Can serum IgE or blood eosinophil count predict postoperative oral corticosteroid response in chronic rhinosinusitis with nasal polyps?*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by inflammatory mucosa and polyp formation in the paranasal sinuses. The study's primary objective was to evaluate the outcomes of postoperative oral corticosteroid (OCS) in treating patients with bilateral CRSwNP. The secondary objective was to determine whether preoperative serum IgE levels (sIgE) and/or blood eosinophil count (BEC) correlate with postoperative outcomes following OCS use.

Methods: Patients with bilateral CRSwNP (n=236) who underwent endoscopic sinus surgery (ESS) were randomly assigned to receive 15 mg OCS twice daily or a placebo for 2 weeks. We investigated the treatment effects based on the subjective visual analogue scale (VAS), Sino-Nasal Outcome Test 22 (SNOT-22), and objective Lund-Kennedy Endoscopy Score (LKES) over 6 months; subgroups were stratified preoperatively as follows: sIgE <150 IU/mL, sIgE ≥150 IU/mL, BEC $<0.39\times10^9$ cells/L, and BEC $\geq0.39\times10^9$ cells/L.

Results: A total of 193 participants completed the study up to the 6-month follow-up; no apparent linear relationship was noted between sIgE and BEC. No significant differences in scores were noted upon assessment of the VAS, SNOT-22, and LKES among the follow-up timepoints in the primary analysis. However, in the primary or subgroup analyses with sIgE or BEC, significant differences in the longitudinal scores of sleep dysfunction were observed at the 1-month follow-up.

Conclusion: Postoperative OCS did not significantly affect bilateral CRSwNP outcomes. sIgE levels and BEC may not be surrogate predictive biomarkers to assess the role of postoperative OCS use. OCS may increase the risk of transient sleep disturbance.

Key words: nasal polyps, paranasal sinuses, sino-nasal outcome test, sinusitis, visual analogue scale

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by persistent inflammation of the nasal mucosa and sinus along with polyp formation. Numerous potential pathophysiological characteristics and variants of CRSwNP have been described, including eosinophilic inflammation, neutrophilic inflammation, chronic bacterial infection, fungal infection, and aspirin-exacerbated respiratory disease [(1)]. Primary bilateral CRS is classified into different endotypes based on its association with type 2 or non-type 2 inflammatory patterns. Type 2 inflammation (eosinophilic) is driven by activation of the Th2 pathway, whereas non-type 2 (non-eosinophilic) inflammation involves Th1 or Th17 pathway [(2,3)]. CRSwNP is typically characterised by Th2-skewed eosinophilic inflammation with high levels of interleukin (IL)-4, IL-5, IL-13, and immunoglobulin E (IgE) [(4-7)].

Type 2 inflammation plays a crucial role in the development of allergic and inflammatory diseases and is closely related to serum IgE (sIgE) levels and blood eosinophil count (BEC) [8-11]. Serum IgE levels and BEC are reported to be significant biomarkers that show a positive correlation with both 22-item Sino-Nasal Outcomes Test (SNOT-22) scores and the recurrence rate of CRSwNP [12-15]. Furthermore, some researchers have also reported that the severity of nasal polyposis load and asthma are positively correlated with BEC levels [16,17]. Recently, the evidence of type 2 inflammation is also characterised by the presence of tissue eosinophils ≥ 10/high-power field (HPF), BEC ≥ 0.25 × 10^9 cells/L, or serum IgE (sIgE) ≥ 100 IU/mL, as defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines [7].

The relationship between eosinophilic chronic rhinosinusitis with nasal polyps (ECRSwNP) and asthma, known as united airway disease, is a complex and multifaceted concept. Evidence suggests that they may share common inflammatory pathways, which are skewed toward type 2 inflammation. Elevated sIgE level and increased BEC have been reported as biomarkers of phenotyping refractory asthma [18]. sIgE levels and BECs can also help guide treatment decisions and predict treatment response, such as the use of biological agents that target IgE (e.g., omalizumab) or eosinophils (e.g., mepolizumab, benralizumab, dupilumab) in individuals with asthma who have high levels of these biomarkers. However, their roles in predicting treatment response among CRSwNP patients remain unclear.
Oral corticosteroids (OCSs) and biological agents that target eosinophil-driven type 2 inflammation are often considered for controlling the eosinophilic subtype of CRS when symptom control is difficult to achieve. These treatments can reduce inflammation in the sinus mucosa, total symptom score, and decrease the size of nasal polyps [19-22]. OCSs are commonly used to manage CRSwNP owing to their low cost and easy administration. According to the Global Allergy and Asthma European Network rhinosinusitis cohort in 2019, a majority of patients with CRSwNP received treatment through the use of OCSs, reaching a reported rate of 61.3% [23]. While a significant proportion of the population uses OCSs to control CRSwNP, it is important to note that OCSs have side effects such as peptic ulcers, diverticulitis, congestive heart failure, and renal insufficiency. Nevertheless, very few studies have investigated the postoperative outcomes of OCS treatment for different CRSwNP endotypes [19,20,24-27].

Additionally, whether preoperative sIgE levels and BECs can predict postoperative OCS treatment outcomes in different endotypes CRSwNP has never been investigated. Therefore, we hypothesized that elevated preoperative sIgE levels and BEC can serve as biomarkers for predicting positive clinical outcomes following postoperative short-term OCS treatment in patients with bilateral CRSwNP. The aim of this study was to determine the overall outcome of postoperative oral steroids and investigate whether sIgE levels or BECs can serve as surrogate biomarkers for predicting the treatment outcomes of patients with bilateral CRSwNP. If proven helpful, the use of preoperative sIgE levels and BECs may enable timely decisions to be made regarding postoperative medical treatment strategies.

Materials and methods

Study design

This single-center, single-surgeon, prospective two-arm, double-blind, randomized, placebo-controlled trial (RCT) was conducted in the Department of Otorhinolaryngology of Mackay Memorial Hospital in Taipei, Taiwan.

Patient selection

Patients with bilateral CRSwNP who had unsuccessful maximal medical treatment for 3 months and subsequently received primary or revised bilateral ESS from January 2017 to December 2020 were enrolled. The exclusion criteria were age <18 years; and any of the following: cystic fibrosis, immunodeficiency, previous gastrointestinal disturbance, hepatic or renal impairment, pregnancy or lactation, and previous systemic corticosteroid treatment within 3 months preoperatively.
Of note, patients who had taken concomitant OCSs as maximal medical treatment were included in this study if the patient underwent ESS beyond 3 months after the initial steroid treatment (Figure 1).

Study treatment

Maximal medical therapy

All enrolled patients received amoxicillin-clavulanate (1 g twice daily [bid]) or doxycycline (200 mg per day [od] when allergic to penicillin) combined with antihistamines, local intranasal steroids, and high-volume nasal saline irrigation to restore sinus mucociliary function over three consecutive months. If a patient still had severe nasal congestion or anosmia for more than 1 month, they were supplemented with OCS 15 mg bid for 2 weeks to achieve maximal medication efficacy [7].

Study medication

The study medication consisted of oral prednisolone 15 mg bid over 2 weeks, which was commenced immediately post-ESS. A 1:1 simple randomisation list was generated using a software program, a copy of which was sent to the pharmacy of the hospital where the study medication was packed into capsules. Identical empty capsules were used as placebos.

The post-ESS care protocol

The post-ESS care protocol consisted of oral antibiotics, namely amoxicillin-clavulanate (1 g bid) or doxycycline (200 mg od) (if

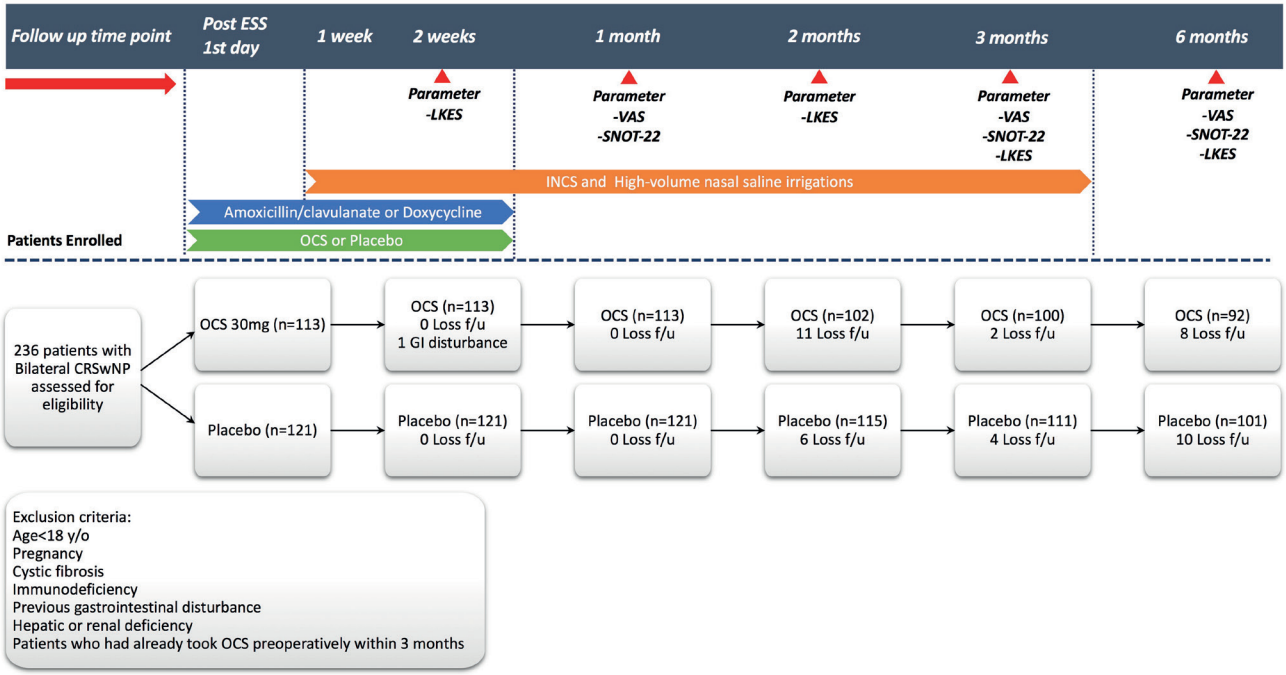

Figure 1. CONSORT flow diagram (Postoperative care protocol and follow-up timeline).

allergic to penicillin) for 14 days after ESS [7]. Intranasal corticosteroids (INCSs) were administered as follows: 100 µg of mometasone furoate od and high-volume nasal saline irrigations bid continuously from the beginning of postoperative week 1 until 12 weeks post-ESS. Intranasal debridement was performed at 1, 2, and 4 weeks postoperatively to remove any crust, discharge, and degraded packing materials (Figure 1).

