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Differential effects of postoperative oral corticosteroid on eosinophilic vs. non-eosinophilic CRSwNP subtypes

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A B S T R A C T

Purpose: The efficacy of postoperative oral corticosteroids on surgical outcomes in chronic rhinosinusitis with nasal polyps (CRSwNP) patients following endoscopic sinus surgery (ESS) remains controversial. This study evaluated the potential benefits of postoperative oral corticosteroids on surgical outcomes in CRSwNP patients and investigated the differential effects on eosinophilic CRSwNP (ECRSwNP) and noneosinophilic CRSwNP (NECRSwNP).

Materials and methods: Patients with bilateral CRSwNP who underwent ESS were enrolled and randomized to receive either oral prednisolone (30 mg/day) or placebo for 2 weeks after surgery. Visual analog scale (VAS) and Sino-Nasal Outcome Test 22 (SNOT-22) scores were chosen as the subjective outcomes, evaluated at preoperative baseline and 1, 3, and 6 months postoperatively. Lund-Kennedy Endoscopic Scores (LKESs) were used as the objective outcome, evaluated at preoperative baseline and at 2 weeks and 2, 3, and 6 months postoperatively.

Results: In total, 100 patients with bilateral CRSwNP were enrolled, of whom only 82 completed the 6-month follow-up. The subjective outcomes showed no significant difference at each follow-up points. Of the objective outcomes, the corticosteroid group reporting a trend of improvement in LKESs at 6 months postoperatively ($p = 0.05$). After stratification by tissue eosinophils, only patients with NECRSwNP (< 10 eosinophils/HPF) demonstrated a significant improvement in LKESs at 3 months postoperatively ($p = 0.03$).

Conclusions: Postoperative oral corticosteroids did not provide additional improvements in VAS and SNOT-22 scores; nevertheless, a trend of LKES improvement was noted at 6 months postoperatively. After stratification by tissue eosinophils, this effect was significant only among NECRSwNP patients at 3 months follow-up.

1. Introduction

Chronic rhinosinusitis (CRS) is a clinical syndrome defined as persistent inflammation of the nasal mucosa and sinuses [1,2]. Two clinical phenotypes of CRS have been documented: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [2]. However, clinical phenotypes may not provide sufficient insight into the pathophysiologic mechanisms of CRSwNP. Therefore, two different endotypes, namely eosinophilic CRSwNP (ECRSwNP) and noneosinophilic CRSwNP (NECRSwNP), have been characterized through distinct pathophysiological findings based on whether eosinophils or neutrophils are predominant [3]. More than 10 eosinophils/high-power field (HPF; 400× magnification) in the sinonasal mucosal tissue is considered indicative of ECRSwNP because this eosinophil count increases the risk of a higher disease recurrence rate, endoscopic scores, and asthma attack frequency, despite surgical or medical treatment [4–14]. These subgroups might permit individualized therapy based on different endotypes for more effective CRSwNP treatment outcomes.

The most commonly used first-line medical treatments for CRSwNP are saline irrigation, topical or systemic corticosteroids, and antibiotics [15]. Patients whose condition does not improve after maximal medical therapy may be offered a surgical approach in the form of endoscopic sinus surgery (ESS) [1]. The endoscopic surgical technique for re-establishing nasal sinus mucosa ventilation and mucociliary function was first described by H. Stammberger in 1984 and subsequently promoted worldwide by D.W. Kennedy in 1985 [16,17]. However, the optimal treatment strategy for minimizing postoperative nasal mucosal inflammation, promoting mucociliary function, and reducing the risk of postoperative complications has yet to be determined [18].

At present, corticosteroids are widely used in patients with various

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inflammatory conditions [2]. These drugs can inhibit the migration of neutrophils, monocytes, and T lymphocytes as well as regulate eosinophils [19–21]. In theory, corticosteroids can regulate nasal mucosal inflammation, increase drainage of nasal mucosa secretion, and reduce granulation formation [22]. Preoperative use of topical or systemic corticosteroids can reduce intraoperative bleeding, improve surgical field quality, and shorten surgical time [22–26]. However, the consensus among otolaryngologists regarding the efficacy of postoperative and perioperative corticosteroid use in patients undergoing ESS is lacking [15,18,25,27–39]. Jorrisen et al. and Wright et al. found considerable differences in endoscopic score improvement in patients treated with oral corticosteroids perioperatively and topical nasal spray postoperatively [25,27]. By contrast, Rudmik et al. and Dautremont et al. showed no significant difference in endoscopic score improvement following the use of oral corticosteroids perioperatively and steroid-eluting spacers postoperatively [18,36].

