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Sinonasal Outcomes Using Oral Corticosteroids in Patients with Chronic Rhinosinusitis with Nasal Polyps and Positive Sinonasal Cultures

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Abstract

Introduction Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and positive sinonasal bacterial cultures may be recalcitrant to topical therapy alone due to the additional local inflammatory burden associated with bacterial infection/colonization.

Objective To evaluate sinonasal outcomes in CRSwNP patients with a positive perioperative bacterial culture, who were treated with postoperative intranasal corticosteroids (INCS) alone versus INCS in combination with a short-term course of oral corticosteroids (OCS).

Methods This is a retrospective chart review of CRSwNP patients. A total of 59 patients met inclusion criteria, including positive perioperative bacterial culture and treatment with INCS with or without concomitant use of OCS. Two cohorts were formed based on the chosen postoperative medical treatment; 32 patients underwent postoperative INCS alone, while 27 underwent INCS plus a $\leq$ 2-week course of OCS. The 22-item sinonasal outcome test (SNOT-22) scores and Lund-Kennedy scores (LKS) were assessed preoperatively, and at 2-week, 4-week, and 4 to 6 months after endoscopic sinus surgery (ESS).

Results There were no statistically significant differences in postoperative sinonasal symptoms or endoscopic scores between the cohorts treated with INCS plus OCS versus those prescribed INCS alone ($p > 0.05$). Our regression model failed to

Keywords

- chronic rhinosinusitis with nasal polyps
- corticosteroids
- culture
- 22-item sinonasal outcome test
- endoscopic sinus surgery

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demonstrate a relationship between the use of OCS and better sinonasal outcomes at 2-week, 4-week, and 4 to 6 months after ESS ($p > 0.05$).

Conclusion Our study suggests that in a cohort of CRSwNP patients with recent bacterial infections, the postoperative use of combined OCS and INCS did not result in a statistical improvement of endoscopic and symptomatic outcomes over INCS irrigation alone. However, both treatment groups had a clinically significant improvement based on the Minimal Clinically Important Difference.

Introduction

There is evidence suggesting that the local inflammation associated with an active bacterial infection in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) plays a crucial role in the postoperative healing process.[1,2] For example, multiple studies suggest that persistent bacterial infections, such as those caused by *Staphylococcus aureus* (*S. aureus*), affect the innate immune system provoking local inflammation, barrier disruption, and bacterial dysbiosis.[3–8] This immune response ultimately leads to an increased production of interleukin-4 (IL-4), IL-5, and IL-13, with a subsequent increase in immunoglobulin-E and eosinophilia.[9] Previous studies have found that active infections at the time of endoscopic sinus surgery (ESS) lead to abnormal postoperative mucosal recovery and worse postoperative prognosis.[2,10] One study looked at patients with purulent drainage noted in the maxillary sinus at the time of their ESS; patient outcomes were analyzed based on culture status, and the group with negative culture results was found to have the best surgical outcome.[2] Another study looked at biofilm potentiating organisms and their effect on postoperative sinus symptoms and endoscopy; they found that both *Pseudomonas* and *S. aureus* had high levels of biofilm formation which was associated with poor control of disease symptoms and endoscopy at 1-year after surgery.[11]

Both the innate and adaptive immune responses play a role in controlling bacterial infections, and in the resolution of resultant inflammatory responses. The epithelial barrier mechanism, mucociliary clearance, and an inflammatory cascade of cytokine and chemokine production characterize the innate and adaptive immune barriers that control or respond to bacterial infection. Once the bacterial response is controlled, macrophages cause apoptosis and phagocytosis of these inflammatory cells leading to the resolution of the acute process.[12] It is likely that treatment targeted at the resolution of this post-infectious phenomenon may be beneficial in controlling inflammation, which may lead to or exacerbate chronic rhinosinusitis (CRS).[13] Corticosteroids inhibit the activation and survival of inflammatory cells stimulated by host defense systems. They thereby affect the recruitment, localization, protein synthesis, and survival of inflammatory cells such as eosinophils.[14] It has been shown that systemic corticosteroids have a modulating effect on the nasal mucosa, promoting the epithelial repair, increasing collagen content, and reducing the eosinophil infiltration in the mucosa and the epithelial hyperplasia.[15] While it is reasonable to assume that the mechanism of action of systemic corticosteroids would show benefit in the setting of an acute infection, there is limited data on the use of oral corticosteroids (OCS) in acute exacerbations of CRS.

