expression of MUC1 may contribute in corticosteroid resistance in patients with CRSwNP and also in asthma. Additionally, MUC4 subunit β inhibits GRα nuclear function. This indicates that the high expression of MUC4 seen in patients with CRSwNP may participate in corticosteroid resistance mechanisms.

Endoscopic sinus surgery (EES) is indicated for patients with inadequate improvement despite medical therapy. ESS aims not only to improve sinus ventilation, mucociliary clearance, and intranasal CSs delivery but also to reduce the load of antigens inciting inflammation by removal of the inflammatory tissue.
Randomized clinical trials (RCTs) have demonstrated that intranasal CSs therapy improves nasal symptoms and polyp size before and after surgery. Although preoperative OCS have proved efficacy and have also shown adverse events, data in postoperative treatment of CRSwNP are more limited.

It has been postulated that the use of intranasal CSs in the immediate postoperative period may increase the risk of sinusitis. However, recent meta-analysis from four studies that used intranasal CSs showed there is no evidence of increased risk of sinusitis with CSs use in postoperative period. Pundir et al. acknowledge that rare adverse events are possibly not detected in RCTs. However, they were extremely low and there was no difference in adverse events between the study groups and control groups in any trial.

To date, data about the efficacy of OCS as add-on treatment in short-term postoperative treatment are lacking.

The aim of our study was to evaluate the efficacy of postoperative CSs on short-term sinonasal symptoms, sense of smell, nasal endoscopy findings, and quality of life (QoL) in patients with CRSwNP.

**MATERIALS AND METHODS**

**Study Population and Design**

**Study Population.** Patients with moderate-to-severe CRSwNP (n = 70) refractory to maximal medical therapy were enrolled to undergo ESS (mean age 46.7 ± 13 years, range 26–74 years, 38.6% female). Patients were randomized (1:1) by computer-based system into two groups: treatment group (n = 35) (15 without asthma, 9 with asthma tolerant to nonsteroidal anti-inflammatory drugs [NSAID], and 11 with aspirin-exacerbated respiratory disease/AERD) and control group (n = 35) (15 without asthma, 10 with NSAID-tolerant asthma, and 10 with AERD). The ethics committee of our institution approved the study, and signed informed consent was obtained from all patients.

**Study Design.** The treatment group first received 30 mg of oral prednisone for 1 week, followed by 20 mg for 1 week, then 10 mg for 1 week, and finally 5 mg for 1 week. Both OCS-treated and control patients were invited to the outpatient clinic before ESS (w0) and 4 weeks after ESS (w4).

**Inclusion and Exclusion Criteria.** The diagnosis of CRSwNP was based on the following criteria of EPOS definition: 1) sinonasal symptoms, 2) visualization of nasal polyps in the middle meatus under nasal endoscopic examination, and 3) bilateral opacification of paranasal sinuses on CT scans. Patients with inverted papilloma, antrochoanal polyps, cystic fibrosis, malignancies, or cerebrospinal fluid fistula were excluded from the study. Patients with past history of aspirin desensitization or with contraindications for treatment with oral steroids were also excluded.

**Surgical Procedure.** ESS was performed under general anesthesia by a single surgeon (I.A.). Extended surgery was required in 13 patients (46.6%). After surgery, patients were instructed to use daily nasal douching after surgery. Nasal packing was placed for 24 hours, and all patients started OCS the day after the surgery. Five mild postoperative complications (7.1%) were recorded: mild postsurgical hemorrhage (N = 3) and periorbital ecchymosis (N = 2) that resolved from 1 to 2 weeks. Anteroposterior ethmoidectomy and sphenoidectomy. The frontal sinus surgery; NSAID = nonsteroidal anti-inflammatory drugs; OCS = oral corticosteroids; SD = standard deviation; SF36 = Medical Outcome Study Short Form-36 questionnaire.

### Outcomes and Assessments

**Sinonasal Symptoms.** All patients were asked to score five sinonasal symptoms (nasal obstruction, facial pressure, anterior rhinorrhea, posterior discharge, and smell loss) from 0 to 4 (0, no symptom; 1, mild symptom; 2, moderate symptom; 3, severe symptom; and 4, very severe symptom) before surgery (w0) and at w4. The total 5 symptom score (TSSS) was obtained with the sum of the individual symptoms (0–20).