Our present study evaluated the potential benefit of postoperative oral corticosteroids on surgical outcomes through visual analog scale (VAS) scores, Sino-Nasal Outcome Test 22 (SNOT-22) scores, and Lund-Kennedy Endoscopic Scores (LKESs) as well as stratified the outcomes by ECRSwNP and NECRSwNP—a distinction that remains poorly understood thus far.

2. Materials and methods

2.1. Study design

This single-center, single-surgeon, prospective, randomized, placebo-controlled study was conducted by the Department of Otorhinolaryngology-Head and Neck Surgery, Mackay Memorial Hospital, Taipei, Taiwan.

2.2. Patient selection

Patients who had undergone unsuccessful maximal medical therapy before bilateral ESS were eligible for this clinical trial. All patients received antibiotics (amoxicillin/clavulanate) in the form of a 3 to 4-week course to restore mucociliary function. A concomitant short-course of oral steroid 30 mg prednisolone for two weeks is administered if the patient has severe nasal blockage or impaired sense of smell (VAS score ≧7). In addition, topical intranasal steroids and saline irrigations were recommended for all patients for > 3 months to achieve the maximal medical therapy. Antihistamine is administered in patients with underlying allergic rhinitis as well [1,40,41]. Once the patient fail to improve after a trial of the maximal medical therapy for 3 months, the endoscopic sinus surgery will be performed. Of note, oral steroid is only prescribed in severe cases and we exclude the patients who took oral steroids within 3 months prior to the surgery. Both primary surgical cases and revision cases were included, and all patients were aged 18 years or older. The diagnosis of CRS was established through the patient history, nasal endoscopy, and computed tomography of the sinuses, according to the European Position Paper on Rhinosinusitis (EPOS) 2012 [1].

Exclusion criteria were single-sided CRS, CRS without nasal polyp, age younger than 18 years, encephalocele, fungal sinusitis, inverted papilloma, cystic fibrosis, immunodeficiency, previous peptic ulcers and diverticulitis, liver or renal deficiency, pregnancy or lactation in women, and concomitant medication with drugs interacting with prednisolone. In addition, patients who had already been treated with systemic corticosteroid preoperatively were excluded.

2.3. Surgical technique

Endoscopic sinus surgery was performed using the Messerklinger technique as described by Stammberger H. and Kennedy DW [16,17]. Patients undergo polypectomy, middle meatal antrostomy, ethmoidectomy, frontal sinusotomy and sphenoidotomy when all the sinus cavities in the face are infected and inflamed. The extent of surgery was determined by the disease present for each patient. Only inflamed sinuses were dissected. Mucosal preservation and preservation of normal sinus of each case was attempted in our study. In our study, 26 patients underwent septoplasty. No inferior turbinate reductions and balloon dilatation were done in our study.

2.4. Sample size calculation

On the basis of other studies on postoperative outcomes of patients with CRSwNP [15,22,42], an initial sample size of 72 was considered, with $\alpha = 0.05$ and 80% power. Because the average dropout rate across all clinical studies was as high as 30%, a sample size of 100 was selected finally [43].

2.5. Subgrouping of patients with CRSwNP by tissue eosinophils

Sinonasal mucosal tissue was obtained from patients' ostiomeatal complex at the time of surgery. These tissue specimens were stained with Hematoxylin and Eosin and examined by the same pathologist under a microscope (400×). The patients were classified into two subgroups based on the tissue eosinophils infiltration; our diagnostic criteria for ECRSwNP was > 10 tissue eosinophils/HPF [4–7].

2.6. Study medication

The study medication, 15 mg of prednisolone, was administered twice a day over a period of 2 weeks based on our literature review and author's anecdotal clinical experience, beginning immediately after ESS [18,22,25,31]. A randomization list was generated by a computer program using a basic coin toss for simple randomization and the list was confidentially stored at the Department of Medical Research at Mackay Memorial Hospital. A copy of the list was sent to the pharmacy of Mackay Memorial Hospital, where the prednisolone 15 mg tablets were packed into capsules. Identical empty capsules served as placebo medication. All enrolled patients were provided with identical dosage instructions.

2.7. Subjective and objective outcome parameters

2.7.1. Subjective outcome

We selected the subjective severity of nasal disease improvement as the subjective outcome of this study, which included the VAS and SNOT-22 scores [1,44]. For the VAS, we scored nine major complaints, namely head fullness, smell, cough, nasal obstruction, headache, foul odor, facial pressure, post nasal drip, and rhinorrhea, on a scale of 0–10 points according to symptom severity. The patients' VAS and SNOT-22 scores were evaluated at preoperative baseline and at 1, 3, and 6 months postoperatively.