Subgrouping patients of CRSwNP

Histopathological evaluation of tissue eosinophilia and Type 2 inflammation

Nasal polyp tissue specimens were collected during surgery. These tissue specimens were prepared with H&E staining and reviewed by the same pathologist at the pathology department under microscopy (400×magnification). A cut-off value of tissue eosinophil count >10/400×HPF was used as our diagnostic criteria for type 2 inflammation based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 criteria [7].

Subgrouping of patients with CRSwNP by sIgE levels

In patients with high sIgE, the risks of allergic rhinitis and asthma are high, which may subsequently increase sinus inflammation risk. Chung et al. reported that the positive predictive value (88%) of those with sIgE ≥150 IU/mL demonstrated a good level of discrimination in determining patients with allergen sensitisation diagnosed by in vitro testing [28]. Another study reported that IgE threshold levels ≥140 IU/ml and BECs greater than 80 cells/ml are likely to correlate with an atopic aetiology [29]. Therefore, we classified participants with sIgE levels <150 and ≥150 IU/mL into low- and high-IgE subgroups, respectively (Figure 2A).

Subgrouping of patients with CRSwNP by BEC

The use of H&E staining for endotyping CRSwNP has been standard practice in Western countries. Type 2 and non-type 2 inflammations are defined by the presence of >10 or <10 eosinophils/400×HPF, respectively. However, in Asian populations, the cut-off for tissue eosinophil counts is less clearly defined; reported estimates have ranged from 5 to >120 eosinophils/HPF [3,30,31]. Studies have reported that blood eosinophil assays can be used to predict disease progression in Asian populations [17,32]. Zhong et al. concluded that a statistically significant correlation was found between the number of H&E eosinophils and CRSwNP endotypes when the BEC cut-off value was set at 0.39×10^9 cells /L in Asian populations. Thus, we classified our patients with BECs less than or greater than 0.39×10^9 cells/L into low- and high-BEC subgroups, respectively (Figure 2B) [33].

Primary outcome parameters and subgroup analyses

Primary outcome parameters

For primary outcome measurements, participants' total symptom severity scores were estimated using the subjective Visual Analog Scale (VAS), SNOT-22, and objective Lund-Kennedy Nasal Endoscopy Score (LKES).

VAS scores

For the VAS scores, we assessed nine major complaints based on symptom severity (i.e., smell, facial pressure, nasal obstruction,

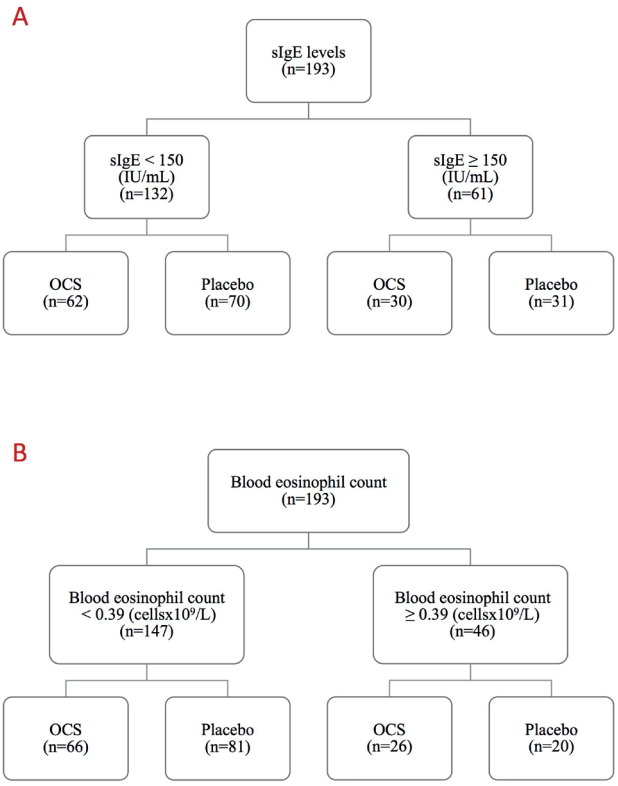

Figure 2. (A) Subgrouping of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) by total sIgE level. (B) Subgrouping of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) by blood eosinophil count.

head fullness, cough, headache, foul odour, post-nasal drip, and rhinorrhea), which were each assigned points between 0 and 10 to reach a maximum out of 90 points [7].

SNOT-22 total scores

The SNOT-22 is a validated patient-reported test, in which 22 items are assessed on a scale of 0 to 5 for symptom severity to reach a maximum score of 110 [34].

SNOT-22 subdomain scores

In addition to the overall SNOT-22 scores, we recorded scores for each of the five SNOT-22 subdomains that are affected differently by treatment namely rhinological (needing to blow nose, sneezing, runny nose, thick nasal discharge, sense of smell, and a blockage of the nose), extranasal rhinological (cough, post-nasal discharge, and thick nasal discharge), and ear-facial symptoms (sneezing, ear fullness, dizziness, ear pain, and facial pain) as well as psychological (waking up tired, fatigue, reduced productivity, reduced concentration, frustration, sadness, and embarrassment), and sleep dysfunction (difficulty falling asleep, waking up at night, lack of a good night's sleep, waking up tired, and fatigue) [34].

5.1.4 LKES

The LKESs were employed to assess objective outcomes related to polyps (0=none, 1=middle meatus only, 2=beyond the middle meatus), oedema (0=absent, 1=mild, 2=severe), discharge (0=none, 1=clear and thin, 2=thick and purulent), postoperative scarring (0=absent, 1=mild, 2=severe), and postoperative crusting (0=absent, 1=mild, 2=severe). Bilateral scores were combined and then averaged to provide a final score out of 10 points [35]. The average LKES was calculated by two individual otolaryngologists blinded to the treatment.

Subgroup analyses

Subgroup analyses were performed to evaluate the outcomes of patients with CRSwNP according to the sIgE and BEC levels. The same parameters as primary outcome parameters were analysed (eg: VAS, SNOT-22 total scores, SNOT-22 subdomain scores, and LKES).

Outcome follow-up time points

The VAS and SNOT-22 scores were evaluated to assess subjective outcomes at baseline, and at 1, 3, and 6 months post-ESS. The LKES was used to assess objective outcomes at baseline, 2 weeks, and 2-, 3-, and 6-months post-ESS (Figure 1) [19,20,24,36].

Safety and adverse events assessment

Potential common adverse events were assessed per the observation criteria based on the label list of OCSs prescribed by the US Food and Drug Administration. These adverse events range from short- to long-term side effects, which include gastrointestinal discomfort (e.g., secondary to peptic ulcers or diverticulitis), fluid retention, congestive heart failure, hypertension, renal insufficiency, and osteoporosis [7,19,37]. New-onset adverse events in the OCS group were assessed in the outpatient clinic over 30 days of follow-up. Given that all patients included in the study had previously undergone maximal medical therapy, we carefully considered the adverse effects of amoxicillin-clavulanate and doxycycline, such as diarrhea, headache, nausea, and vomiting. We avoided antibiotics that had previously caused such adverse reactions during the postoperative period.

Statistical analysis

Sample size calculation

The sample size was calculated based on studies demonstrating that the SNOT-22 scores and LKES would improve post-ESS in primary outcome and subgroup analyses [24,27,38,39]. Based on a pilot study of 40 patients with bilateral CRSwNP using SNOT-22 and LKES at 3 months post-ESS as preliminary outcome evaluation, we found that the ratios of low- to high-IgE and -BEC case numbers were 2.1:1 and 3.4:1 in the subgroup analyses, respectively. To obtain a 90% effect size with a 10% margin for a noninferiority trial that would aim for a 6-month patency, 20

Table 1. Demographic data for the CRSwNP postoperative oral corticosteroid and placebo groups.