**Nasal Endoscopic Findings.** Using a nasal rigid endoscope, nasal polyp size (NPS) was scored using modified Lildholdt system (0, no nasal polyps; 1, small nasal polyps not reaching the inferior border of the middle turbinate; 2, nasal polyps reaching beyond the inferior border of the middle turbinate; 3, large nasal polyps reaching the lower edge of the inferior turbinate; and 4, very large nasal polyps in contact with the floor of nasal cavity). Total (bilateral) NPS score goes from 0 to 8 and patients with total NPS score ≥ 4 (with a minimum of 2 in each nasal cavity) were classified as moderate-severe CRSwNP. Hyperemia, edema, epistaxis, mucus, and crusts were also scored using 0: no; 1: mild; 2: moderate, and 3: severe.

**Smell Test.** Barcelona Smell Test 24 (BAST-24) was used to measure the sense of smell. BAST-24 consists of 24 odors, and after being exposed for 5 seconds to an odor, patients were asked to answer a number of questions to score smell detection, identification, and memory.

### Table I.

Baseline Characteristics of Patients With Nasal Polyposis Treated by Endoscopic Sinus Surgery With or Without Postoperative Oral Corticosteroids.

| Age, years (mean ± SD) | 46.8 ± 13.3 | 46.6 ± 12.7 | 0.80 |
| Male gender, N (%) | 22 (62.9) | 21 (60.0) | 0.96 |
| Asthma, N (%) | 20 (57.1) | 19 (54.2) | 0.81 |
| AERD, N (%) | 11 (31.4) | 10 (28.6) | 0.88 |
| Total symptoms score, 0–20 | 12.0 ± 3.1 | 12.3 ± 3.6 | 0.61 |
| (mean ± SD) Nasal polyp size score, 0–8 | 7.0 ± 1.3 | 6.9 ± 1.1 | 0.50 |
| (mean ± SD) Smell detection, % | 15.1 ± 13.2 | 9.4 ± 15.6 | 0.29 |
| (mean ± SD) Smell memory, % | 10.4 ± 8.7 | 5.1 ± 12.0 | 0.33 |
| (mean ± SD) Smell identification, % | 5.1 ± 11.4 | 5.3 ± 9.6 | 0.91 |
| (mean ± SD) SF36 physical summary, 0–100 (mean ± SD) | 72.2 ± 28.1 | 68.5 ± 20.9 | 0.26 |
| SF36 mental summary, 0–100 (mean ± SD) | 71.4 ± 35.2 | 73.9 ± 27.6 | 0.95 |

CSS = corticosteroids; ESS = endoscopic sinus surgery; NSAID = nonsteroidal anti-inflammatory drugs; OCS = oral corticosteroids; SD = standard deviation; SF36 = Medical Outcome Study Short Form-36 questionnaire.

AERD = aspirin exacerbated respiratory disease; ESS = endoscopic sinus surgery; NSAID = nonsteroidal anti-inflammatory drugs; OCS = oral corticosteroids; SD = standard deviation; SF36 = Medical Outcome Study Short Form-36 questionnaire.

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Medical Outcome Study Short Form-36

The Medical Outcome Study Short Form (SF-36) questionnaire consists of 36 self-administered questions that cover eight health domains: physical functioning, role physical, and bodily pain; and general health, vitality, role emotional, social functioning, and mental health. Scale scores range from 0 to 100 and higher scores indicate better QoL. In addition, the physical component summary (PCS) and the mental component summary (MCS) scores were calculated. The Spanish version of the SF-36 has been previously used to measure QoL, showing a good reproducibility and validity.

Statistical Analysis

Data analysis was performed with the statistical package SPSS 24.0 for Windows (IBM, Armonk, NY) using mean ± standard deviation. Δ differential score between baseline (w0) and w4 was calculated to compare the effect of CSs between both groups. P-values of <0.05 were considered statistically significant. The T5SS, endoscopy score, and BAST-24 scores were not normally distributed. Therefore, a nonparametric statistical test (Mann-Whitney U test) was used.