Therapeutic options for CRSwNP include treatment with topical or systemic agents, surgical intervention, or a combination thereof.[16,17] The effect of corticosteroid treatment, both topically and orally, on symptomatology and endoscopic scores has already been studied in CRS patients.[18–24] However, the effectiveness of postoperative combined therapy with OCS and intranasal corticosteroids (INCS) in CRSwNP patients with a positive sinonasal culture remains unexplored, leaving a gap in the literature. We aim to evaluate the postoperative sinonasal outcomes in culture-positive CRSwNP patients who received INCS alone, compared with those who received INCS in combination with a short course of OCS.

Methods

This retrospective study was approved by the Mayo Clinic Institutional Review Board (IRB 19–009794). Patients with a diagnosis of CRSwNP that underwent ESS from 2012 to 2020 and had a positive sinonasal culture taken preoperatively or intraoperatively were identified. The diagnosis of CRSwNP was based on criteria from the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) guidelines.[25] All patients were treated with INCS (budesonide respule 0.5 mg/2 ml in 240 ml saline, twice a day). Patients were divided into two groups based on whether they received immediate treatment postoperatively, with a combined therapy of INCS and short-term course of OCS ($<$ 2-weeks), or not. Patients were excluded if there was a diagnosis of cystic fibrosis, primary ciliary dyskinesia, immunodeficiency, sarcoidosis, or vasculitis disorders.

Patient-reported symptom scores were assessed using the 22-item Sinonasal Outcome Test (SNOT-22).[26] Additionally, endoscopy scores were evaluated using the Lund-Kennedy endoscopic score (LKS).[27] Patients filled out the SNOT-22 questionnaire in the preoperative visit and at each postoperative follow-up. Additionally, the LKS was also calculated preoperatively and at each postoperative visit, according to the endoscopic findings. Data from the preoperative, 2-weeks, 4-weeks, and 4–6 months postoperative visits were collected and analyzed for this study. Electronic medical

records were also reviewed for the following clinical characteristics: demographics, surgical history, urinary leukotriene E4 (LTE4), and comorbidities. All clinical data, including results of sinonasal cultures and sinonasal outcomes, were collected and placed in the Research Electronic Data Capture (REDCap, Vanderbilt University. Nashville, TN, US) software.

Statistical analysis was performed on the Statistical Package Social Sciences (SPSS, IBM Corp, Armonk, NY, US) software, version 25.0. Standard descriptive statistics were obtained and presented as percentages and mean ± standard deviations (SD). According to data distribution of quantitative variables, a parametric analysis (paired *t*-test) and non-parametric analysis (Wilcoxon signed-rank and Mann-Whitney U tests) were performed to compare means of sinonasal outcomes over time within and between treatment groups. A square root transformation of the data was completed to correct the skewed distribution of the LKS and perform a regression analysis. A linear regression model was used with preoperative SNOT-22 and LKS scores as fixed factors in the analysis and aimed to evaluate: 1) The effect of postoperative use of OCS on sinonasal outcomes among the overall cohort. 2) The effect of postoperative use of OCS on sinonasal outcomes among patients with aspirin-exacerbated respiratory disease (AERD). 3) The effect of concurrent oral antibiotics during the short oral corticosteroid regimen on both sinonasal outcomes. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

We identified an initial cohort of 212 patients, but only a total of 59 patients met the criteria for this study. The mean age of the overall cohort was 53 (±14) with a 1.2:1 female/male ratio. The median time between the preoperative visit and surgical intervention was 20 days. Thirty-two patients received postoperative INCS only, while twenty-seven received combined therapy with INCS and a short-term course of OCS. Six patients received an oral dose of prednisone ≥30mg, and 21 individuals received a course of < 30 mg/day. The treatment period in both scenarios was between five to fourteen days. No differences were observed between the groups at baseline regarding the gender, age, AERD diagnosis, medical history of asthma, allergic rhinitis, smoking, culture results, and preoperative SNOT-22 or LKS ($p > 0.05$).

The majority of our patients (97%) had purulent drainage cultured. The most common bacteria identified with S. aureus which was present in 27 patients, (45.7%), while six patients (10.1%) grew *Pseudomonas*. Other isolated bacteria included: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Propionibacterium acnes*, *Klebsiella*, *Serratia rubidaea*, *Enterobacter aerogenes*, *Stenotrophomonas maltophilia*, and coagulase-negative *Staphylococci*. (►**Fig. 1**). When collecting the clinical information, we noted that 10 patients received a culture-directed oral antibiotic regimen for two weeks as part of the postoperative treatment. Prescribed oral antibiotic agents included amoxicillin/clavulanate, levofloxacin, doxycycline, and trimethoprim/sulfamethoxazole. (►**Table 1**).