	All patients (n=193)		
	OCS (n=92)	Placebo (n=101)	p
Sex (Male/Female)	63/29	79/22	0.14
Age (years)	45.00(33.00-54.00)	47.00(36.00-58.00)	0.42
Smoking	23(25%)	21(20%)	0.49
Previous-OP	22(24%)	23(22%)	0.86
Asthma	16(17%)	11(10%)	0.21
Drug allergy	14(15%)	7(7%)	0.10
Tissue eosinophilia (> 10/HPF)	63(68%)	73(72%)	0.33
sIgE (IU/mL)	82.36(20.53-191.56)	59.40(18.41-191.00)	0.83
LM Score	16.00(12.00-19.50)	15.00(12.00-19.00)	0.66
BNC (cells × 10^9/L)	4.39(3.62-5.56)	4.62(3.60-5.44)	0.84
Blood neutrophil %	59.35(53.70-66.35)	57.10(51.90-64.70)	0.30
BEC (cells ×10^9/L)	0.20(0.09-0.41)	0.20(0.12-0.34)	0.52
Blood eosinophil %	2.60(1.10-5.55)	2.40(1.70-4.80)	0.55
BBC (cells × 10^9/L)	0.05(0.04-0.07)	0.05(0.04-0.07)	0.32
Blood basophil %	0.70(0.50-0.90)	0.70(0.50-0.89)	0.12
Baseline VAS	35.00(22.00-46.00)	37.00(26.00-51.00)	0.16
Baseline SNOT-22	49.00(31.50-58.00)	45.00(30.00-62.00)	0.92
Baseline LKES	3.50(2.63-4.00)	3.25(2.75-3.75)	0.75

Values are presented as median with interquartile range (IQR). * =Statistically significant difference between the study groups. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; OCS, oral corticosteroid; LM score, Lund–Mackay Computed Tomography Score; BNC, blood neutrophil count; 10/HPF, ten per 400× high-power field; BEC, blood eosinophil count; BBC, blood basophil count; VAS, Visual Analog Scale; SNOT-22, 22-item Sino-nasal Outcome Test Scores; LKES, Lund-Kennedy Nasal Endoscopy Score.

patients per treatment group or 176 patients in total would be needed (alpha=5%, power=80%). Considering that the average dropout rate across clinical studies is 20%, we aimed to recruit 220 patients [40].

Data analysis

A paired t-test (two-tailed) was used to compare paired parametric data. Unpaired comparisons of continuous variables were performed using the independent t-test or Mann–Whitney U test. A one-way analysis of variance was used to compare continuous variables in the subgroup analysis. Unpaired comparisons of categorical variables were performed using the Pearson chi-square test or Fisher exact test (when the expected count was <5). Statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS (version 21.0; IBM Corp., Armonk, NY, USA).

Ethical considerations

The study design and clinical trial protocol (IRB- MMHIS210e) were approved by the Institutional Review Board (Supplement 1). All participants provided written informed consent prior to taking part in the clinical trial, which was conducted in accordance with the tenets of the Declaration of Helsinki.

Results

A total of 193 participants, divided into the OCS (n=92) and placebo (n=101) groups, completed the study up to the 6-month follow-up visit (Figure 1). Both groups exhibited comparable baseline and clinical characteristics (Table 1). The ratio of the number of type 2 inflammation to non-type 2 inflammation was 136:57. Type 2 inflammation accounted for nearly 70% of the participants. In the BEC subgroups analysis, high BECs were statistically significantly different to tissue eosinophilia >10/HPF (p=0.001). The high-BEC group exhibited a higher prevalence of asthma comorbidity than did the low BEC subgroup (26% vs 10%) (p=0.01) (Table 2). Moreover, no apparent linear relationship was noted between total sIgE and BEC (r^2=0.015, p=0.091; Figure 3). Of the 92 patients who received OCSs, only one experienced gastrointestinal discomfort and no patients exhibited serious side effects within 30 days of surgery. Compared with the placebo group, the OCS group did not exhibit an increase in the incidence of short-term adverse events.

Table 2. Baseline characteristics of the different serum IgE and blood eosinophil count subgroups.

	sIgE < 150 IU/mL (n=132)	sIgE ≥ 150 IU/mL (n=61)	p	BEC < 0.39 cells × 10^9/L (n=147)	BEC ≥ 0.39 cells × 10^9/L (n=46)	p
Sex (Male/Female)	97/35	45/16	0.55	110/37	32/14	0.29
Age (years)	43.50(34.00-54.00)	50.00(37.00-56.00)	0.22	47.00(34.00-58.00)	43.00(37.00-53.00)	0.66
Smoking	31(23%)	13(21%)	0.85	36(24%)	8(17%)	0.42
Previous-OP	31(23%)	14(23%)	0.54	35(23%)	10(21%)	0.47
Asthma	16(12%)	11(18%)	0.27	15(10%)	12(26%)	0.01*
Drug allergy	13(10%)	8(13%)	0.61	13(9%)	8(17%)	0.11
Tissue eosinophilia (> 10/HPF)	90(68%)	46(61%)	0.19	92(63%)	44(96%)	0.001*
OCS/Placebo use	62/70	30/31	0.87	66/81	26/20	0.18
LM Score	16.00(12.00-19.50)	15.00(12.00-19.00)	0.79	53.00(16.64-187.11)	109.25(40.80-199.30)	0.27
BNC (cells × 10^9/L)	4.81(3.86-5.65)	4.21(3.32-5.15)	0.47	4.63(3.66-5.77)	4.28(3.54-5.30)	0.02*
Blood neutrophil %	58.95(53.15-66.10)	56.20(50.90-65.00)	0.43	61.00(54.70-66.80)	52.22(48.40-55.90)	0.001*
BEC (cells ×10^9/L)	0.17(0.09-0.37)	0.26(0.14-0.37)	0.77	0.15(0.09-0.25)	0.60(0.48-0.76)	0.001*
Blood eosinophil %	2.15(1.20-4.80)	3.70(2.00-5.70)	0.21	2.00(1.10-3.20)	7.45(6.50-9.60)	0.001*
BBC (cells × 10^9/L)	0.05(0.04-0.07)	0.05(0.04-0.06)	0.93	0.05(0.03-0.06)	0.07(0.05-0.10)	0.001*
Blood basophil %	0.70(0.50-0.90)	0.70(0.50-0.90)	0.49	0.60(0.50-0.80)	0.90(0.70-1.20)	0.001*
Baseline VAS scores	36.50(26.00-50.50)	35.00(25.00-45.00)	0.35	35.00(24.00-49.00)	38.00(30.00-44.00)	0.64
Baseline SNOT-22 scores	48.00(31.00-63.00)	47.00(30.00-59.00)	0.44	45.00(29.00-61.00)	53.50(41.00-61.00)	0.14
Baseline LKES	3.50(3.00-4.00)	3.25(2.50-4.00)	0.18	3.25(2.50-3.75)	3.25(2.75-3.75)	0.92

Primary outcome analysis in all patients

No significant differences in scores were noted upon assessment of the VAS, SNOT-22, and LKESs among the follow-up timepoints in the primary analysis (Supplement 2).

Subgroup analyses

Stratification analysis by serum IgE levels

After stratification of all patients into two subgroups based on their preoperative sIgE levels, 132 (68%) and 61 (32%) patients were included in the low and high IgE subgroups, respectively. sIgE levels ranged from 0.54 to 3287 IU/mL in our samples. The baseline and clinical characteristics of these subgroups are listed (Table 2).

High- and low-IgE subgroup analyses

No significant differences were noted in the VAS scores, SNOT-22 scores, and LKESs among the follow-up timepoints in the high- or low-IgE subgroup analyses (Supplement 3).

Stratification analysis by preoperative BEC

After stratification of all patients into two subgroups based on their preoperative BECs, 147 (76%) and 46 (24%) patients were included in the low- and high-BEC subgroups, respectively. Among our patients, the BEC ranged from 0.01×10^9 to 1.81×10^9 cells/L. The baseline and clinical characteristics of these subgroups are listed in Table 2.

High- and low-BEC subgroup analyses

No significant differences were noted in the VAS, SNOT-22, and LKESs among the follow-up timepoints in the high- and low-BEC subgroup analyses (Supplement 4).

SNOT-22 score subdomain analysis

In longitudinal analysis of the SNOT-22 subdomains, there were no significant differences between the OCS and placebo groups in terms of the scores for the rhinological, extranasal rhinological, ear and facial symptoms, and psychological dysfunction subdomains. However, when subgroups based on different levels of sIgE and BEC were examined, significant differences were observed in the longitudinal scores for sleep dysfunction between the OCS and placebo groups at the 1-month follow-up. The primary analysis showed a significant difference in the SNOT-22 sleep dysfunction subdomain scores when comparing the changes of baseline to one month scores (OCS : 3.37±6.77, Placebo : 6.97±5.05 ; p=0.01). Additionally, the subgroup analyses also revealed significant differences in the SNOT-22 sleep dysfunction subdomain scores among the low-sIgE subgroup (OCS : 3.61±6.85 , Placebo : 7.30±5.22 ; p=0.01), high-sIgE subgroup (OCS : 2.87±6.69 , Placebo : 6.23±4.63 ; p=0.02), low-BEC subgroup (OCS : 3.30±6.51 , Placebo : 6.40±4.80 ; p=0.01), and high-BEC subgroup (OCS : 3.54±7.53 , Placebo : 9.30±5.45 ; p=0.01) when comparing the changes of baseline to one month scores. These findings suggest that OCSs may have a temporary

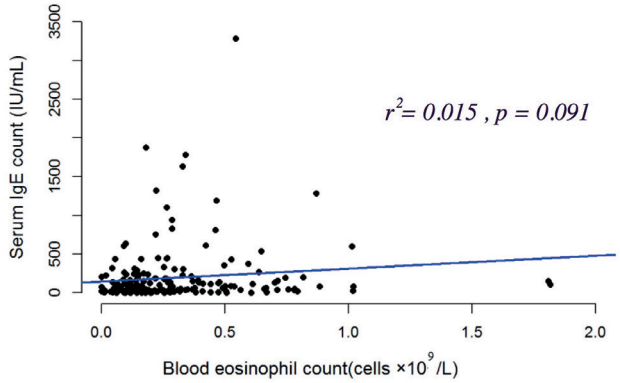

Figure 3. Linear regression analysis of the correlation between total sIgE level and blood eosinophil count (BEC); $r^2 = 0.015$, $p = 0.091$.

effect on sleep dysfunction (Figures 4A-C). However, it is important to note that these transient sleep disturbances caused by OCS usage disappeared after the treatment period and did not have a lasting impact at 3,6- month follow-up. (Supplement Data 2, 3, 4)

Safety assessment

In the present study, no significant adverse effects were noted, and the study medication did not result in higher rates of short-term adverse events than did placebo. From the 92 patients who received OCS treatment, only one experienced gastrointestinal discomfort with the onset of peptic ulcers, and no other adverse events were reported.