2.7.2. Objective outcome

We used the LKES system as the secondary outcome of this study. Five specific endoscopic appearance findings of the nose were quantified preoperative baseline and at 2 weeks and 2, 3, and 6 months postoperatively: the presence of polyps (0 = absence of polyp, 1 = confined to middle meatus, 2 = beyond middle meatus) and discharge (0 = no discharge, 1 = clear and thin discharge, 2 = thick and purulent discharge) as well as for edema, scarring, and crusting (for each: 0 = absent, 1 = mild, 2 = severe) [45].

2.8. Postoperative management

The protocol included postoperative management is summarized as follows: Antibiotics were administered as 2 g of amoxicillin/clavulanate per day for 10–14 days after ESS. Once there is a penicillin allergic

reaction, we will shift our antibiotics to Doxycycline 200 mg per day [1,31,46–49]. A nasal spray of 100 μg of mometasone furoate was administered once per day and high-volume nasal saline irrigations were performed two times per day beginning at postoperative week 1 until postoperative month 3. Endoscopic debridement was performed at 1, 2, and 4 weeks postoperatively.

2.9. Safety and side effects assessment

From the list on the Food and Drug Administration mandated drug label for oral corticosteroids, we selected potential common adverse events ranging from short-term side effects, such as fluid retention (e.g., congestive heart failure, hypertension, or renal insufficiency) to moderate effects, such as gastrointestinal tract discomfort (e.g., peptic ulcers and diverticulitis). We assessed the new-onset adverse events for both the steroid and placebo groups in outpatient clinics within 30 days of filling a prescription or a placebo.

2.10. Follow-up

Perioperative nasal symptom outcomes of the VAS and SNOT-22 scores were recorded before ESS and at 1, 3, and 6 months postoperatively. Perioperative healing assessments of polyps, edema, crusting, discharge, and scarring were performed before ESS and again at 2 weeks and 2, 3, and 6 months postoperatively by using the validated LKES system. The average score was calculated by two individual otolaryngologists, blinded to the treatment.

2.11. Statistical analysis

Descriptive data are presented as percentages and means ± standard deviations. A paired *t*-test (two-tailed) was used for comparisons of paired parametric data. Unpaired comparisons of continuous variables were performed using *t*-test. Unpaired comparisons of categorical variables were performed using Pearson's chi-square test or Fisher's exact test (when an expected count was < 5). Statistical analyses were performed using SPSS (version 21.0; IBM Corp., Armonk, NY, USA).

3. Results

Between December 2014 and January 2018, 100 patients were enrolled and randomized either to the prednisolone or placebo group. In total, 43 and 57 patients were allocated to the prednisolone and placebo group, respectively. The two groups exhibited comparable baseline and clinical characteristics (Table 1). After stratification by tissue eosinophils, patients with ECRSwNP had a significantly higher serum eosinophil count but lower neutrophil count (Table 2). During the study period, 8 and 10 patients in the prednisolone and placebo groups, respectively, were lost to follow-up at the end of 6 months postoperatively. Finally, 35 and 47 patients in the prednisolone and placebo groups were analyzed, respectively (Fig. 1).

3.1. Subjective parameters

3.1.1. VAS scores (subjective severity of nasal disease)

This parameter was evaluated by on the VAS (0 − 10). More favorable subjective nasal health status was represented by corresponding lower values; the average decrease in score for this parameter from baseline to 6 months postoperatively was 34.83 and 37.30 in the prednisolone and placebo group, respectively. However, the difference was nonsignificant ($p = 0.45$), even after stratification (Table 3).

3.1.2. SNOT-22 scores

The mean change in SNOT-22 scores from baseline to 6 months postoperatively was 39.59 and 39.28 in the prednisolone and placebo group, respectively. However, the difference was nonsignificant ($p = 0.94$), even after stratification (Table 3).

Table 1
Demographic data for the chronic rhinosinusitis with nasal polyps post-operative-steroid and placebo groups.

	Steroid	Placebo	*p*-Value
Number	43	57	
Gender			0.37*
Male	29(67%)	43(75%)	
Female	14(33%)	14(25%)	
Age	45.21(± 14.76)	47.16(± 14.40)	0.50
CT score (Lund-Mackay score)	15.33(± 5.38)	16.35(± 4.09)	0.28
Smoking	11(25%)	10(17%)	0.32
Previous-operation	14(32%)	18(31%)	0.91
Asthma	4(9%)	2(3%)	0.22
Drug allergy	6(14%)	4(7%)	0.25
Tissue eosinophilia (> 10/HPF 400×)	27(62%)	32(56%)	0.50
Serum eosinophil count (cells/μL)	261.4(± 239.2)	303.19(± 299.1)	0.45
Serum eosinophil %	3.53%(± 3.13%)	3.61%(± 3.07%)	0.90
Serum neutrophil count (cells/uL)	4718.3(± 1673.8)	5128.8(± 2206.2)	0.31
Serum neutrophil %	60.45%(± 8.39%)	60.06%(± 9.87%)	0.83
IgE level (serum)	125.00(± 31.09)	220.72(± 62.53)	0.19
Nasal polyp grading (right)	2.00(± 0.92)	1.95(± 1.02)	0.79
Nasal polyp grading (left)	1.98(± 1.05)	1.88(± 1.03)	0.64

* Statistically significant difference between the study groups.