Of the 59 included patients, 37 had a diagnosis of AERD based on clinical history and confirmed by elevated levels of LTE4 on liquid chromatography-mass spectrometry (> 166 pg/mg Cr). Among the AERD patients, 20 received combined therapy with OCS and INCS, while seventeen were treated with INCS alone. No statistically significant difference was

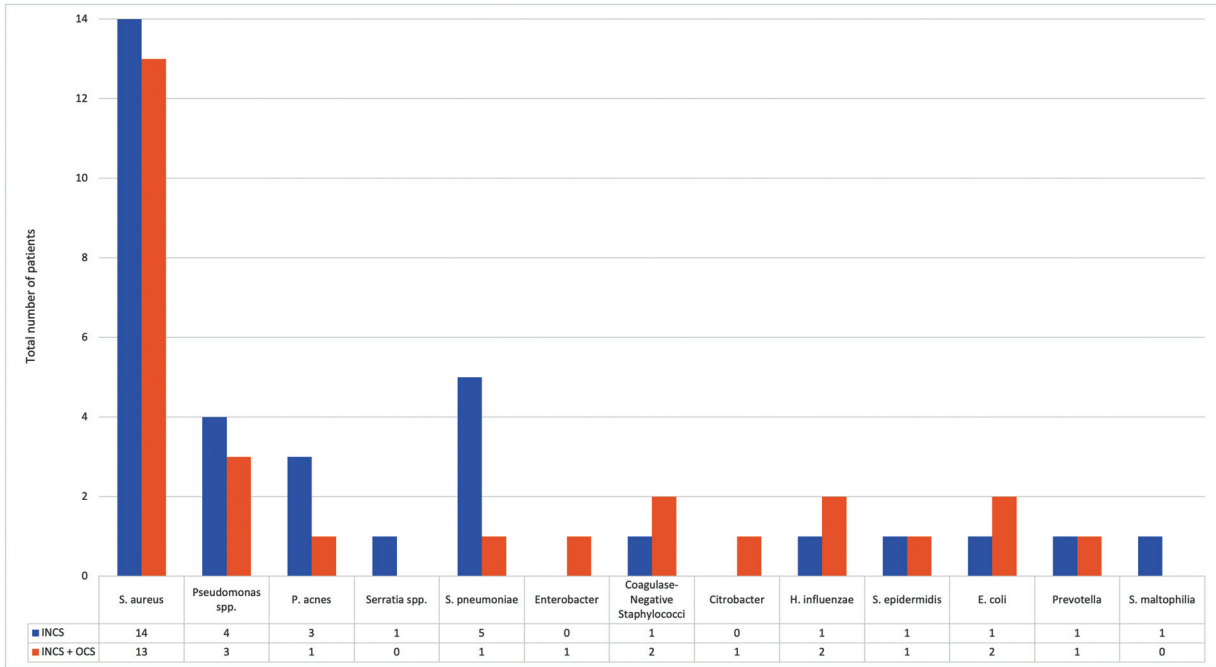

Fig. 1 Bacteria distribution among different groups of patients. **Abbreviations:** INCS, intranasal corticosteroids; INCS + OCS, intranasal corticosteroids + oral corticosteroids.

Table 1 Demographic and clinical data of the overall cohort

Characteristics	n = 59
Gender, no. (%), female	33 (55.9)
Mean age, years (SD)	53 (14)
CRS subtypes	
AERD, no. (%)	37 (62.7)
All other (non-characterized CRS), no. (%)	22 (37.3)
Disease status at presentation	
History of previous ESS, no. (%)	39 (66.1)
Number of previous ESS, mean (range)	2.1 (1 -8)
Comorbidities	
Asthma, no. (%)	45 (76.3)
Allergic rhinitis, no. (%)	33 (55.9)
Smoking, no. (%)	23 (39)
Obesity, no. (%)	24 (40.7)
OSA, no. (%)	15 (25.4)

Abbreviations: AERD, aspirin-exacerbated respiratory disease; CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery; OSA, obstructive sleep apnea.

found when comparing the distribution of AERD patients between groups (p-value = 0.10).

