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ORIGINAL ARTICLE

Post-operative steroid treatment for eosinophilic-type sinonasal polyposis

GIUSEPPE BRESCIA^{*1}, GINO MARIONI^{*1}, SEBASTIANO FRANCHELLA¹,
GIULIA RAMACCIOTTI¹, ALFONSO LUCA PENDOLINO¹, FILIPPO CALLEGARO¹,
LUCIANO GIACOMELLI², FILIPPO MARINO² & ALESSANDRO MARTINI¹

¹Department of Neurosciences DNS, Otolaryngology Section, Padova University, Padova, Italy and ²Department of Medicine DIMED, Padova University, Padova, Italy

Abstract

Conclusions: The preliminary finding of significantly lower eosinophilic-type CRSwNP recurrence rates in patients with associated asthma or ASA intolerance treated post-operatively with local nasal and oral steroids warrants further investigation in larger, prospective series. **Objective:** A high recurrence rate after functional endoscopic sinus surgery (FESS) has been widely reported in patients with eosinophilic-type chronic rhinosinusitis with nasal polyps (CRSwNP). This study compared the influence of two post-operative medical treatments – local nasal steroids alone vs local nasal and oral steroids – on the recurrence of eosinophilic-type CRSwNP. **Method:** Between January 2009–December 2010, 32 patients with eosinophilic-type CRSwNP received local steroid nasal therapy after FESS (Group A); from January 2011 onwards, another 28 patients were treated post-operatively with the same nasal treatment plus two cycles a year of oral steroids (Group B). All patients in both groups had a follow-up of at least 36 months. **Results:** Groups A and B did not differ significantly in recurrence rate (31.25% vs 32.14%, $p = 1$) or disease-free interval ($p = 0.91$), but Group B patients who were asthmatic or ASA-intolerant had a significantly lower recurrence rate than Group A patients with asthma or ASA intolerance ($p = 0.04$ and $p = 0.004$, respectively).

Keywords: Sinonasal polyposis, eosinophilic-type, FESS, recurrence, post-operative medical treatment

Introduction

Despite advances in surgical and medical therapies for chronic rhinosinusitis with nasal polyps (CRSwNP), various authors [1–3] have reported significant recurrence rates necessitating revision surgery in 4–20% of cases, depending on the length of follow-up. In particular, there are widespread reports of an association between the histological evidence of polyps with a rich eosinophilic component and a relatively high disease recurrence rate after functional endoscopic sinus surgery (FESS). In 2010, Tosun et al. [4] analyzed 42 patients who had undergone endoscopic sinus surgery for massive nasal polyposis and found that eosinophil-rich nasal polyps (with four or more eosinophils per 1000 μm^2)

coincided with a higher post-operative recurrence rate. After examining the results of a prospective study, Nakayama et al. [5] concluded that patients with mucosal eosinophilia had a higher rate of recurrent polyps. In a very recent prospective monocenter study involving 96 patients with CRSwNP, Vlamincx et al. [6] also found a recurrence rate of 48% in CRSwNP patients with eosinophilic tissue involvement, and in cases with additional eosinophilic mucin the recurrence rate rose to 56%. In a prospective trial on 30 surgically-treated adult patients with CRSwNP, Grgić et al. [7] also concluded that a greater eosinophil infiltration significantly predicted a higher risk of recurrent polyps.

Given the high rate of recurrent eosinophilic-type CRSwNP after FESS, we decided in 2011 to intensify

Correspondence: Giuseppe Brescia, MD, Department of Neurosciences DNS, Otolaryngology Section, Padova University, Via Giustiniani 2, 35128 Padova, Italy.
Fax: +39 049 8213113. E-mail: giuseppe.brescia@sanita.padova.it

*These authors contributed equally to the manuscript's preparation.

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our previously-adopted post-operative medical approach involving local nasal steroids by adding courses of oral steroids too (see Materials and methods for details). The aim of the present study was to compare the results, mainly in terms of recurrence rate, of the two different post-operative medical treatments in eosinophilic-type CRSwNP (i.e. local nasal steroids alone vs local nasal plus oral steroids).