Table 2
Demographic data for the chronic rhinosinusitis with nasal polyps groups stratified by tissue eosinophils.

	ECRSwNP	NECRSwNP	*p*-Value
Number	59	41	
Gender			0.25
Male	45(76%)	27(67%)	
Female	14(24%)	14(33%)	
Age	46.00(± 13.40)	46.78(± 16.13)	0.79
CT score (Lund-Mackay score)	16.05(± 4.75)	15.71(± 4.64)	0.72
Smoking	17(29%)	6(14%)	0.22
Previous-operation	20(33%)	12(29%)	0.62
Asthma	6(10%)	0(0%)	0.07
Drug allergy	7(9%)	3(6%)	0.45
Post operatively oral steroid	27(45%)	16(39%)	0.50
IgE level (serum)	199.52(± 48.60)	145.29(± 56.52)	0.46
Serum eosinophil count (cells/uL)	359.73(± 304.99)	178.00(± 177.78)	0.001*
Serum eosinophil %	4.57%(± 3.37%)	2.14%(± 1.88%)	0.001*
Serum neutrophil count (cells/uL)	4639.8(± 1476.3)	5402.2(± 2519.4)	0.06
Serum neutrophil %	58.01%(± 8.45%)	63.41%(± 9.45%)	0.004*
Nasal polyp grading (right)	2.02(± 0.91)	1.90(± 1.06)	0.56
Nasal polyp grading (left)	1.95(± 0.99)	1.88(± 1.14)	0.74

ECRSwNP = eosinophilic-type chronic rhinosinusitis with nasal polyps.
NECRSwNP = noneosinophilic-type chronic rhinosinusitis with nasal polyps.
* Statistically significant difference between the study groups.

3.2. Objective parameters and stratification

3.2.1. Endoscopic assessment (LKESs)

Nasal endoscopy scores were provided as values from 0 to 10. The initial mean baseline values preoperatively were comparable between the two groups (3.35 and 3.37 in the prednisolone and placebo groups, respectively). At 2 months postoperatively, the mean score change was 1.33 and 1.42 in the prednisolone and placebo groups, respectively; however, the difference between the two groups was nonsignificant ($p = 0.79$). At 3 months postoperatively, the mean score change