Discussion

Pathophysiologically, both high BEC and sIgE levels play critical roles in the pathogenesis of airway inflammation, resulting in paranasal mucosal tissue hyperplasia and contributing to the severity of nasal polyp loads and recurrence in CRSwNP patients. As systemic corticosteroids may be a beneficial adjunct to intranasal corticosteroid treatment in patients with CRSwNP [7], it is important to explore the potential of high BECs and sIgE levels in predicting the response to OCSs in such patients. There have been only two RCTs in the literature addressing the postoperative use of systemic steroids in patients with CRSwNP. Both studies reported no significant difference in SNOT-22 or VAS scores up to 6-month follow-up [27,37]. However, one study did demonstrate a significant improvement in Lund-Kennedy endoscopic score in the systemic steroid group after stratifying by eosinophilia counts status at 3 months. Given these findings, the current study aimed to investigate the overall postoperative systemic steroid effects in a large randomised controlled trial and for the first time, evaluate the potential differential effects in different subgroups based on sIgE and BEC stratification. Herein, the subjective parameters (self-rated nasal health measured using VAS and SNOT-22 scores) and objective parameters

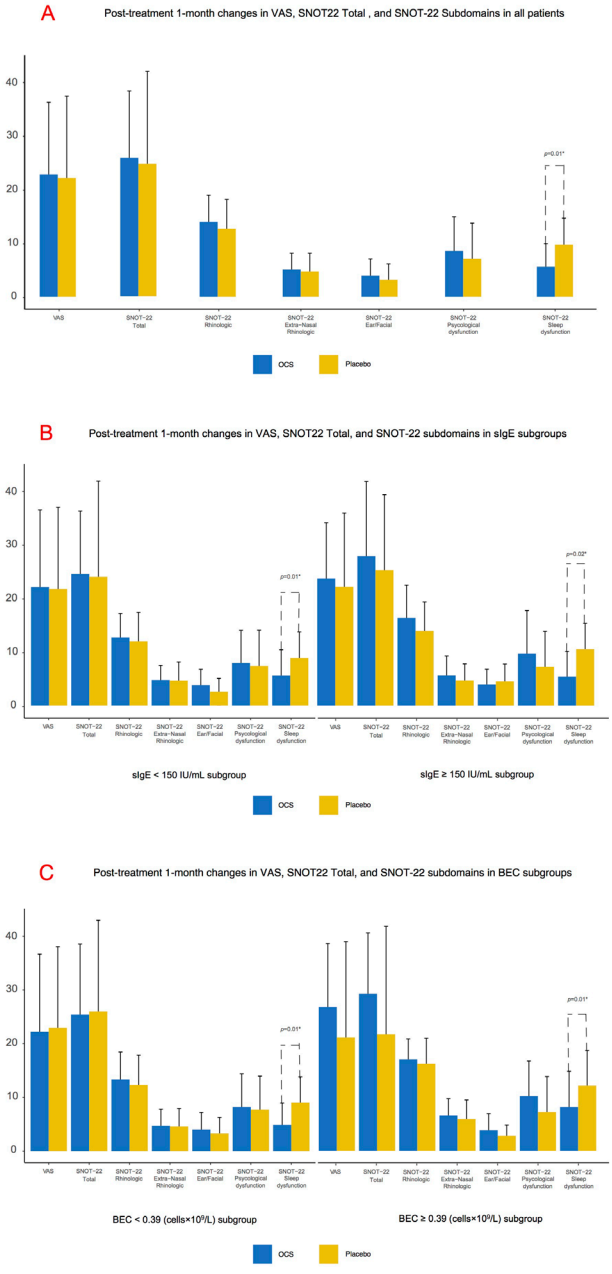

Figure 4. (A) Post-treatment 1-month changes in VAS, SNOT22 Total, and SNOT-22 Subdomains in all patients, (B) Post-treatment 1-month changes in VAS, SNOT22 Total, and SNOT-22 subdomains in sIgE subgroups, (C) Post-treatment 1-month changes in VAS, SNOT22 Total, and SNOT-22 subdomains in BEC subgroups.

(LKESs) improved in both groups over time, yet they did not differ significantly between the OCS and placebo groups. Notably, this result indicates that short-term OCS use may temporarily affect sleep quality in patients (Supplements 2-4, and Figures 4A-C). However, no particular effect on sleep was noted after 3 and 6 months following OCS cessation. Nonetheless, sleep disturbances may be caused by OCS use in patients with CRSwNP, particularly in those with pre-existing sleep disorders.

The roles of systemic IgE-dependent inflammation in the pathophysiology of allergic rhinitis have been highlighted. Atopy is a negative prognostic factor in patients with CRSwNP; however, the allergy - CRSwNP relationship remains controversial [5,6]. Hussien et al. reported that elevated sIgE levels have a significant positive correlation with the SNOT-22, Lund–Mackay CT (LM) score, and nasal polyps recurrence rate ($p<0.001$, $p=0.005$, and $p=0.032$, respectively) [12]. However, our results are consistent with those of Newman et al. and Lemos et al., which assigned participants to different subgroups based on sIgE levels and showed no significant difference in the Rhinosinusitis Disability Index (RSDI) and LM scores [41,42]. Herein, low and high sIgE levels were not directly associated with the preoperative VAS, SNOT-22, LKES, and LM scores ($p=0.35$, 0.44, 0.18, and 0.79, respectively) (Table 2). Furthermore, different sIgE levels were not correlated with the outcome in those who received postoperative OCSs (Supplement 3).

In Asian countries, 20% to 63% of patients with CRSwNP have type 2 inflammation; our study reported that nearly 70% of participants exhibited type 2 inflammation by H&E staining. Contrastingly, more than 80% of patients with nasal polyps present with type 2 inflammatory signatures in Western countries [4]. In 2021, Zhong et al. reported that BEC can be used to distinguish CRSwNP endotypes in a Chinese population by using a BEC cut-off value of 0.39×10^9 cells/L and indicated that a BEC $>0.73\times10^9$ cells/L could predict polyp recurrence in patients with Eosinophilic CRSwNP [33]. Considering that our study population's ethnicity and geographical region were similar to those of the study population of Zhong et al., we used their criteria as the basis for the subgroup analysis of BEC. Hu et al. also reported that a BEC cut-off $>0.21\times10^9$ cells/L yields a sensitivity and specificity of 74.2% and 86.5%, respectively, for an eosinophilic CRSwNP diagnosis [32]. Furthermore, Moriyama et al. have recommended the administration of postoperative OCSs to prevent CRSwNP recurrence in patients with concurrent asthma and BECs $\geq 0.52 \times 10^9$ cells/L [17]. These studies corroborate the routine use of BEC for preoperative workup of patients with CRSwNP and can provide accurate prognostic information. Herein, the high-BEC subgroup exhibited a higher prevalence of comorbid asthma than the low-BEC subgroup ($p=0.01$) (Table 2). These results are compatible with the study conducted by Drake et al., which revealed that BEC may be a useful diagnostic biomarker for asthma concurrent with ECRSwNP [16]. In line with the findings of sIgE subgroup analysis, our study also found no significant differences in the preoperative VAS scores, SNOT-22 scores, LKESs, and LM scores between the low-BEC and high-BEC subgroups ($p=0.64$, 0.14, 0.92, and 0.27, respectively) (Table 2). Furthermore, no correlation was observed between different BEC subgroups and the outcomes when postoperative OCSs were used (Supplement 4).

We also utilized the sIgE and BEC cutoff values (BEC $\geq 0.25 \times 10^9$ cells/L or sIgE $\geq$ 100 IU/mL) defined by EPOS 2020 for Type 2 inflammation to investigate the impact of short-term postoperative OCS administration on VAS scores, SNOT-22 scores, and LKESs in different subgroups based on different sIgE levels and BECs. In both primary and subgroup analyses, these outcome parameters did not show any significant differences (Supplements 5 and 6).

Patients with CRSwNP who are identified as having a type 2 immune response often have higher polyp recurrence rates and difficult-to-treat asthma [16]. Notably, comorbid asthma incidence is typically 40% to 67% in patients with CRSwNP in Western countries; yet, the incidence thereof was only 14% in our study [43,44]. A literature review of CRSwNP with asthma concurrence rates revealed that our result was comparable to that of Korea (11.8%), China (14.8%), Japan (15.7%), and India (12.9%) [45-48], which may reflect geographic and racial differences. Besides, a study conducted in Austria also reported a low asthma concurrence rate with CRS (6.6%) [49]. Owing to the low concurrent rate of asthma in our study (n=27, 14%), an asthma subgroup analysis could not be performed in our OCS treatment results. Large-scale studies in this field are warranted to assess the pathophysiological relationships among CRSwNP, asthma, BEC, and IgE levels in the future.

Strengths and limitations

To the best of our knowledge, this is the first study to investigate the postoperative effects of OCS use in a large sample size and perform simultaneous sIgE and BEC subgroup analyses. However, it does have some limitations. Firstly, CRSwNP is associated not only with BEC and sIgE but also with eosinophilic cationic protein, IL-4, -5, and -13 as an eosinophilic inflammation mediator. Therefore, we analysed only one biomarker - sIgE or BEC - neither of which can completely predict postoperative OCS effects. Hence, the use of BEC or sIgE in combination with other factors of high prognostic value warrants further study.