Materials and methods

Surgical indications and pre-operative diagnostic workup

According to the clinical guidelines adopted by our group, patients with CRSwNP are eligible for FESS if they meet the following criteria: (i) failure to respond to medical treatment with local mometasone furoate 200 µg daily (100 µg/nostril) [8] or fluticasone furoate 110 µg daily (55 µg/nostril) for 3 months, and oral therapy with methylprednisolone (32 mg daily on days 1–5, then 16 mg daily on days 6–10, then 8 mg daily on days 11–20) [9]; and (ii) grade II nasal polyposis (polyps in two or more nasal recesses not extending into the nasal cavity), or grade III nasal polyposis (polyps extending beyond the recesses) [10].

These patients are usually tested pre-operatively for allergy (based on history and laboratory data), asthma (based on history, spirometry, and bronchial challenge test), and intolerance of acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs. For all patients, the pre-operative diagnostic workup included: nasal endoscopy with rigid 0° and 30° optical instruments (Ø = 4 mm); serum eosinophil and basophil counts (percentages and absolute values); total and specific serum IgE assays for common allergens; serum eosinophil cationic protein assay and paranasal high-resolution computerized tomography [11]. All laboratory tests were performed prior to surgery at the same laboratory (EIA Unit, Laboratory Medicine Service, Padova General Hospital), at least 3 months after stopping oral steroids, and at least 1 month after stopping nasal steroid treatment.

Patients

This retrospective investigation concerned 60 adult patients who had CRSwNP with histological evidence of a rich eosinophilic component (> 10 eosinophils per 400× high-power field), who had undergone FESS between January 2009 and December 2011, all at the hands of the same surgeon (GB). These patients were the result of a preliminary selection process to exclude: all FESS-treated eosinophilic-type CRSwNP patients with a histological diagnosis of eosinophilic

granulomatosis with polyangitis (EGPA) (formerly Churg-Strauss syndrome); all patients with cystic fibrosis, diabetes, glaucoma, or severe osteoporosis; and any patients with a post-operative follow-up of less than 36 months.

From January 2009 to December 2010, 32 patients with eosinophilic-type CRSwNP (group A) were treated post-operatively with nasal irrigations of isotonic saline solution twice a day (20 ml per irrigation) and local nasal therapy with mometasone furoate 200 µg daily (100 µg per nostril) [8], or fluticasone furoate 110 µg daily (55 µg per nostril). From January 2011 onwards, another 28 patients with eosinophilic-type CRSwNP (group B) received the above post-operative nasal treatment plus two cycles a year of oral steroids [9]. Allergic patients in both groups were treated with antihistamines during pollination periods. Patients with asthma received appropriate therapy.

Follow-up

After FESS, follow-up nasal endoscopies were performed under topical anesthesia (lidocaine 20 mg/ml plus xylometazoline 1 mg/ml, volume ratio 1:1) in both groups using rigid 0° and 30° (Ø = 4 mm) instruments, and scheduled at 12, 24, and 36 months after surgery. Patients were classified as cases of recurrence if they had endoscopic evidence of at least grade I polyposis. In Group B, the endoscopic evaluations were performed ~ 4 months after the end of oral steroid course, in order to reduce the influence of the short-term effect of the systemic therapy as described by Van Zele et al. [9].

Statistical analysis

For our univariate model, the statistical methods applied were Fisher's exact test, the Mann-Whitney U-test, and the log-rank test, as appropriate. A *p*-value < 0.05 was considered significant.

The STATA™ 8.1 statistical package (Stata Corp, College Station, TX) was used for all analyses.

Results

Demographic, clinical, and laboratory variables

No significant differences emerged between Groups A and B in the distribution of the pre-operative medical treatments (local therapy with mometasone furoate vs local therapy with fluticasone furoate) (Fisher's exact test, *p* = 1). The statistical analysis also ruled out any significant differences between the two groups (Group A vs Group B) in terms of sex, age

Table I. Comparison between Groups A and B patients with eosinophilic-type CRSwNP in terms of main demographic, laboratory, clinical, and surgical variables.