Sinonasal outcomes

As outlined in ►**Fig. 2**, sinonasal outcomes were collected and compared over time and between treatment groups. The SNOT-22 scores significantly improved from the preoperative visit to 4-weeks postoperation, and from the preoperative visit to 4 to 6 months after ESS, in both the INCS only and combined OCS and INCS groups ($p < 0.05$). However, there was no statistically significant difference in mean change in the SNOT-22 scores detected between the INCS group and combined OCS and INCS group at the 2-weeks, 4-weeks, or 4 to 6 months postoperative visits. (►**Table 2**).

A sequential improvement in the mean LKS was found at 2-weeks, 4-weeks, and 4 to 6 months after surgery in both the OCS and INCS group and the INCS only group. However, the overall change in mean LKS between groups did not reach statistical significance ($p > 0.05$). In the INCS only group, there was a statistically significant change in the mean LKS from preoperative to 2-weeks, 4-weeks, and 4 to 6 months postoperative scores ($p < 0.05$). A statistically significant change in the mean LKS was also noted among the combined therapy group from the preoperative visit to 4-weeks and 4 to 6 months after surgery ($p = 0.003$, $p = 0.001$). However, no significant difference was noted when comparing the mean preoperative LKS to 2-weeks after ESS ($p = 0.22$) (►**Table 3**).

Similar results were found among the sub-cohort of AERD patients. The SNOT-22 had a progressive and statistically significant improvement over time between the preoperative and the 4-weeks and 4 to 6 months postoperative assessments in both the INCS only group and the combined OCS and INCS group ($p < 0.05$). There was no significant difference in the mean change of SNOT-22 between the AERD patients who had received OCS compared with those who did not. (►**Table 4**). The LKS had a significant long-term

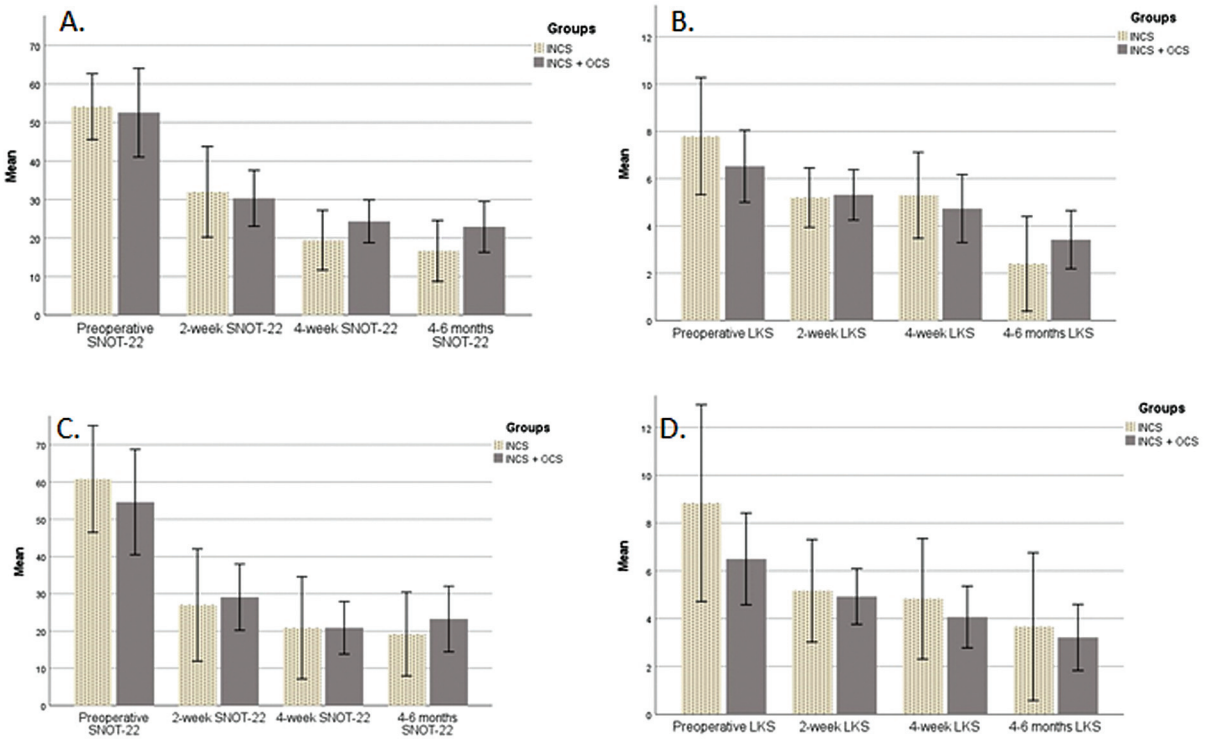

Fig. 2 **(A)** Change over time in 22-item sinonasal outcome test (SNOT-22) among the overall cohort. **(B)** Change over time in Lund-Kennedy endoscopic score (LKS) among the overall cohort. **(C)** Change over time in SNOT-22 among aspirin-exacerbated respiratory disease (AERD) patients. **(D)** Change over time in LKS among AERD patients.