RESULTS

At baseline, treatment and control groups did not show any differences regarding age, gender, asthma or aspirin/NSAID sensitivity. T5SS, polyp size, BAST-24, and SF-36 values were similar in both groups (Table I). All patients completed the study without any withdrawal. A subgroup analysis was done for the AERD and asthma cohorts. OCS treatment had no significant additive benefit compared to those without OCS on any study postoperative outcome, even in patients with asthma or AERD.

Sinonasal Symptoms

At baseline, patients scored loss of smell and nasal obstruction as the major complaints in both groups (Fig. 1). Significant improvement in T5SS was observed after surgery either with (4.6 ± 2.7) or without (4.0 ± 2.1) OCS therapy compared to baseline (12.0 ± 3.1 and 12.3 ± 3.6, respectively). No significant differences on differential values (Δ) and no additional positive effect of OCS on sinonasal symptoms were observed (Fig. 1).

Fig. 1. Total five sinonasal symptoms score at baseline and 4 weeks postoperatively. (A) Oral corticosteroids group. (B) Control group. (C) Mean difference Δ between baseline and 4 weeks postoperative values for corticosteroid group and control group. *P < 0.05; ***P < .001. NS = nonsignificant; postop = postoperative.

Fig. 2. Nasal endoscopic findings at baseline and 4 weeks postoperatively. (A) Oral corticosteroids group. B) Control group. (C) Mean difference Δ between baseline and 4 weeks postoperative values for corticosteroid group and control group. *P < 0.05; ***P < .001. NS = nonsignificant; postop = postoperative.
Nasal Endoscopic Findings

No polyps were found at w4 visit in both groups compared to baseline (7.0/C6 1.3 and 6.9/C6 1.1, respectively). Hyperemia, edema, and mucus but not epistaxis significantly improved after surgery in both groups. Crusting was the only endoscopic finding that increased after surgery due to the scar process. No additional positive effect of OCS on nasal endoscopic findings was observed (Fig. 2).

Smell Test

At baseline, patients with and without OCS therapy had significant loss of smell on detection (15.1 ± 13.2 and 9.4 ± 15.6), memory (10.4 ± 8.7 and 5.1 ± 12.0), and identification (5.1 ± 11.4 and 5.3 ± 9.6) compared to the general population (99.2% ± 1.5%, 54.7% ± 4.9%, 72.2% ± 6.8%, respectively; \(P < 0.05\)). After surgery, patients in both groups experienced significant improvement in all BAST-24 characteristics. There were no differences on the total improvement after OCS (\(\Delta w_{0-4}\)) on smell detection, memory, and identification between both groups, suggesting no additional positive effect of OCS on sense of smell after surgery (Fig. 3).

DISCUSSION

The main findings of our study were the following: 1) endoscopic sinus surgery in CRSwNP patients improves all sinonasal symptoms, endoscopic findings, sense of smell, and quality of life; 2) there is a lack of short-term additive benefit of OCS on postoperative outcomes in patients with CRSwNP; and 3) OCS had no significant additional effect on any postoperative outcome of the study in patients with either asthma or AERD compared to those without.

There is no data in the scientific literature regarding the effect of OCS without intranasal CSs on postoperative outcomes in patients with CRSwNP. To our knowledge, the present study is the first randomized trial (Ib) using oral prednisone in monotherapy during 4 weeks after ESS. Patients were allowed to apply saline irrigation but without using intranasal CSs.

Medical Outcome Study Short Form-36

At baseline, patients with and without OCS therapy had poorer QoL on PCS (72.2 ± 28.1 and 68.5 ± 20.9) and MCS (71.4 ± 35.2 and 73.9 ± 27.6) compared to the Spanish general population (78.8 ± 25.6 and 79.7 ± 28.4, respectively; \(P < 0.05\)), suggesting that CRSwNP impaired physical and mental health. After surgery, patients with OCS showed significant improvement on role physical, bodily pain, general health, and social functioning. However, those without OCS therapy improved significantly on general health and social functioning (Fig. 4). No significant differences on \(\Delta\) differential values between OCS and control groups was found.
The aim of ESS is to eliminate nasal polyps (sinonasal inflammation), improve sinonasal symptoms, and facilitate the treatment with intranasal CSs (to reach the deeper part of the sinuses and act on the mucosa that previously was inaccessible). CSs have been used preoperatively, intraoperatively, and postoperatively in ESS for CRSwNP.