Conclusion

Herein, postoperative short-course moderate-dose OCSs did not affect SNOT-22, VAS, or LKES in participants with CRSwNP. Serum IgE and BEC may not be surrogate predictive biomarkers for outcomes of postoperative OCS use in patients with CRSwNP. Significant differences in the longitudinal scores of sleep dysfunction were observed at the 1-month follow-up. The potential benefits of OCSs are limited; therefore, the risk of complications must be considered in patients with sleep disorders.

Acknowledgement

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Conflicts of interest

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

KHS: Completed the final data collection and analysis; revised and wrote the paper with input from all authors. JYJ: Major revision of this paper; verified the analytical methods and results; discussed the results and commented on the manuscript. PYH: Major revision of this paper; revised the tables and figures; discussed the results and commented on the manuscript. JCYL: Drafting (introduction, study design and method, results, discussion), data collection, and data analysis for the initial report; revised the tables and figures. WHH: Developed the theoretical formalism and performed the surgery; provided critical feedback and helped shape the manuscript. PSW: Performed the nasal polyps tissue pathology exam; provided critical feedback and helped shape the manuscript. YPW: Supervised the project, developed the theoretical formalism, and performed the surgery; verified the analytical methods and results; discussed the results and commented on the manuscript.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplement 1. Clinical trial protocol.

Mackay Memorial Hospital
Trial Protocol (IRB- MMHIS210e)

Protocol title
Can Serum IgE or Blood Eosinophil Count Predict Postoperative Oral Corticosteroid Response in Chronic Rhinosinusitis with Nasal Polyps ?

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ABSTRACT

Importance Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by inflammatory mucosa and polyp formation in the paranasal sinuses. Blood biomarker–based diagnosis is simpler and more cost effective than traditional nasal biopsy diagnosis. Long-term studies have identified several biomarkers for CRSwNP diagnosis, endotyping, treatment response, and recurrence risk.

Objective The primary objective was to evaluate the patient reported outcomes after a 2 week course of postoperative oral corticosteroid (OCS) in treating patients with CRSwNP. The secondary objective was to determine whether preoperative serum IgE and/or blood eosinophil count (BEC) correlate with postoperative patient reported outcomes after a 2 week course of postoperative OCS in treating patients with CRSwNP.

Design Randomized controlled trial

Setting Single center

Participants 236 patients with bilateral CRSwNP for whom medical treatment failed and who underwent endoscopic sinus surgery (ESS) from January 2017 to December 2020 were enrolled.

Interventions Patients were randomly assigned to receive 15mg OCS twice daily or a placebo for 2 weeks after ESS. We investigated the treatment effects on the basis of visual analog scale (VAS) scores, Sino-Nasal Outcome Test 22 (SNOT-22) scores, and Lund-Kennedy nasal endoscopy scores (LKESs) over 6 follow-up months in all patients, and subgroups were stratified preoperatively as follows: serum IgE < 150 IU/mL, serum IgE ≥ 150 IU/mL, BEC < 0.39×10^9 cells/L, and BEC > 0.39×10^9 cells/L.

Main outcomes and measures For primary outcome measurement, patients' total symptom severity scores were estimated using their VAS and Sino-Nasal Outcome Test-22 (SNOT-22) scores.For VAS scores, we assessed nine major complaints (i.e., smell, facial pressure, nasal obstruction, head fullness, cough, headache, foul odor, post nasal drip, and rhinorrhea) on a VAS of 0 to 10 on the basis of symptom severity, for a maximum total score of 90.
SNOT-22 is a validated patient-report sinonasal outcomes measure, in which 22 items are assessed on a scale of 0 to 5 on the basis of symptom severity, for a maximum total score of 110.
In addition to the overall SNOT-22 scores, we recorded scores for each of the five SNOT-22 subdomains that are differentially affected by treatment: rhinologic symptoms (needing to blow nose, sneezing, runny nose, thick nasal discharge, sense of smell, blockage of nose), extranasal rhinologic symptoms (cough, postnasal discharge, thick nasal discharge), ear-facial symptoms (sneezing, ear fullness, dizziness, ear pain, facial pain), sleep dysfunction (waking up tired, fatigue, reduced productivity, reduced concentration, frustration, sadness, embarrassment), and psychological dysfunction (difficulty falling asleep, waking up at night, lack of a good night's sleep, waking up tired, fatigue).
The LKES was employed to assess secondary outcomes related to polyps (0 = none, 1 = middle meatus only, 2 = beyond the middle meatus), edema (0 = absent, 1 = mild, 2 = severe), discharge (0 = none, 1 = clear and thin, 2 = thick and purulent), postoperative scarring (0 = absent, 1 = mild, 2 = severe), and postoperative crusting (0 = absent, 1 = mild, 2 = severe). Bilateral scores were combined and then averaged to provide a final score, with 10 being the maximum. To avoid errors in the judgment of LKES, the final LKES was calculated by two otolaryngologists blinded to the treatment protocol and then averaged. The discrepant scores were reviewed by a third investigator, with the mean of all reviewers' scores considered the final assigned score.

Follow-up Time points
Nasal symptom outcomes based on VAS and SNOT-22 scores were recorded before and 1, 3, and 6 months after ESS. LKESs were recorded before ESS as well as 2 weeks and 2, 3, and 6 months after surgery.

1. PURPOSE

A. In layperson's language state the purpose of the study in 3-5 sentences.

After patients with chronic rhinosinusitis with polyps undergo sinus surgery, they are typically instructed to take oral steroids for several days to weeks. However, there is limited data to suggest this is a beneficial practice, and oral steroids have been shown to have significant and unpleasant side effects. This study will investigate whether there is truly evidence based utility to the use of steroids after sinus surgery.

B. State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by persistent inflammation of the nasal mucosa and sinus along with polyp formation. Its symptoms include nasal obstruction, nasal discharge, facial pain, and olfactory dysfunction.

In the management of postoperative impaired mucociliary function, oral corticosteroid(OCS) can not only inhibit eosinophil recruitment to the inflammation site but also reduce the levels of eosinophilic cationic protein, interleukin (IL) 4, IL-5, and IL-13 in sinus tissue. Few studies have investigated the postoperative OCS requirements for different CRSwNP endotypes; however, no consensus has been reached on the efficacy of postoperative OCS use.

The aim of conducting this study, therefore, is to evaluate the effects of postoperative oral corticosteroid (OCS) in treating patients with CRSwNP and to determine whether serum immunoglobulin E (IgE) level and blood eosinophil count (BEC) are surrogate predictors of postoperative OCS use.

This study would contribute a wealth of important data to the field of Rhinology and the management of CRSwNP. The role of steroids in the postoperative period would be further elucidated, providing randomized controlled data with which providers may make informed therapeutic decisions. In summary, the results of this study have significant potential to influence current practice and management guidelines.

C. Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment).

The purpose of the study is to test the efficacy of a medication in individuals with CRSwNP, which is not a disease known to be accurately duplicated in any other model.

2. STUDY PROCEDURES

A. Please summarize the research procedures, screening through closeout, which the human subject will undergo.

Screening

Patients who have been recommended to undergo endoscopic sinus surgery by our department will be recruited for the study and informed of its purpose pre-operatively. Visual analog scale (VAS) scores, SNOT- 22 scores and Lund-Kennedy endoscopic exam scores will be recorded in their medical records. This is the same protocol performed for all patients seen in our clinic regardless of their enrollment in the study.

Surgical indications and preoperative diagnostic workup

On the basis of our clinical guidelines, patients with CRSwNP who had undergone unsuccessful maximal medical therapy for 3 months were eligible for this RCT. These patients are typically tested preoperatively for allergies (on the basis of patient history and laboratory data) and asthma (on the basis of patient history, spirometry, and a bronchial challenge test followed by confirmation by a respiratory specialist at our hospital). For the included patients, the preoperative diagnostic workup comprised nasal endoscopy with rigid 0° and 30° optical instruments (Ø = 4 mm), BECs and blood basophil counts (percentages and absolute values), serum IgE levels, and paranasal high-resolution computed tomography (CT) with calculation of Lund–Mackay endoscopic scores (LKESs). All laboratory tests were performed before surgery at the same laboratory (EIA Unit, Laboratory Medicine Service, Mackay Memorial Hospital).

Maximal medical therapy

All enrolled patients received amoxicillin-clavulanate (1 g twice daily) or doxycycline (200 mg per day when allergic to penicillin) combined with antihistamine, local intranasal steroids and high-volume nasal saline irrigation to restore sinus mucociliary function over the course of 3 month. If a patient still had severe nasal congestion or anosmia for more than one month, they were also supplemented with 15mg OCS twice daily for 2 weeks to achieve maximal medication efficacy.

Randomization and treatment groups

The patients that wish to participate will be randomized into two treatment arms by our nurse practitioner based on a random number generator. They will receive one of the following post-operative regimens:

1) oral corticosteroid (treatment) + steroid spray (treatment)
2) oral placebo (control) + steroid spray (treatment) .

Surgery

Routine endoscopic sinus surgery will be performed per our institution's standard protocol. In this step there will be no difference in treatment from those patients not enrolled in the study.

Postoperative care protocol

Post-ESS care protocol for the patients with CRSwNP comprised oral antibiotics amoxicillin-clavulanate (1 g twice daily) for 14 days after ESS. If an allergic reaction to penicillin occurred, doxycycline (200 mg per day) was administered. Intranasal corticosteroids (INCSs) were administered as follows: 100 μg of mometasone furoate administered once per day and high-volume nasal saline irrigations two times per day beginning at postoperative week 1 and continuing until 12 weeks after ESS. Intranasal debridement was performed 1, 2, and 4 weeks postoperatively to remove crust, discharge, and degraded packing materials .

Statistical analysis

A paired t test (two-tailed) was used for comparisons of paired parametric data. Unpaired comparisons of continuous variables were performed using the independent t test or Mann–Whitney U test. One-way analysis of variance was used to compare continuous variables in subgroup analysis. Unpaired comparisons of categorical variables were performed using the Pearson chi-square test or Fisher exact test (when the expected count was <5). A p of <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS (version 21.0; IBM, Armonk, NY, USA).