Table 2 Changes over time on SNOT-22 among the overall cohort (mean, SD)

	SNOT-22		
	INCS group	INCS + OCS group	Comparison between groups (*p*-value)
Preoperative	54 ± 20	53 ± 22	0.82
2-weeks postoperative	32 ± 22 [a]	30 ± 14 [b]	0.80
4-weeks postoperative	19 ± 16 [c]	24 ± 10 [d]	0.32
4–6 months postoperative	17 ± 15 [e]	23 ± 12 [f]	0.23

Abbreviations: INCS, intranasal corticosteroids; LKS, Lund-Kennedy endoscopic score; OCS, oral corticosteroids; SNOT-22, 22-item sinonasal outcome test. **Notes:** [a] *p-value* between preoperative and 2-weeks postoperative in the INCS group= 0.074. [b] *p-value* between preoperative and 2-weeks postoperative in the INCS + OCS group= 0.24. [c] *p-value* between preoperative and 4-weeks postoperative in the INCS group = **0.0001.** [d] *p-value* between preoperative and 4-weeks postoperative in the INCS + OCS group = **0.003.** [e] *p-value* between preoperative and 4 to 6 months postoperative in the INCS group = **0.0001.** [f] *p-value* between preoperative and 4 to 6 months postoperative in the INCS + OCS group = **0.002.**

Table 3 Changes over time on LKS among the overall cohort (mean, SD)

	LKS		
	INCS group	INCS + OCS group	Comparison between groups (p-value)
Preoperative	7 ± 3	6 ± 3	0.39
2-weeks postoperative	5 ± 2 [g]	5 ± 2 [h]	0.44
4-weeks postoperative	5 ± 2 [i]	5 ± 3 [j]	0.71
4–6 months postoperative	2 ± 3 [k]	3 ± 3 [l]	0.14

Abbreviations: INCS, intranasal corticosteroids; LKS, Lund-Kennedy endoscopic score; OCS, oral corticosteroids; SNOT-22, 22-item sinonasal outcome test. **Notes:** [g] *p-value* between preoperative and 2-weeks postoperative in the INCS group= **0.004**. [h] *p-value* between preoperative and 2-weeks postoperative in the INCS + OCS group= 0.22. [i] *p-value* between preoperative and 4-weeks postoperative in the INCS group = **0.001**. [j] *p-value* between preoperative and 4-weeks postoperative in the INCS + OCS group = **0.003**. [k] *p-value* between preoperative and 4 to 6 months postoperative in the INCS group = **0.001**. [l] *p-value* between preoperative and 4 to 6 months postoperative in the INCS + OCS group = **0.001**.

improvement in both groups, but no difference was found between treatment groups ($p > 0.05$). (►**Tables 4** and **5**).

Linear regression

When analyzing the impact of the postoperative use of a short-term course of OCS on sinonasal outcomes among the overall cohort, our linear regression model failed to demonstrate a detectable effect on the 2-weeks, 4-weeks, or 4 to 6 months postoperative SNOT-22 ($p = 0.29$, $p = 0.35$, and $p = 0.18$), and on the 2-weeks, 4-weeks or 4 to 6 months postoperative LKS ($p = 0.74$, $p = 0.18$, and $p = 0.06$, respectively). (►**Table 6**) Our linear regression model for concurrent therapy with OCS on sinonasal outcomes among AERD patients did not show any effect on the postoperative SNOT-22 at 2-weeks, 4-weeks, or 4–6 months after treatment ($p = 0.47$, $p = 0.84$, and $p = 0.57$, respectively).