The data on the adverse effects associated with short courses of OCS indicate that there may be an increase in insomnia and gastrointestinal disturbances; however, it is not clear whether there is an increase in mood disturbances.15

Preoperative intranasal (mometasone furoate nasal sprays for 4 weeks)23 and systemic (30 mg prednisolone for 5 days preoperatively)24 CSs have demonstrated a significant decrease on operative time and estimated blood loss, the quality of the surgical field being significantly better compared to the nonsteroid group.18

The effect of intraoperative CSs (8 mg dexamethasone intravenously)25 did not show any significant improvement in postoperative pain score at 6 hours and 24 hours compared to the nonsteroid group.

Although the EPOS consensus clearly recommends the use of oral and intranasal CSs before and after ESS in CRSwNP patients, there are still discrepancies on the use of postoperative CSs. A systematic review on the use of intranasal CSs following ESS reported a significant improvement in symptoms, endoscopic findings, and delay in polyp recurrence.26 Also, a Cochrane review27 based on two studies showed the benefit of CSs on symptom scores on patients undergoing sinus surgery.28,29 They concluded that patients with previous ESS have a greater response to intranasal CSs than patients without ESS in polypl size reduction, the improvement in symptoms and nasal airflow being not statistically different between the two subgroups. Recently, Pundir et al.18 concluded that the limited data available do not address a significant benefit of postoperative CSs in improving symptom scores. Moreover, CSs improve postoperative endoscopic scores and reduce the risk of recurrences. These discrepancies between studies could be due to different inclusion criteria among them. Either in the severity or in the history and number of previous sinus surgeries, including polypectomies.

On the other hand, we have only found two studies that combined oral and intranasal CSs after ESS.26,30 In a randomized, double-blind, placebo-controlled, prospective study, Jorissen and Bachert30 used oral betamethasone 2 mg for 7 days, followed by topical mometasone furoate sprays for 6 months in both chronic rhinosinusitis without nasal polypos (CRSSNP) and CRSwNP patients. Compared to our study, this trial used combined oral and intranasal CSs and included CRS with and without nasal polypos. Analysis of the combination score for the clinically relevant features of inflammation, edema, and nasal polypos after ESS showed a significant improvement in the CSs group compared with placebo-treated CRS patients, specifically in CRSwNP but not CRSSNP patients.

Another study by Wright and Agrawal30 could not find any improvement in subjective symptoms after treatment with CSs. Study participants were randomized to receive either 30 mg of prednisone or placebo for 5 days preoperatively and 9 days postoperatively. In terms of postoperative symptoms, there was no difference between treatment groups, with both placebo and CSs significantly improving over baseline up to 4 weeks postoperatively. Postoperative endoscopic assessment, however, demonstrated healthier sinus cavities in patients treated with CSs.

As described in the introduction, there are numerous steroid resistance mechanisms in patients with CRSwNP. It is a possibility that the absence of additive benefit observed in the present study was due to this phenomenon. This could explain the lack of response to medical treatment before surgery and also to postoperative OCS.

Study Limitations The main potential limitation of our study are:

1) Although our study included a small sample, there was enough statistical power regarding sinonasal outcomes. Larger samples in OCS and placebo groups should be included in future studies. 2) There was a short-term follow-up (1 month) because our objectives were mainly to investigate the immediate effect of OCS on sinonasal findings. We missed, however, relevant data on long-term effect on nasal polypl recurrence. 3) We included seven patients with previous ESS. Although prior surgery had no further effect on study outcomes, comparison with other studies is difficult to carry out.

CONCLUSION
The results of the present study suggest that there is a lack of short-term additive benefit of postoperative OCS in the treatment of patients with CRSwNP; thus, they should not be routinely recommended.

ACKNOWLEDGMENT
This article was supported by a research project from Storz Company that offered instruments and equipment to perform the surgical approaches.

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