Sample size calculation

Sample size was calculated based on studies demonstrating that SNOT-22 scores and Lund-Kennedy scores would improve after ESS as primary and secondary outcomes evaluation. Based on a pilot study of 40 patients with bilateral CRSwNP which using SNOT-22 scores and Lund-Kennedy scores at 3 month after ESS as preliminary outcome evaluation. We found the ratio of low-IgE to high-IgE case numbers was 2.1:1 and the ratio of low-BEC to high-BEC case numbers was 3.4:1 in the subgroup analysis. For a noninferiority trial with regard to 6-month patency with a 90% effect size of and a 10% margin, 20 patients per treatment group or 176 patients total would be needed (alpha = 5% , power = 80%) . Considering that the average dropout rate across clinical studies is 20%, we aimed to recruit 220 patients.

B. Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

This study does not seek to evaluate a novel research procedure. Rather, we endeavor to determine if a procedure already in place nearly universally is, in fact, beneficial, as there is a distinct lack of evidence of suggest so. Overall, we are investigating a procedural method that will have fewer side effects than the currently accepted practice.

C. State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

N/A

D. Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

All reasonable alternatives are included as a treatment arm in this study. There is no standard of care that is being withheld from patients in any group.

E. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes, patients will stop all experimental therapies at the 2 weeks mark. They will then be placed on the typical post-operative regimen, which includes a nasal steroid spray and twice daily saline irrigations. They will continue to be followed in our clinic after the 4 week mark, and their therapies tailored to their current symptoms and the endoscopic appearance of the nasal cavity.

3. BACKGROUND

A. Describe past experimental and/or clinical findings leading to the formulation of the study.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by persistent inflammation of the nasal mucosa and sinus along with polyp formation. Its symptoms include nasal obstruction, nasal discharge, facial pain, and olfactory dysfunction. 1Numerous potential pathophysiological characteristics and variants of CRSwNP have been described; they include eosinophilic inflammation, neutrophilic inflammation, chronic bacterial infection, fungal infection, and aspirin-exacerbated respiratory disease. CRSwNP is classified into different endotypes on the basis of its association with type 2 or non–type 2 inflammatory patterns. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines, CRSwNP is classified into two endotypes on the basis of the presence of tissue eosinophils: eosinophilic CRSwNP (ECRSwNP) and non-eosinophilic CRSwNP (NECRSwNP) [1]. ECRSwNP has been defined as an inflammatory disease frequently associated with type 2 inflammation and IgE sensitization to atopy [2,3]. Drake et al. indicated that CRSwNP and BEC are positively correlated. Thus, BEC may be a useful biomarker to test for eosinophilia and asthma in patients with CRSwNP [4]. Brescia et al. also revealed that preoperative BEC may be related to CRSwNP recurrence [5]. Zhong et al. addressed the strong correlation between preoperative BEC and tissue eosinophilia to predict CRSwNP recurrence (6). Bresciani et al. and Robinson et al. reported that IgE and eosinophil inflammation severity affect the inflammation of the sinus mucosa, but the underlying associations have not been elucidated [7,8]. Wang et al. revealed that BEC combined with asthma

history may predict CRSwNP recurrence [9]. These findings suggest that elevated BEC and serum IgE levels may increase CRSwNP risk in this population. However, these studies have not investigated the association of CRSwNP patient outcome with either total serum IgE or BEC after endoscopic sinus surgery and postoperative oral corticosteroid (OCS) use.

In the management of postoperative impaired mucociliary function, OCSs can not only inhibit eosinophil recruitment to the inflammation site but also reduce the levels of eosinophilic cationic protein, interleukin (IL) 4, IL-5, and IL-13 in sinus tissue. Few studies have investigated the postoperative OCS requirements for different CRSwNP endotypes; however, no consensus has been reached on the efficacy of postoperative OCS use [10-17]. Whether preoperative serum IgE and BEC, rather than sinus tissue biopsy during endoscopic sinus surgery (ESS), can be used to predict postoperative OCS treatment outcomes warrants investigation. This is particularly because hematoxylin and eosin (H&E) staining of sinus tissue eosinophils after ESS and the interpretation of its results for CRSwNP phenotyping may be time-and labor-intensive processes; as a result, making accurate and timely decisions regarding postoperative medical treatment strategies may be difficult. We investigated the overall postoperative oral steroid effects and evaluated whether serum IgE and BEC can be used as simple and reliable preoperative surrogate biomarkers for predicting the postoperative short-term OCS clinical effects on patients with CRSwNP.

B. Describe any animal experimentation and findings leading to the formulation of the study.

None.

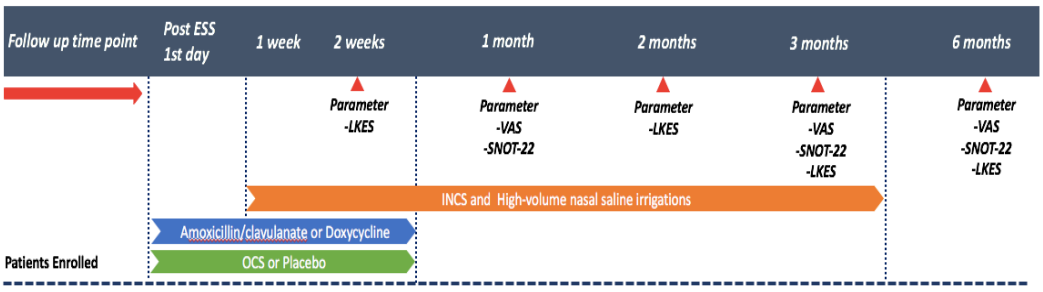
4. RADIOISOTOPES OR RADIATION MACHINES

N/A

5. DEVICES

N/A

6. TIME LINE



7. MEDICAL EQUIPMENT FOR HUMAN SUBJECTS AND LABORATORY ANIMALS

N/A

8. PARTICIPANT POPULATION

Patients with bilateral CRSwNP who had unsuccessful maximal medical treatment for 3 months and subsequently received primary or revised bilateral ESS from January 2017 to December 2020 were enrolled; all surgical procedures were performed by the same surgeon at Mackay Memorial Hospital. The exclusion criteria were age < 18 years, cystic fibrosis, immunodeficiency, previous gastrointestinal disturbance, hepatic or renal deficiency, pregnancy or lactation, and previous systemic corticosteroid treatment within 3 months preoperatively. In total, 236 patients were included and randomly selected to receive postoperative OCS or the placebo. Patients were asked to provide inform consent, and we obtained approval from the Institutional Review Board of Mackay Memorial Hospital for this study.

9. SAFETY AND SIDE EFFECT ASSESSMENT

We selected potential common adverse events in the label list of OCSs prescribed by the US Food and Drug Administration as the observation criteria; they ranged from short-term side effects, such as fluid retention (e.g., congestive heart failure, hypertension, or renal insufficiency), to mid-term side effects, such as gastrointestinal discomfort (e.g., peptic ulcer and diverticulitis). We assessed the new-onset adverse events in the OCS group in our outpatient clinic over 30 days of follow-up.

The study will officially terminate for each patient after the 5th post-operative visit. If a patient is experiencing an adverse outcome from surgery or from post-operative therapy, their participation in the study will be terminated early in the interest of well-being. In this event, patients will be promptly seen in subspecialty clinics (or by inpatient consultants if the patient is admitted to the hospital) that may assist in managing these complications. Additionally, if a patient is having an emergency, they are able to contact one of our house staff 24 hours per day for advice. As a last resort, our Emergency Department is available for expedited work up of major events.

10. BENEFITS

The current standard of care in the management of CRSwNP

patients after endoscopic sinus surgery involves a non-standardized regimen of antibiotics and systemic steroids. However, the use of oral steroids in this period is based on anecdotal evidence and expert opinion. Given the known risks of oral steroid use, it is important to definitively establish their utility and to investigate alternatives. Our study first seeks to more clearly define the role of postoperative oral corticosteroids. Whether preoperative serum IgE and BEC, rather than sinus tissue biopsy during endoscopic sinus surgery (ESS), can be used to predict postoperative OCS treatment outcomes warrants investigation. This is particularly because hematoxylin and eosin (H&E) staining of sinus tissue eosinophils after ESS and the interpretation of its results for CRSwNP phenotyping may be time-and labor-intensive processes; as a result, making accurate and timely decisions regarding postoperative medical treatment strategies may be difficult. We investigated the overall postoperative oral steroid effects and evaluated whether serum IgE and BEC can be used as simple and reliable preoperative surrogate biomarkers for predicting the postoperative short-term OCS clinical effects on patients with CRSwNP.

This information will be invaluable to the field and practice of Rhinology. There is a great need for additional investigation to determine whether steroids truly have a beneficial role in post-operative CRS patients. We endeavor to provide randomized, controlled data on which clinicians may base their therapeutic decisions. For patients, this may transform their post-operative care into one that is more easily tolerated with less detrimental effects on health.

11. PRIVACY AND CONFIDENTIALITY

All interactions with patients will take place in a private clinical setting, which is no different from our current practice. Data collection will also be performed at this time based on the physical exam as well as a questionnaire the patient will be asked to complete in privacy while lone in the exam room. Any telephone communication will be available only via our secure electronic medical record. All e-mail will be done using electronic devices that are password protected, backed up, and encrypted with institution specific software.

12. POTENTIAL CONFLICT OF INTEREST

All investigators declare no financial interests related to this protocol.

13. FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

14. DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

15. ETHICAL APPROVAL

The study was approved by the Ethics Committee of Mackay Memorial Hospital, Taipei, Taiwan (MMHIS210e).