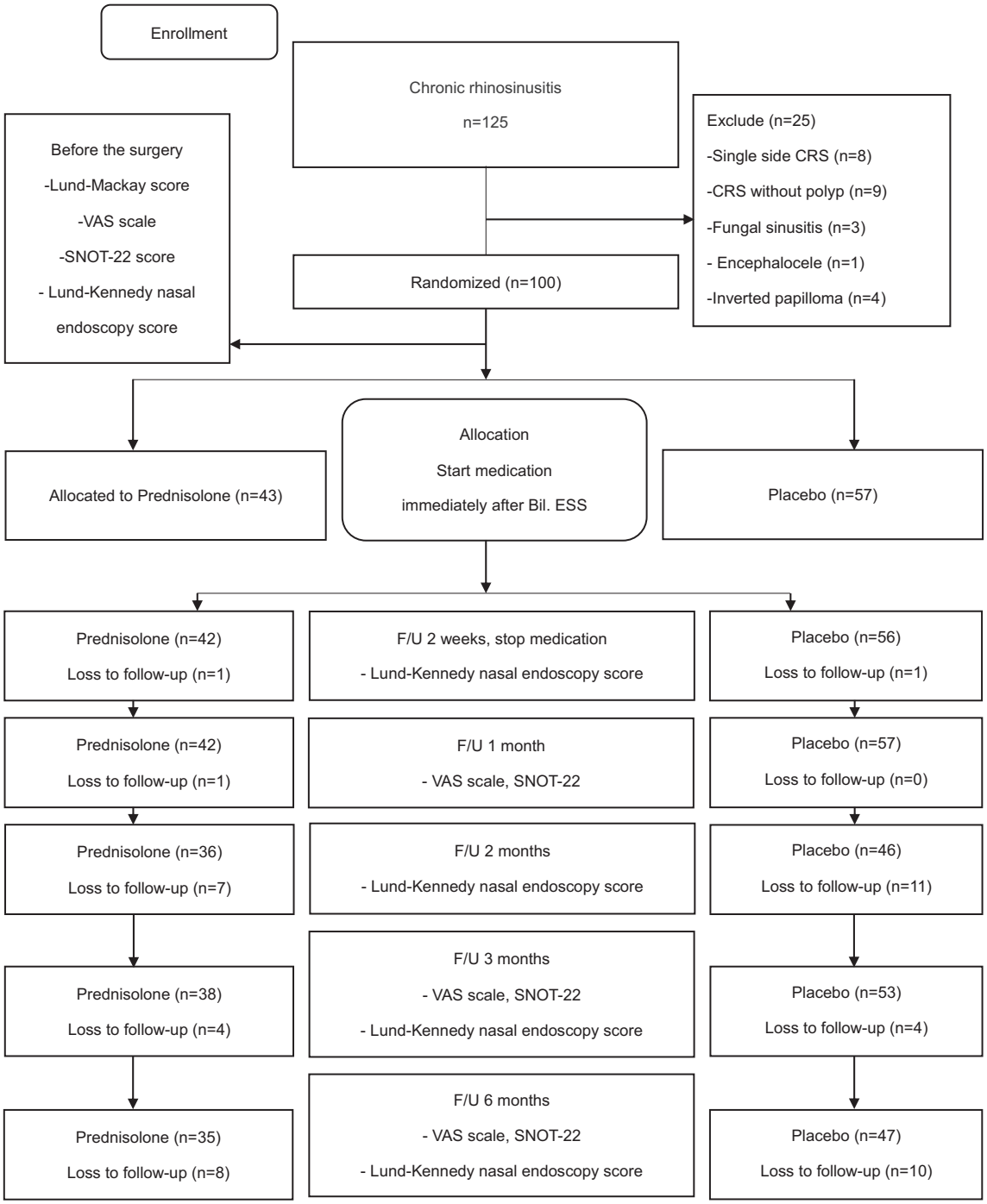

Fig. 1. Randomized controlled trial study design and patient flow diagram.
VAS = Visual analogue scale; SNOT-22 = Sino-Nasal Outcome Test 22 score.

remained 1.33 and 1.42 in the prednisolone and placebo groups, respectively, and the difference between the two groups remained non-significant ($p = 0.40$). Of note, we noted a trend of improving the mean change in LKESs from baseline to 6 months postoperatively between the two groups ($p = 0.05$, Fig. 2).

Notably, after stratification by tissue eosinophils, statistically significant differences in LKES improvement were noted at 3 months postoperatively ($p = 0.03$) in the NECRSwNP group (Fig. 3). The mean change in the score from baseline to 3 months postoperatively was 2.27 and 1.22 in the prednisolone and placebo groups, respectively. Furthermore, a trend of LKES improvement was noted in the NECRSwNP group ($p = 0.05$) at 6 months postoperatively (Table 3).

4. Discussion

The optimal method for controlling chronic inflammation after a patient with CRS undergoes ESS has become a crucial consideration in determining surgical outcomes. Although many studies have demonstrated the effectiveness of sinus surgery for CRS, such surgery should not be considered the only treatment option, but rather a modality for managing disease burden and increasing the efficacy of postoperative medical therapy [1]. In addition, positive ESS outcomes in patients with CRS are heavily dependent on reducing postoperative scarring, edema, and crusting, all of which can inhibit sinus drainage.

Corticosteroids are vital in CRS treatment because of their anti-

Table 3
Outcomes of the two randomization groups and stratified by tissue eosinophils.