Variables	Group A (32 cases)	Group B (28 cases)	<i>p</i> -value
Sex (M/F)	20/12	20/8	0.58*
Age (mean $\pm$ SD, years)	46.06 $\pm$ 12.87	51.07 $\pm$ 13.58	0.28**
Serum eosinophil count (mean $\pm$ SD, cells $\times$ 10 ⁹ /L)	0.44 $\pm$ 0.26	0.40 $\pm$ 0.18	0.79**
Serum eosinophil % (mean $\pm$ SD)	6.22 $\pm$ 3.01	5.67 $\pm$ 2.84	0.33**
Serum basophil count (mean $\pm$ SD, cells $\times$ 10 ⁹ /L)	0.04 $\pm$ 0.03	0.04 $\pm$ 0.02	0.25**
Serum basophil % (mean $\pm$ SD)	0.55 $\pm$ 0.32	0.59 $\pm$ 0.30	0.43*
Allergy (yes/no)	17/15	11/17	0.31*
Asthma (yes/no)	12/20	6/22	0.25*
ASA intolerance (yes/no)	3/29	5/23	0.45*
Maxillectomy (yes/no)	28/4	27/1	0.35*
Ethmoidectomy (yes/no)	28/4	28/0	0.11*
Sphenoidectomy (yes/no)	10/22	13/15	0.29*
Frontal sinusectomy (yes/no)	6/26	6/22	1*
Septoplasty (yes/no)	11/21	10/18	1*
Turbinoplasty (yes/no)	7/25	6/22	1*
Recurrence rate	10/32 (31.25%)	9/28 (32.14%)	1*
Disease-free interval (mean $\pm$ SD, months)	31.88 $\pm$ 8.28	31.29 $\pm$ 8.69	0.91 [†]

SD, Standard deviation.

*Fisher's exact test.

**Mann Whitney U-test.

[†]Log-rank test.

(46.06 $\pm$ 12.87 years vs 51.07 $\pm$ 13.58 years), serum eosinophil count (0.44 $\pm$ 0.26 cells $\times$ 10⁹/L vs 0.40 $\pm$ 0.18 cells $\times$ 10⁹/L), serum basophil count (0.04 $\pm$ 0.03 cells $\times$ 10⁹/L vs 0.04 $\pm$ 0.02 cells $\times$ 10⁹/L), asthma (37.5% vs 21.4%), allergy (53.1% vs 39.3%), or ASA intolerance (9.4% vs 17.9%) (Table I).

Sinonasal surgery for eosinophilic CRSwNP

When the distribution of the surgical procedures performed for eosinophilic-type CRSwNP in Groups A and B was submitted to statistical analysis, Fisher's exact test ruled out any differences in the frequency of the procedures used in Group A vs Group B (Table I for details on the comparison of the surgical procedures).

Post-operative medical treatment and prognosis:

Inter-group analysis

Comparing Groups A and B as a whole (i.e. the two different post-operative medical treatments), no significant differences were found in terms of CRSwNP recurrence rate (Fisher's exact test, $p = 1$) or disease-free interval (log-rank test, $p = 0.91$).

When Groups A and B were further divided into sub-cohorts of patients with eosinophilic-type

CRSwNP and asthma, Group B asthma patients (given both nasal and oral steroids post-operatively) had a significantly lower recurrence rate (1/6 [16.7%]) than Group A asthma patients (8/12 [66.7%]) (log-rank test, $p = 0.04$). When the two groups were further divided into sub-cohorts of patients with ASA intolerance, Group B patients with ASA intolerance again had a significantly lower CRSwNP recurrence rate (0/5 [0%]) than Group A patients (3/3 [100%]) (log-rank test, $p = 0.004$). On the other hand, the sub-cohorts of patients in Groups A and B who had neither asthma nor ASA intolerance did not differ in terms of CRSwNP recurrence rate (log-rank test, $p = 0.07$ and $p = 0.24$, respectively). Statistical analysis also ruled out any significant differences in the recurrence rates when sub-cohorts of patients with and without allergy were compared between the two groups (log-rank test, $p = 0.94$ and $p = 0.47$, respectively).

Discussion

After a detailed review of the available literature, Fandiño et al. [12] concluded that post-operative topical nasal steroids for patients undergoing endoscopic surgery for CRSwNP is safe, and is likely to reduce recurrences; these conclusions were drawn,

however, on the strength of outdated, low-to-moderate quality evidence. The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) [13] mentioned 17 investigations (conducted since 1982) on the outcome of intra-nasal corticosteroids vs placebo for the post-operative treatment of CRSwNP, 12 of which supported the use of nasal steroids. In analyzing the evidence and recommendations for the post-operative treatment of adults with CRSwNP, the same EPOS 2012 Position Paper [13] said that the value of both topical and oral steroids was supported by a Ia level of evidence and an A grade of recommendation.