Table 4 Changes over time on SNOT-22 among AERD patients (mean, SD)

	SNOT-22		
	INCS group	INCS + OCS group	Comparison between groups (p-value)
Preoperative	61 ± 23	55 ± 22	0.52
2-weeks postoperative	27 ± 20[a]	29 ± 13[b]	0.80
4-weeks postoperative	21 ± 18[c]	21 ± 10[d]	0.99
4–6 months postoperative	19 ± 16[e]	23 ± 12[f]	0.57

Abbreviations: AERD, aspirin-exacerbated respiratory disease; INCS, intranasal corticosteroids; LKS, Lund-Kennedy endoscopic score; OCS, oral corticosteroids; SNOT-22: 22-item sinonasal outcome test. p-values were calculated within groups and results are as follows: [a]*p-value* between preoperative and 2-weeks postoperative in the INCS group= 0.096. [b]*p-value* between preoperative and 2-weeks postoperative in the INCS + OCS group= 0.24. [c]*p-value* between preoperative and 4-weeks postoperative in the INCS group = **0.01**. [d] *p-value* between preoperative and 4-weeks postoperative in the INCS + OCS group = **0.007**. [e]*p-value* between preoperative and 4–6 months postoperative in the INCS group = **0.015**. [f]*p-value* between preoperative and 4–6 months postoperative in the INCS + OCS group = **0.008**.

Table 5 Changes over time on LKS among AERD patients (mean, SD)

	LKS		
	INCS group	INCS + OCS group	Comparison between groups (p-value)
Preoperative	8 ± 3	6 ± 3	0.28
2-weeks postoperative	5 ± 2 [g]	5 ± 2 [h]	0.94
4-weeks postoperative	5 ± 3 [i]	4 ± 2 [j]	0.79
4–6 months postoperative	4 ± 3 [k]	3 ± 2 [l]	0.48

Abbreviations: AERD, aspirin-exacerbated respiratory disease; INCS, intranasal corticosteroids; LKS, Lund-Kennedy endoscopic score; OCS, oral corticosteroids; SNOT-22: 22-item sinonasal outcome test. p-values were calculated within groups and results are as follows: [g] *p-value* between preoperative and 2-weeks postoperative in the INCS group= **0.008.** [h] *p-value* between preoperative and 2-weeks postoperative in the INCS + OCS group= 0.22. [i] *p-value* between preoperative and 4-weeks postoperative in the INCS group = **0.008**. [j] *p-value* between preoperative and 4-weeks postoperative in the INCS + OCS group = 0.06. [k] *p-value* between preoperative and 4–6 months postoperative in the INCS group = **0.003**. [l] *p-value* between preoperative and 4–6 months postoperative in the INCS + OCS group = **0.01**.

Table 6 Linear regression analysis of the effect of postoperative short-term use of oral corticosteroids on sinonasal outcomes over time among overall cohort

	β value	Standard Error	(95% CI)	*p*-value
2-weeks after treatment				
SNOT-22				
Postoperative oral corticosteroids	-9.25	8.5	(-27.1–8.6)	0.29
*LKS**				
Postoperative oral corticosteroids	0.28	0.87	(-1.5–2)	0.74
4-weeks after treatment				
SNOT-22				
Postoperative oral corticosteroids	5	5.3	(-5.9–15.9)	0.35
*LKS**				
Postoperative oral corticosteroids	-0.07	0.18	(-0.4–0.25)	0.68
4–6 months after treatment				
SNOT-22				
Postoperative oral corticosteroids	8.7	6.2	(-4.3–21.7)	0.18
*LKS**				
Postoperative oral corticosteroids	0.56	0.29	(-0.02–1.1)	0.06*

Abbreviations: LKS, Lund-Kennedy endoscopic score; SNOT-22, 22-item sinonasal outcome test. **Notes:** * This analysis was calculated based on square-root transformed data.

Additionally, no statistically significant effect on the 2-weeks, 4-weeks, or 4–6 months postoperative LKS was found ($p = 0.56$, $p = 0.40$, and $p = 0.82$, respectively). (►**Table 7**).

Regarding the impact of concurrent therapy with oral antibiotic regimens in a portion of our patients, our linear regression model did not show any effect on the 2-week postoperative SNOT-22 score ($\beta = -8.5$ [95% CI: -23–6.3] $p = 0.25$), 4-weeks postoperative SNOT-22 score ($\beta = -2.6$ [95% CI: -13–7.8] $p = 0.61$), and 4 to 6 months postoperative SNOT-22 score ($\beta = 9.2$ [95% CI:-1.7–20] $p = 0.09$). Additionally, we found no statistically significant effect on the 2-weeks LKS ($\beta = -0.03$ [95% CI: -1.2–1.2] $p = 0.95$), 4-weeks postoperative LKS ($\beta = 0.53$ [95% CI: -1.0–2.1] $p = 0.50$), nor on the 4 to 6 months postoperative LKS ($\beta = 0.2$ [95% CI: -1.3–1.8] $p = 0.74$).