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Supplement 2. Pre- and post-treatment changes in VAS, SNOT-22, SNOT-22 subdomains, and LKES of all patients.

	All patients (n=193)		
Parameter follow-up time	**OCS (n=92)**	**Placebo (n=101)**	**p**
Visual Analog Scale	63/29	79/22	0.14
Baseline	34.79±16.14	38.02±15.87	0.16
1-month's difference	22.59±13.76	25.45±15.61	0.18
3-months' difference	26.22±17.17	28.84±15.16	0.26
6-months' difference	28.65±16.73	32.22±16.22	0.13
SNOT-22 Total	14(15%)	7(7%)	0.10
Baseline	46.52±18.75	46.24±21.21	0.92
1-month's difference	26.83±12.74	28.65±17.64	0.41
3-months' difference	32.45±15.98	32.45±19.03	0.99
6-months' difference	36.63±17.01	37.87±20.99	0.65
SNOT-22 (Rhinological symptoms)	59.35(53.70-66.35)	57.10(51.90-64.70)	0.30
Baseline	15.91±5.63	15.32±6.10	0.48
1-month's difference	11.91±5.13	11.60±5.59	0.68
3-months' difference	12.86±5.31	12.86±5.99	099
6-months' difference	13.71±5.56	13.30±6.20	0.63
SNOT-22 (Extranasal rhinological symptoms)	35.00(22.00-46.00)	37.00(26.00-51.00)	0.16
Baseline	7.70±3.34	7.87±3.75	0.73
1-month's difference	4.63±3.12	4.97±3.48	0.47
3-months' difference	4.66±3.57	4.05±2.76	0.18
6-months' difference	6.26±3.52	6.42±3.89	0.77
SNOT-22 (Ear/facial symptoms)			
Baseline	10.72±4.52	10.50±4.56	0.73
1-month's difference	7.17±4.07	7.39±4.33	0.72
3-months' difference	8.22±4.10	8.46±4.55	0.70
6-months' difference	9.04±5.20	9.41±4.49	0.60
SNOT-22 (Psychological dysfunction)			
Baseline	15.18±9.60	14.19±9.40	0.46
1-month's difference	9.52±8.73	9.33±7.87	0.87
3-months' difference	11.01±8.80	10.85±8.69	0.90
6-months' difference	12.63±8.99	12.33±9.27	0.81
SNOT-22 (Sleep dysfunction)			
Baseline	10.73±5.64	10.12±6.08	0.47
1-month's difference	3.37±6.77	6.97±5.05	0.01*
3-months' difference	7.65±5.34	7.65±5.49	0.99
6-months' difference	8.59±5.46	8.69±6.09	0.89
Lund-Kennedy Nasal Endoscopy Scores			
Baseline	3.23±0.93	3.19±0.83	0.75
2-weeks' difference	1.33±1.22	1.21±1.17	0.49
2-months' difference	1.50±1.55	1.12±1.33	0.06
3-months' difference	1.72±1.61	1.78±1.30	0.75
6-months' difference	2.18±1.30	2.11±1.19	0.67

Values presented as mean ± standard deviation; * = Statistically significant difference. OCS, oral corticosteroid; VAS, Visual Analog Scale; SNOT-22, 22-item Sino-nasal Outcomes Test; LKES, Lund-Kennedy Nasal Endoscopy Score.

Supplement 3. Pre- and post-treatment changes in VAS scores, SNOT-22 total scores, SNOT-22 subdomain scores, and LKESs for patients with sIgE < 150 IU/mL and those with sIgE ≥ 150 IU/mL.

Parameter follow-up time	sIgE < 150 IU/mL (n=132)			sIgE ≥ 150 IU/mL (n=61)		
	OCS (n=62)	Placebo (n=70)	p	OCS (n=30)	Placebo (n=31)	p
Visual Analog Scale						
Baseline	34.40±17.10	39.70±15.79	0.06	35.60±14.22	34.23±15.62	0.72
1-month's difference	22.19±15.33	27.17±16.25	0.07	23.40±9.97	21.55±13.15	0.54
3-months' difference	25.63±17.98	30.86±15.99	0.07	27.43±15.57	24.29±12.11	0.38
6-months' difference	28.95±17.99	34.27±17.00	0.08	28.00±13.92	27.58±13.45	0.90
SNOT-22 Total						
Baseline	45.73±17.87	48.36±21.68	0.45	48.17±20.68	41.45±19.61	0.19
1-month's difference	27.16±12.51	30.29±19.04	0.27	26.13±13.39	24.97±13.52	0.73
3-months' difference	32.03±14.12	35.17±20.61	0.31	33.30±19.51	26.29±13.19	0.10
6-months' difference	36.74±16.24	39.91±22.30	0.35	36.40±18.79	33.26±17.12	0.49
SNOT-22 (Rhinological symptoms)						
Baseline	15.90±5.38	16.03±6.03	0.90	15.93±6.21	13.71±6.06	0.16
1-month's difference	11.60±4.76	12.00±5.75	0.66	12.57±5.85	10.67±5.18	0.18
3-months' difference	12.76±4.99	13.51±6.00	0.43	13.07±6.01	11.33±5.80	0.26
6-months' difference	13.92±5.49	13.83±6.35	0.93	13.27±5.76	12.07±5.74	0.42
SNOT-22 (Extranasal rhinological symptoms)						
Baseline	7.42±3.48	8.16±3.78	0.24	8.27±2.99	7.23±3.64	0.22
1-month's difference	4.32±2.92	5.07±3.69	0.20	5.27±3.47	4.73±2.97	0.52
3-months' difference	4.02±3.30	3.70±2.45	0.53	6.00±3.80	4.84±3.28	0.20
6-months' difference	6.18±3.61	6.71±4.12	0.43	6.43±3.40	5.74±3.30	0.42
SNOT-22 (Ear/facial symptoms)						
Baseline	11.03±4.74	10.90±4.72	0.87	10.07±4.05	9.58±4.10	0.64
1-month's difference	7.24±4.20	7.67±4.68	0.58	7.03±3.85	6.74±3.40	0.75
3-months' difference	8.26±4.18	8.99±4.79	0.35	8.13±3.99	7.26±3.75	0.38
6-months' difference	9.23±5.79	9.80±4.79	0.53	8.67±3.76	8.52±3.65	0.87
SNOT-22 (Psychological dysfunction)						
Baseline	14.95±9.39	15.14±9.77	0.90	15.67±10.18	12.03±8.26	0.13
1-month's difference	9.21±8.31	9.87±8.44	0.65	10.17±9.65	8.10±6.38	0.32
3-months' difference	10.87±8.37	11.93±9.23	0.49	11.30±9.77	8.42±6.85	0.18
6-months' difference	12.69±8.83	13.20±9.68	0.75	12.50±9.46	10.35±8.06	0.34
SNOT-22 (Sleep dysfunction)						
Baseline	10.77±5.70	10.47±6.26	0.77	10.63±5.60	9.32±5.66	0.36
1-month's difference	3.61±6.85	7.30±5.22	0.01*	2.87±6.69	6.23±4.63	0.02*
3-months' difference	7.74±5.28	8.17±5.67	0.65	7.47±5.56	6.48±4.95	0.46
6-months' difference	8.95±5.24	9.11±6.10	0.87	7.83±5.90	7.74±6.06	0.95
Lund-Kennedy Nasal Endoscopy Scores						
Baseline	3.31±0.91	3.23±0.80	0.60	3.07±0.98	3.10±0.90	0.90
2-weeks' difference	1.35±1.16	1.16±1.17	0.33	1.27±1.36	1.32±1.19	0.86
2-months' difference	1.52±1.58	1.09±1.47	0.10	1.47±1.52	1.19±0.98	0.40
3-months' difference	1.84±1.59	1.87±1.36	0.89	1.47±1.65	1.58±1.17	0.75
6-months' difference	2.29±1.23	2.13±1.20	0.44	1.97±1.45	2.06±1.20	0.77

Values are presented as mean ± standard deviation; * =Statistically significant difference. OCS, oral corticosteroid; VAS, Visual Analog Scale, SNOT-22, 22-item Sino-nasal Outcomes Test; LKES, Lund-Kennedy Nasal Endoscopy Scores.

Supplement Data 4. Pre- and post-ESS changes in VAS, SNOT-22, and LKES of BEC subgroups.