The purpose of our study was to compare the results we obtained, in terms of recurrence rate, with two post-operative medical treatments (local nasal steroids alone vs local nasal plus oral steroids) in patients with eosinophilic-type CRSwNP. We focused on cases of eosinophilic-type CRSwNP because this histological variant is generally associated with a high recurrence rate after sinonasal surgery. Our own group's clinical experience confirms as much: whatever the post-operative therapy administered, 19 of 60 eosinophilic-type CRSwNP (31.7%) recurred after a median disease-free interval of 24 months (mean = 22.1 ± 9.7 months). Reasons why eosinophilic infiltration should significantly affect the outcome have been advanced in the recent literature. It has been suggested that eosinophilic and non-eosinophilic polyps are two distinct entities, not only in histological appearance, but also in genetic and protein expression patterns, so they might need to be treated differently [7]. Little information is available as yet on the comparative efficacy of different post-operative medical treatments for eosinophilic-type CRSwNP. The main strengths of the present study lie in the homogeneous series of patients considered, given that: (i) the histological diagnosis was established by the same pathologist; (ii) the laboratory tests were performed at the same laboratory; (iii) the post-operative medical treatments were standardized within the two groups considered here; and (iv) all surgical treatments were performed consecutively by the same surgeon. Moreover, given the evidence that the extent of sinus surgery for CRSwNP might correlate with the revision rate [2], we statistically compared the surgical procedures performed in our two groups, finding no significant differences between them. Only patients with a reasonably long post-operative endoscopic follow-up (at least 36 months) were included in our study. On the other hand, the main weaknesses of our study concern the limited number of cases of eosinophilic CRSwNP investigated (and of recurrent cases in particular) and the retrospective setting.

A preliminary statistical analysis ruled out any significant differences between our two groups of patients with eosinophilic-type CRSwNP in terms of their demographic, laboratory, and comorbidity variables. The results obtained with the two post-operative medical treatments (local nasal steroids alone vs local nasal plus oral steroids) were compared from the prognostic viewpoint, analyzing the recurrence rates and disease-free intervals. When the two groups were compared as a whole, there were no significant differences in terms of CRSwNP recurrence rate (31.25% in Group A vs 32.14% in group B, $p = 1$) or disease-free interval (31.88 ± 8.28 vs 31.29 ± 8.69 , $p = 0.91$). However, when the groups were divided into sub-cohorts of patients with asthma, ASA intolerance, or allergy, the picture changed: patients in Group B (treated post-operatively with local nasal plus oral steroids) who also had asthma or ASA intolerance had a significantly lower rate of recurrent eosinophilic-type CRSwNP than their counterparts in Group A ($p = 0.04$ and $p = 0.004$, respectively). Cellular differences between nasal polyps from patients with CRSwNP and aspirin-exacerbated respiratory disease (AERD) are poorly understood [14]. This could be reasonably due to different patho-physiological characteristics of patients with AERD in comparison by other CRSwNP [15]; a possible consequence could be a better response to glucocorticoid therapy in patients suffering from AERD than those with other CRSwNP. Juergens et al. [16] found that monocytes of AERD patients produced larger amounts of both thromboxanes (TXs) and leukotriens (LTs) compared to normal individuals. This indicated a generalized acceleration in the arachidonic acid metabolic rate through both the cyclooxygenase (CO) and lipooxygenase (LO) pathways in these patients. They also found subsequent ingestion of ASA resulted in a significant decrease in TXs and a significant increase in cysteinyl LTs release [15]; this was clinically associated with bronchospasm and formation of nasal polyps. On the other hand, steroids are able to inhibit both the CO and the LO, decreasing the levels of metabolites.

Conclusions

When we compared two groups of patients with eosinophilic-type CRSwNP (a histological variant of CRSwNP that carries a high risk of recurrence after FESS) who were treated post-operatively with local nasal steroids alone vs local nasal plus oral steroids, we found no significant differences in the two groups' recurrence rates and disease-free intervals. On the other hand, it is worth further investigating in a larger

series (and ideally in a prospective setting) our preliminary observation that administering a combination of post-operative local nasal and oral steroids was associated with a significantly lower recurrence rate than the use of local nasal steroids alone in patients with eosinophilic-type CRSwNP who also had asthma or ASA intolerance.

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