Discussion

The purpose of this study was to determine if the addition of OCS had an impact on sinonasal outcomes by modulating the post-infectious inflammatory response in CRSwNP patients who underwent ESS and had a positive preoperative or intraoperative bacterial sinonasal culture. To our knowledge, this is the first study to focus on the effect of combined OCS and INCS treatment on patients with CRSwNP and positive sinus cultures. The results of this study noted that all groups met the Minimal Clinically Important Difference (MCID) threshold for SNOT-22 after treatment but failed to show a statistically significant difference in the postoperative sinonasal symptoms score when compared. Additionally, our results showed that OCS did not have a statistically

Table 7 Linear regression analysis of the effect of postoperative short-term use of oral corticosteroids on sinonasal outcomes over time among AERD patients

	β value	Standard Error	(95% CI)	*p*-value
2-weeks after treatment				
SNOT-22				
Postoperative oral corticosteroids	-9.1	12.1	(-36 to 18.2)	0.47
*LKS**				
Postoperative oral corticosteroids	-0.67	1.1	(-3.1 to 1.7)	0.56
4-weeks after treatment				
SNOT-22				
Postoperative oral corticosteroids	1.6	8.3	(-16.7 to 20)	0.84
LKS				
Postoperative oral corticosteroids	-0.22	0.26	(-0.7 to 0.3)	0.40
4–6 months after treatment				
SNOT-22				
Postoperative oral corticosteroids	6.2	10.7	(-18.1 to 30.5)	0.57
LKS				
Postoperative oral corticosteroids	0.08	0.38	(-0.7 to 0.8)	0.82

Abbreviations: LKS, Lund-Kennedy endoscopic score; SNOT-22, 22-item sinonasal outcome test. **Notes:** * This analysis was calculated based on square-root transformed data.

significant effect on the LKS at 4 to 6 months in the overall cohort. When we analyzed these results in the subgroup of patients with AERD, the combined therapy had no impact on patients with positive sinonasal cultures.

The pathogenesis of CRSwNP is not completely understood due to its heterogeneous pattern of histologic inflammation, clinical presentation, and responses to medical therapy. Although we could not find a statistical difference in the sinonasal outcomes, our findings demonstrated that all groups of patients met the previously established MCID threshold for SNOT-22 after treatment with the combined therapy.[28,29] While some previous studies have also reported that the use of OCS had no statistical improvement in SNOT-22 scores,[30–32] there has not been significant discussion on the potential reasons this medication does not have a clinical effect. The possibility of glucocorticoid insensitivity has been described in both asthma and rhinology literature. Chense et al. looked at the role of IL-17 in patients with severe asthma; based on their literature review, they suggest that the presence of TH17 cells may be responsible for the steroid insensitivity seen in patients with low TH2 phenotype.[33] From a rhinologic perspective, dysregulation in glucocorticoid receptors and *S. aureus* exotoxin have been associated with steroid insensitivity.[34] The likelihood that a portion of our patients had *S. aureus* exotoxin is significant, as it has previously been reported that close to 70% of patients with positive *S. aureus* cultures also had *S. aureus* exotoxin present.[34]

Another possible explanation for the lack of improvement with the addition of OCS is that these patients had a type 3 inflammatory response, which could have led to glucocorticoid insensitivity. Our traditional understanding of CRS has categorized this disease into type 1 or type 2 endotype. Recently, more information has been published about a third type of inflammatory response, which is described as occurring in both CRS with and without nasal polyps, and is associated with TH-17, neutrophils, and protection against extracellular bacteria and fungi.[35,36] Stevens et al. found that a portion of the study's patients had a mixed inflammatory response; in their study from 2019, they found that patients with CRSwNP identified as having type-2 and type-3 endotypes were more likely to have purulent drainage.[37] The presence of nasal polyps and positive cultures in our patient population may represent this previously described mixed endotype, which could potentially explain the lack of improvement with corticosteroid treatments.

Several studies have looked at the use of OCS as a monotherapy for acute rhinosinusitis. A Cochrane review found that this treatment regimen had no statistically significant effect on clinical response rates compared with placebo.[38] Additionally, the included studies focused on the resolution of individual symptoms instead of overall effect on quality of life or endoscopic exams, and did not identify if an underlying CRS condition was present.[20,39] A recent study by Ho et al. showed that patients with eosinophilic CRSwNP and aspirin sensitivity tend to require systemic therapy with OCS and/or biologic agents after ESS because of acute exacerbation of the disease in the postoperative setting.[40] However, no study has reviewed INCS in addition to OCS in the immediate postoperative setting for CRSwNP patients with positive bacterial cultures.