Parameter follow-up time	BEC < 0.39 cells × 10⁹/L (n=147)			BEC ≥ 0.39 cells × 10⁹/L, (n=46)		
	OCS (n=66)	Placebo (n=81)	p	OCS (n=26)	Placebo (n=20)	p
Visual Analog Scale						
Baseline	34.95±17.01	37.19±16.41	0.42	34.38±14.00	41.40±13.26	0.09
1-month's difference	21.77±14.46	24.86±15.08	0.21	24.65±11.83	27.80±17.85	0.47
3-months' difference	25.80±17.70	28.38±15.17	0.34	27.27±16.02	30.70±15.34	0.46
6-months' difference	28.15±17.83	31.69±16.80	0.22	29.88±13.84	34.35±13.82	0.28
SNOT-22 Total						
Baseline	45.76±19.21	44.72±21.87	0.76	48.46±17.74	52.40±17.44	0.45
1-month's difference	25.48±13.09	27.70±16.97	0.38	30.23±11.33	32.50±20.13	0.63
3-months' difference	30.98±16.38	31.93±19.17	0.75	36.15±14.54	34.55±18.76	0.74
6-months' difference	35.44±17.51	37.23±21.29	0.58	39.65±15.56	40.45±20.00	0.88
SNOT-22 (Rhinological symptoms)						
Baseline	15.05±5.95	14.74±6.35	0.76	18.12±4.02	17.65±4.39	0.71
1-month's difference	10.73±5.11	10.85±5.56	0.89	14.92±3.82	14.60±4.76	0.80
3-months' difference	11.76±5.25	12.40±6.17	0.50	15.65±4.44	14.70±4.97	0.49
6-months' difference	12.92±5.73	13.05±6.35	0.90	15.69±4.61	14.30±5.59	0.36
SNOT-22 (Extranasal rhinological symptoms)						
Baseline	7.45±3.25	7.52±3.89	0.91	8.31±3.55	9.30±2.73	0.30
1-month's difference	4.21±3.05	4.50±3.31	0.58	5.69±3.10	6.85±3.58	0.24
3-months' difference	4.29±3.54	3.85±2.78	0.40	5.62±3.54	4.85±2.64	0.42
6-months' difference	6.08±3.47	6.21±4.00	0.83	6.73±3.68	7.25±3.40	0.62
SNOT-22 (Ear/facial symptoms)						
Baseline	10.95±4.71	10.35±4.73	0.43	10.12±4.05	11.10±3.86	0.40
1-month's difference	7.11±4.17	7.21±4.23	0.88	7.35±3.87	8.10±4.77	0.55
3-months' difference	8.29±4.28	8.46±4.61	0.82	8.04±3.66	8.45±4.40	0.73
6-months' difference	9.23±5.87	9.42±4.55	0.82	8.58±2.94	9.35±4.35	0.47
SNOT-22 (Psychological dysfunction)						
Baseline	14.65±9.93	13.79±9.71	0.59	16.54±8.75	15.80±8.03	0.77
1-month's difference	8.55±9.02	8.88±8.01	0.14	12.00±7.54	11.15±7.19	0.70
3-months' difference	9.62±8.71	10.63±8.98	0.49	14.54±8.14	11.75±7.55	0.24
6-months' difference	11.91±9.16	12.20±9.53	0.85	14.46±8.43	12.85±8.34	0.52
SNOT-22 (Sleep dysfunction)						
Baseline	10.00±5.69	9.74±6.05	0.79	12.58±5.17	11.65±6.12	0.58
1-month's difference	3.30±6.51	6.40±4.80	0.01*	3.54±7.53	9.30±5.45	0.01*
3-months' difference	6.33±5.12	7.42±5.47	0.22	11.00±4.41	8.60±5.60	0.11
6-months' difference	7.64±5.56	8.49±6.00	0.37	11.00±4.45	9.50±6.53	0.36
Lund-Kennedy Nasal Endoscopy Scores						
Baseline	3.27±0.95	3.15±0.85	0.40	3.12±0.90	3.35±0.74	0.35
2-weeks' difference	1.32±1.31	1.25±1.17	0.73	1.35±0.97	1.05±1.19	0.35
2-months' difference	1.39±1.68	1.09±1.39	0.22	1.77±1.17	1.25±1.07	0.13
3-months' difference	1.55±1.69	1.84±1.27	0.23	2.15±1.31	1.55±1.43	0.14
6-months' difference	2.15±1.41	2.14±1.20	0.94	2.27±1.00	2.00±1.21	0.41

Values are presented as mean ± standard deviation; * =Statistically significant difference. OCS, oral corticosteroid; BEC, blood eosinophil count; VAS, Visual Analog Scale; SNOT-22, 22-item Sino-nasal Outcomes Test; LKES, Lund-Kennedy Nasal Endoscopy Score.

Supplement 5. Additional analysis Table 1. Pre- and post-ESS changes in VAS scores, SNOT-22 total scores, and LKESs for patients with sIgE < 100 IU/mL and those with sIgE ≥ 100 IU/mL.

	ALL n=193			sIgE < 100 IU/mL (n=114)			sIgE ≥ 100 IU/mL (n=79)		
Score type and time point	**OCS n=92**	**Placebo n=101**	**p-value**	**OCS n=49**	**Placebo n=65**	**p-value**	**OCS n=43**	**Placebo n=36**	**p-value**
Visual Analog Scale									
Baseline	34.79±16.14	38.02±15.87	0.16	33.14±16.89	39.18±15.87	0.06	36.67±15.23	35.92±15.86	0.83
1 month Dif.	22.59±13.76	25.45±15.61	0.18	21.51±15.87	26.75±16.45	0.08	23.81±10.95	23.08±13.87	0.79
3 months Dif.	26.22±17.17	28.84±15.16	0.26	24.14±18.41	30.72±16.28	0.06	28.58±15.51	25.44±12.38	0.33
6 months Dif.	28.65±16.73	32.22±16.22	0.13	27.82±18.21	34.12±17.27	0.06	29.62±14.99	28.78±13.69	0.79
Sino-Nasal Outcome Test 22 Scores									
Baseline	46.52±18.75	46.24±21.21	0.92	42.37±17.82	47.65±21.50	0.16	51.26±18.86	43.69±20.74	0.09
1 month Dif.	26.83±12.74	28.65±17.64	0.41	24.61±11.65	29.88±18.73	0.08	29.35±13.58	26.44±15.49	0.37
3 months Dif.	32.45±15.98	32.45±19.03	0.99	29.10±13.66	35.12±20.69	0.08	36.26±17.66	27.61±14.63	0.32
6 months Dif.	36.63±17.01	37.87±20.99	0.65	33.78±16.51	39.91±22.36	0.10	39.88±17.18	34.19±17.96	0.15
Lund-Kennedy Nasal Endoscopy Score									
Baseline	3.23±0.93	3.19±0.83	0.75	3.31±0.94	3.23±0.78	0.64	3.14±0.94	3.11±0.91	0.89
2 weeks Dif.	1.33±1.22	1.21±1.17	0.49	1.33±1.23	1.08±1.17	0.27	1.33±1.22	1.44±1.15	0.66
2 months Dif.	1.50±1.55	1.12±1.33	0.06	1.43±1.59	1.02±1.46	0.15	1.58±1.53	1.31±1.06	0.36
3 months Dif.	1.72±1.61	1.78±1.30	0.75	1.82±1.60	1.85±1.38	0.91	1.60±1.63	1.67±1.17	0.85
6 months Dif.	2.18±1.30	2.11±1.19	0.67	2.27±1.27	2.11±1.22	0.50	2.09±1.36	2.11±1.16	0.95

Values are presented as mean ± standard deviation; * =Statistically significant difference , Dif. = Baseline to Postoperative score difference. OCS, oral corticosteroid; BEC, blood eosinophil count; VAS, Visual Analog Scale; SNOT-22, 22-item Sino-nasal Outcomes Test; LKES, Lund-Kennedy Nasal Endoscopy Score.

Supplement 6. Additional analysis Table 2. Pre- and post-ESS changes in VAS scores, SNOT-22 total scores, and LKESs for patients with BEC < 0.25 × 10^9 cells/L and BEC ≥ 0.25 × 10^9 cells/L.

	ALL n=193			BEC < 0.25 cells × 10^9/L (n=111)			BEC ≥ 0.25 cells × 10^9/L (n=82)		
Score type and time point	**OCS n=92**	**Placebo n=101**	**p-value**	**OCS n=52**	**Placebo n=59**	**p-value**	**OCS n=40**	**Placebo n=42**	**p-value**
Visual Analog Scale									
Baseline	34.79±16.14	38.02±15.87	0.16	35.38±16.54	37.63±15.64	0.46	34.03±15.80	38.57±16.36	0.20
1 month Dif.	22.59±13.76	25.45±15.61	0.18	21.69±14.61	25.92±14.21	0.12	23.75±12.66	24.79±17.55	0.76
3 months Dif.	26.22±17.17	28.84±15.16	0.26	26.67±17.00	28.75±14.60	0.49	25.63±17.59	28.98±16.08	0.37
6 months Dif.	28.65±16.73	32.22±16.22	0.13	28.90±17.51	32.19±16.25	0.31	28.33±15.89	32.26±16.38	0.27
Sino-Nasal Outcome Test 22 Scores									
Baseline	46.52±18.75	46.24±21.21	0.92	44.81±17.57	45.19±21.07	0.91	48.75±20.19	47.71±21.58	0.82
1 month Dif.	26.83±12.74	28.65±17.64	0.41	24.06±11.97	28.00±15.75	0.14	30.43±12.96	29.57±20.17	0.82
3 months Dif.	32.45±15.98	32.45±19.03	0.99	29.75±14.57	31.61±18.74	0.56	35.95±17.19	33.62±19.59	0.56
6 months Dif.	36.63±17.01	37.87±20.99	0.65	35.69±15.55	37.85±20.60	0.54	37.85±18.87	37.90±21.77	0.99
Lund-Kennedy Nasal Endoscopy Score									
Baseline	3.23±0.93	3.19±0.83	0.75	3.42±0.84	3.17±0.91	0.13	2.98±1.00	3.21±0.71	0.21
2 weeks Dif.	1.33±1.22	1.21±1.17	0.49	1.40±1.17	1.27±1.25	0.56	1.23±1.29	1.12±1.06	0.68
2 months Dif.	1.50±1.55	1.12±1.33	0.06	1.42±1.69	1.00±1.49	0.16	1.60±1.37	1.29±1.06	0.24
3 months Dif.	1.72±1.61	1.78±1.30	0.75	1.67±1.67	1.71±1.37	0.89	1.78±1.54	1.88±1.21	0.73
6 months Dif.	2.18±1.30	2.11±1.19	0.67	2.29±1.28	2.12±1.32	0.49	2.05±1.33	2.10±1.00	0.86

Values are presented as mean ± standard deviation; * =Statistically significant difference , Dif. = Baseline to Postoperative score difference. OCS, oral corticosteroid; BEC, blood eosinophil count; VAS, Visual Analog Scale; SNOT-22, 22-item Sino-nasal Outcomes Test; LKES, Lund-Kennedy Nasal Endoscopy Score.