Score type and time point	ALL n = 82			ECRSwNP n = 45			NECRSwNP n = 37		
	Steroid n = 35	Placebo n = 47	*p*-Value	Steroid n = 20	Placebo n = 25	*p*-Value	Steroid n = 15	Placebo n = 22	*p*-Value
Visual analog scale									
Baseline	42.19 ± 15.53	43.72 ± 15.64	0.60	42.22 ± 13.86	39.59 ± 14.44	0.48	42.13 ± 13.41	49.00 ± 15.80	0.15
1 month dif.	26.31 ± 11.95	28.68 ± 14.25	0.38	26.85 ± 11.62	24.97 ± 12.76	0.56	25.44 ± 12.81	33.44 ± 14.90	0.08
3 months dif.	33.16 ± 12.80	34.77 ± 15.06	0.59	34.17 ± 15.04	31.45 ± 13.73	0.48	31.43 ± 7.79	39.45 ± 15.91	0.08
6 months dif.	34.83 ± 12.54	37.30 ± 16.09	0.45	35.73 ± 14.42	34.22 ± 15.29	0.72	33.31 ± 8.79	41.45 ± 16.59	0.11
Sino-nasal outcome test 22 scores									
Baseline	52.02 ± 16.25	50.61 ± 20.06	0.70	50.00 ± 16.30	45.78 ± 19.71	0.38	55.44 ± 16.10	56.80 ± 19.13	0.81
1 month dif.	29.45 ± 14.49	31.39 ± 17.42	0.56	28.54 ± 13.04	28.50 ± 15.41	0.99	30.94 ± 16.94	35.08 ± 19.40	0.48
3 months dif.	36.29 ± 16.14	37.83 ± 19.67	0.69	36.38 ± 16.64	34.29 ± 17.30	0.65	36.14 ± 15.87	42.82 ± 22.05	0.33
6 months dif.	39.59 ± 16.62	39.28 ± 20.93	0.94	37.29 ± 17.27	34.74 ± 18.05	0.64	43.31 ± 15.45	45.40 ± 23.37	0.77
Lund-Kennedy nasal endoscopy score									
Baseline	3.35 ± 0.78	3.37 ± 0.77	0.90	3.30 ± 0.82	3.34 ± 0.71	0.81	3.43 ± 0.72	3.40 ± 0.86	0.88
2 weeks dif.	1.45 ± 1.01	1.46 ± 0.73	0.91	1.44 ± 1.05	1.45 ± 0.67	0.97	1.47 ± 0.99	1.48 ± 0.82	0.96
2 months dif.	1.33 ± 1.72	1.42 ± 1.29	0.79	1.29 ± 1.48	1.48 ± 1.32	0.64	1.40 ± 2.06	1.24 ± 1.26	0.77
3 months dif.	2.16 ± 1.38	1.91 ± 1.33	0.40	2.09 ± 1.34	2.36 ± 1.22	0.46	2.27 ± 1.48	1.22 ± 1.21	0.03*
6 months dif.	2.47 ± 1.42	1.89 ± 1.28	0.05*	2.45 ± 1.50	2.00 ± 1.50	0.32	2.50 ± 1.36	1.74 ± 0.93	0.05*

Dif. = Baseline to Postoperative score difference, ECRSwNP = eosinophilic-type chronic rhinosinusitis with nasal polyps, NECRSwNP = noneosinophilic-type chronic rhinosinusitis with nasal polyps.
* Statistically significant difference between the study groups.

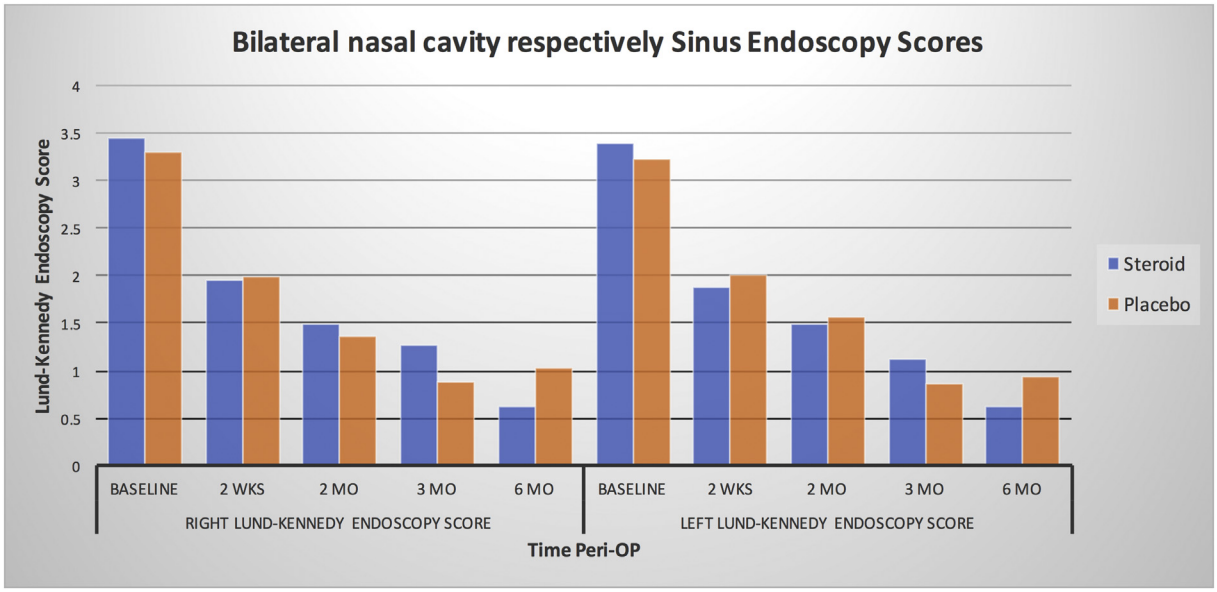

Fig. 2. Bilateral nasal cavity respectively sinus endoscopy scores.
wks: weeks; MO: Month; Peri-OP: perioperative.

inflammatory and immunosuppressant effects, wherein they inhibit both eosinophils and neutrophils [2]. Corticosteroids are easy to administer and generally are low cost. In addition, reduced inflammation during the postoperative period may improve long-term surgical outcomes [15,18,50]. EPOS 2012 recommended oral steroids for the postoperative management of CRSwNP (Level Ia, Grade A) and CRSsNP (Level IV, Grade C), but without any clinical appraisal of trials addressing the effect of postoperative steroid use. Because the results of postoperative oral steroid use in patients with CRSwNP undergoing ESS are conflicting and lack subgroup analysis by tissue eosinophils, we here evaluated the effects of postoperative oral steroid treatment and investigated possible subgroup differences.