The most recent International Consensus Statement on Allergy and Rhinology (ICAR) on rhinosinusitis recommended the use of short-term therapy with OCS as a part

of adequate medical management in CRSwNP but did not address the use of OCS in the setting of an acute exacerbation triggered by bacterial infection.[41] Most of the studies looking at OCS and acute rhinosinusitis did not use SNOT-22 and had a mean follow-up period of 2 to 8 weeks.[30,42–44] Our data showed no differences in the endoscopic and symptomatic outcomes between the two postoperative medical treatment protocols at 2-weeks, 4-weeks, and 4 to 6 months after ESS.

These results differ from a randomized, double-blind, placebo-controlled study from 2007, which evaluated the impact of perioperative OCS on the Sinus Symptom Questionnaire (SSQ) and LKS during the first 6 months after ESS. This study included patients with recalcitrant CRSwNP that were deemed appropriate candidates for ESS based on failure or refusal of maximal medical therapy. Maximal medical therapy in this study included 3 months of INCS and culture-directed antibiotics for 4 to 6 weeks, if indicated. However, the timing and number of patients who received oral antibiotics was not described. In the perioperative period all participants received saline sprays and INCS. Patients were further randomized to receive medical treatment with OCS or placebo. Similar to our study, they found that OCS had no effect on the postoperative symptoms score and showed a progressive improvement in the LKS. They did note a statistically significant improvement in the postoperative endoscopic score at 2-weeks, which differs from our study.[45] This difference in the LKS suggests that the presence of bacteria at the time of surgery may hinder positive response to OCS. Previous publications looking at bacterial exotoxins and steroid insensitivity support this hypothesis.[34] This information is valuable to clinicians when considering the risk and benefits of postoperative oral steroids.

Known to be a particularly challenging phenotype of CRS, AERD is a severe form of CRSwNP associated with adult-onset asthma and aspirin intolerance.[46,47] Almost 50% of AERD patients require a mean equivalent of 8 mg of oral prednisone, and up to 25% require intravenous corticosteroids every year to stabilize the disease.[48] Appropriate additional medical treatments, such as ESS, are needed to maintain control of the disease and decrease the recurrence of nasal polyps.[49,50] The use of INCS in AERD patients has already been shown to have a beneficial effect on endoscopic score.[19] Given the challenge in managing these patients post-operatively, we chose to look at this subgroup separately to determine the impact of combined therapy in the presence of a positive bacterial culture. Our results did not find a significant impact of postoperative combined therapy on either SNOT-22 or LKS in the AERD group when compared with CRSwNP patients without AERD.

As a retrospective study focused on the results of medical intervention, there are several intrinsic limitations to consider. For example, because of the retrospective nature of our study, a large number of patients without complete SNOT-22 and LKS data had to be excluded. Consequently, our small sample size limits the statistical power and may have obscured a difference in the SNOT-22 and LKS scores. However, our findings are consistent with other studies looking at both combined therapy and oral steroid treatment alone. The patients in our study had ESS at the onset of the study, which makes separating the surgery's effect from the medical therapy impossible. We noted that INCS irrigations provided a clinically meaningful benefit in patients with CRSwNP.[19] A future randomized study that focuses on this patient population and compares sinonasal outcomes in those treated with and without OCS would eliminate confounders and potentially identify a benefit of OCS therapy alone. The length of OCS use was not standardized in our study. A future study with standardized length and dosage of therapy may detect a difference between the two groups. The average number of patients with positive cultures at the time of surgery has not been reported to our knowledge, but this patient population is essential to understand because of the potential worsening postoperative course and long-term outcomes. Also, there is limited information on the risk of combining oral and topical corticosteroids. However, a recent meta-analysis looking at the adverse effects of INCS in the adult population found that the use of these medications is safe, with minimal risk of increased ocular pressure, hypothalamic-pituitary-axis dysfunction, or headache when compared with placebo.[51] Finally, future studies investigating the effect of different medical therapy based on endotype are important to prevent recalcitrant and recurrent disease.

Conclusion

Our study suggests that in a cohort of CRSwNP patients with recent bacterial infections, the postoperative use of combined OCS and INCS did not result in a statistical improvement of endoscopic and symptomatic outcomes, when compared with INCS irrigation alone. However, the change in the mean SNOT-22 score for both treatment groups was associated with a clinically significant difference based on the MCID.

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Conflict of Interests
The authors have no conflicts of interest to declare.

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