To improve ESS outcome in the early postoperative period, several clinical trials of postoperative corticosteroid use have been conducted. In a randomized controlled trial, Jorissen et al. administered 200 μg of mometasone two times daily before surgery in combination with 2 mg of oral betamethasone for 7 days postoperatively and demonstrated significant improvement in endoscopic scores, but not in symptom scores, in the CRSwNP group [27]. Dijkstra et al. also revealed no significant difference in VAS scores after administering 40 mg of oral prednisolone perioperatively for 2 weeks and 400 μg of fluticasone spray two times daily for 1 year postoperatively [34]. Wright et al. found significant differences in endoscopic assessment in the CRSwNP groups after orally administering 30 mg of prednisolone for 5 days preoperatively and 9 days postoperatively, but no difference in symptom score improvement was noted [25]. Rudmik et al. administered 30 mg of prednisolone for 1 week, followed by ESS and 30 mg of prednisolone for 10 days with dexamethasone sinus spacers postoperatively, to patients CRSsNP and noted no improvement in endoscopic scores [36]. Dautremont et al. administered 30 mg of

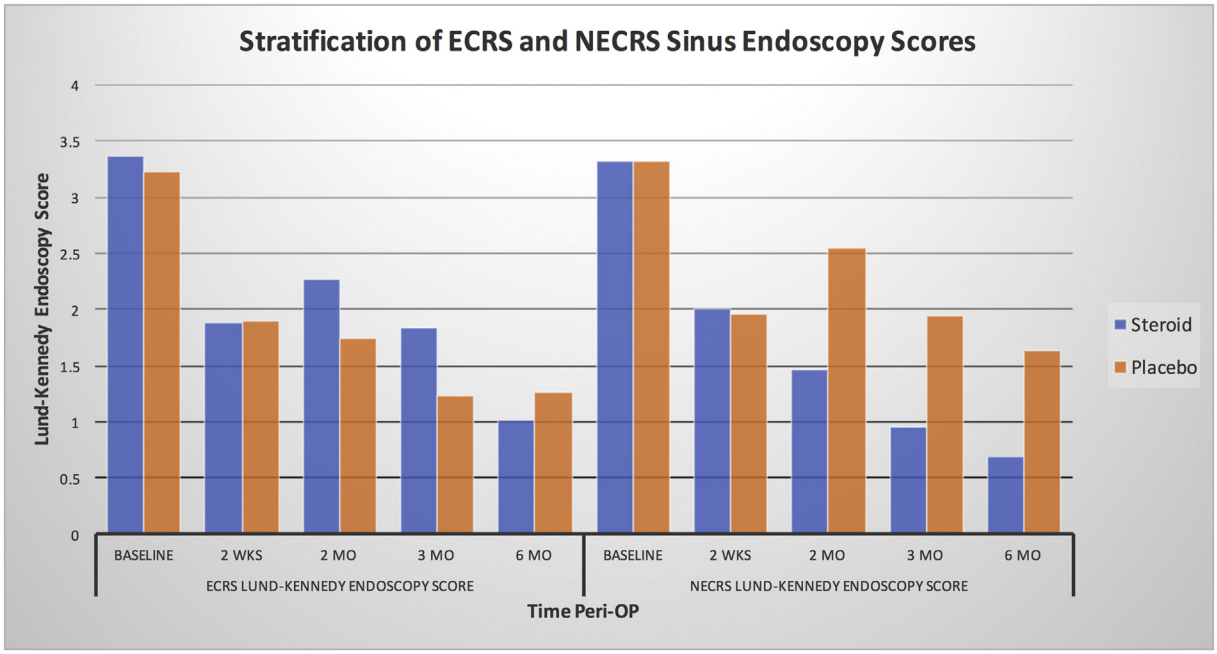

Fig. 3. Stratification of ECRS and NECRS sinus endoscopy scores.
wks: weeks; MO: Month; Peri-OP: perioperative.

prednisolone for 1 week preoperatively, followed by ESS and 30 mg of prednisolone for 1 week with Triamcinolone sinus spacers postoperatively, to patients with CRSwNP and reported considerable improvement in endoscopic scores, but not symptom scores [18].

In a meta-analysis, Pundir et al. evaluated 12 randomized controlled trials for postoperative outcomes in response to topical or systemic corticosteroids. No significant difference was demonstrated in postoperative subjective symptom scores ($p = 0.94$) between the steroid and nonsteroid groups, but statistically significant differences were observed in postoperative endoscopic score outcomes ($p = 0.0004$) and recurrence rates ($p = 0.01$) in the CRSwNP groups [22]. However, their meta-analysis mixed different modes of steroid delivery, such as topical nasal steroid spray, oral systemic steroids, and steroid-eluting spacers/stents, and thus it could not completely assess the effects of a single mode of steroid delivery. Taken together, these studies indicate a lack of consensus but provide several conflicting results regarding modes of steroid delivery.

In such researches, subgroup analysis has been limited with regard to the different phenotypes of CRS (i.e., CRSwNP and CRSsNP). From a pathophysiological perspective, eosinophils and neutrophils both are crucial in the pathogenesis of airway inflammation, particularly in patients with asthma, and these can cause paranasal mucosal tissue hyperplasia [1,51]. Because corticosteroids have become a cornerstone in CRS treatment, identifying whether the presence of eosinophilic or neutrophilic inflammation affects the response to corticosteroids in patients with CRS is important.

A primary focus of our study was on the role of moderate-dose oral corticosteroids administered postoperatively in different endotypic CRS patients undergoing ESS—a subject that was not evaluated thus far. In the present study, we prescribed a moderate dose of 15 mg of prednisolone administered twice per day postoperatively over a period of 2 weeks. The subjective parameters, including self-rated nasal health on the VAS and SNOT-22, decreased in both groups over time, but demonstrated no statistically significant differences between the corticosteroid and placebo groups (Table 3). Notably, the objective parameter, LKES, revealed a trend of improvement in the prednisolone-treated patients compared with the placebo group at 6 months postoperatively (Table 3). After stratifying by tissue eosinophils, the present study revealed significant improvements in LKESs after 3 months ($p = 0.03$) in patients with NECRSwNP who took oral steroids (Table 3).

In the current study, no severe side effects were observed, and the study medication did not cause increase the rates of short-term adverse events compared with the placebo group. Of the 43 patients who were treated with prednisolone, only one had gastrointestinal tract discomfort, and this did not increase the rate of postoperative sinusitis.

The clinical implications of this study's findings remain uncertain as tissue eosinophilia is typically not revealed preoperatively; however, a significantly higher preoperative peripheral blood eosinophil count and percentage were noted in the ECRSwNP group compared with the NECRSwNP group in our study (both $p = 0.001$, Table 2). Furthermore, a strong positive linear correlation was noted between absolute peripheral eosinophil count and tissue eosinophil count in CRSwNP patients [52]. Thus, peripheral blood eosinophil counts may a useful surrogate to predict tissue eosinophilia of CRSwNP preoperatively: this will be the focus of our future study.

The strengths of the present study include the large sample size and the eosinophils subgroup analysis, which has never been performed previously. However, several limitations should be considered when evaluating the findings of this study. First, we followed the guidance of EPOS 2012, which recommends treatment with topical corticosteroid for CRSwNP and CRSsNP after ESS [1]. The patients in both groups received postoperative topical corticosteroids (100 μg of mometasone furoate nasal spray once per day for 3 months), which can result in residual effects in the postoperative period. Second, the relatively short length of follow-up for our final outcome (i.e., 6 months) may have been a limiting factor. Steroids are clearly removed from the body long before 6 months after a follow-up is conducted. However, there may be a long-term benefit of oral steroids with regards to mucosal healing even after 6 months from the time of operation. Future basic study is needed to investigate the pathophysiology of long-term steroid effect on mucosal healing. Third, we used simple randomization to decide participant assignment. This randomization approach resulted in an unequal number of patients among the groups in our study (43:57). Further statistical analysis revealed that both groups were balanced with respect to baseline demographic factors, clinical characteristics, and several known confounding variables (Table 1); therefore, the simple randomization still provided valid statistical tests of significance for

comparing the treatment effects.

5. Conclusion

Postoperative oral corticosteroids administered immediately after ESS for CRSwNP did not provide additional improvements in VAS and SNOT-22 scores. However, a trend of improvement in LKESs was observed at 6 months postoperatively in bilateral CRSwNP patients. After stratification by tissue eosinophils, this effect was significant only in patients with NECRSwNP at 3 months postoperatively. The optimum corticosteroid dose and duration have yet to be established and long-term follow-up studies are required.

Compliance with ethical standards

Conflict of interests

We declare that there is no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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None

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