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ORIGINAL ARTICLE

The effects of erythromycin towards the treatment of persistent rhinosinusitis after functional endoscopic sinus surgery: A randomized, active comparator-controlled study

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Abstract

Background: Long-term, low-dose macrolide treatment has been in recent use to treat chronic rhinosinusitis. In this study, we investigated the effect of long-term, low-dose erythromycin on patients who had persistent rhinosinusitis after functional endoscopic sinus surgery (FESS).

Methods: Patients with persistent rhinosinusitis for 3 months after FESS were recruited and randomly assigned to two groups. Patients in the erythromycin group took erythromycin (250 mg twice a day) for 12 weeks, while those in the intranasal steroid group were administered with mometasone furoate nasal spray for 12 weeks. Both before and after treatment, sino-nasal symptoms were assessed via questionnaires. Patients also received an endoscopic examination, acoustic rhinometry, smell test, and saccharine transit test. A bacterial culture was obtained from the middle meatus.

Results: Seventy-two patients completed the study, with 35 in the erythromycin group and 37 in the intranasal steroid group. Endoscopic scores decreased significantly after treatment in both groups. Erythromycin improved the smell threshold and saccharine transit time better than the intranasal steroid. In contrast, the intranasal steroid increased the second minimal cross-sectional area of the nasal cavity at a level greater than erythromycin had.

Conclusion: Our study showed that long-term, low-dose erythromycin treatment improved the endoscopic score, smell threshold, and saccharine transit time in patients with persistent rhinosinusitis after FESS.

Keywords: Erythromycin; Sinusitis; Steroids

1. INTRODUCTION

Functional endoscopic sinus surgery (FESS) has become a standard modality for treating chronic rhinosinusitis (CRS).[1] Although FESS has shown to have a good success rate, postoperative mucosal inflammation requires continuous management after surgery.[2] Therefore, it has been emphasized that postoperative care is very important toward a successful outcome of FESS.[3] Many measures, procedures, and medications have been advocated for use in postoperative care, including nasal saline irrigation and topical steroids.[4]

Recently, macrolides have been considered to contain anti-inflammatory and immune-modulatory capacities, primarily through the inhibition of cytokine production, mucus synthesis and secretion, and inflammatory cells migration and adhesion.[5] In some clinical trials, the use of macrolides exhibited improvements in symptoms, endoscopic findings, and saccharine transit time in CRS patients.[6] However, the meta-analysis did not find enough evidence to support macrolide therapy for CRS but it only included CRS patients who have not received a prior surgery for treatment.[7]

A few studies had reported positive effects from macrolide therapy for refractory CRS patients after FESS.[2,6] Macrolide seems to be a promising treatment modality for refractory CRS after FESS. In this study, we investigated the effect of long-term, low-dose erythromycin on postoperative CRS patients with persistent rhinosinusitis.

2. METHODS

2.1. Study population

CRS patients who responded poorly to medical treatment, and subsequently underwent standard bilateral FESS, were collected between June 2012 and March 2016. The diagnosis of CRS was established by the patient's history, nasal endoscopy, and CT of the sinuses, according to the European position paper on rhinosinusitis and nasal polyps (EPOS) criteria.[8] Any patient with a history of immunodeficiency or previous sinus surgery was not eligible for enrollment. After surgery, follow ups were held at the outpatient clinic, where local nasal treatment was done to remove crusts and discharge from the nasal cavities. One month after surgery, all subjects received nasal irrigation for 2 months, through the use of a Sanvic SH903 pulsatile irrigator (Yun-Wang

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Industrial Co., Tainan, Taiwan). Nasal irrigation was performed daily with 500 mL warm saline. No antibiotic, intranasal or oral antihistamine, intranasal or oral steroid were prescribed.

After nasal irrigation, the patients were examined again. Those who still complained of sinus symptoms, which included nasal obstruction, mucopurulent nasal discharge, postnasal drip and loss of smell function, or/and whose endoscopic examination revealed mucopus, edematous mucosa or polypoid mucosa in sinonasal cavities, were subsequently enrolled in this study. They were randomly divided into two groups. Randomization assignments were generated by an independent statistician. Patients in the study group were treated with oral erythromycin (250 mg, twice a day) for 12 weeks, while those in the active control group were treated with an intranasal steroid (mometasone furoate nasal spray, 4 puffs, once a day) for 12 weeks. Any patient who suffered from an acute flare of rhinosinusitis and needed other antibiotics for management during this period was excluded from the study. This study was approved by the Ethics Committee of Taichung Veterans General Hospital (IRB TCVGH No: CF12123A-3). Written consent was obtained from each patient.

2.2. Assessments

Preoperatively, all CRS patients completed a Taiwanese version of the 22-item Sino-Nasal Outcome Test (TWSNOT-22) questionnaire.[9] Patients also received an endoscopic examination, acoustic rhinometry, smell test, and saccharine transit test. Bacterial cultures were then done by taking swab specimens from the bilateral middle meatus, using a cotton-tipped swab. The endoscopic appearances were quantified on a 0- to 2-point scale, according to the staging system devised by Lund and Mackay.[10] Acoustic rhinometry was performed to measure the second minimal cross-sectional area (MCA_2) of the nasal cavity. The MCA_2 of the right and left nasal cavity was averaged to give a mean MCA_2 (cm^2). The smell function was evaluated using the Smell Threshold Test (Sensonics, Inc., Hadden Heights, NJ, USA) along with a traditional Chinese version of the University of Pennsylvania Smell Identification Test (UPSIT-TC) (Sensonics, Inc., Hadden Heights, NJ).[11] The saccharine transit test was performed by putting saccharine granules under the head of the inferior turbinate in the nostril which was experiencing more severe disease, then measuring the time interval between placement of the saccharine granules and the sensation of sweetness in the patient's throat.

All study subjects underwent FESS by the senior author (R.S. Jiang). Nasal specimens harvested by FESS were evaluated by pathologists: Polyps with eosinophils that outnumbered 10% of inflammatory cells by microscopic examination were regarded as eosinophilic polyps.[12] Patients with persistent rhinosinusitis for 3 months after FESS filled out the TWSNOT-22 questionnaire for a second time and received another endoscopic examination, acoustic rhinometry, smell test, and saccharine transit test before receiving treatment. Swab specimens from the bilateral middle meati were obtained for bacterial cultures. After 12-weeks of erythromycin or intranasal steroid treatment, patients filled out another TWSNOT-22 questionnaire, and received an endoscopic examination, acoustic rhinometry, smell test, saccharine transit test, and middle meatal bacterial cultures.

2.3. Sample size and statistical analysis

The sample size was calculated using the study design of the Mann–Whitney *U* test, through use of the power analysis program G* Power 3.[13] The clinically significant difference was set at 8.9, according to the results of validation of the SNOT-22.[14] With an α value of 0.05 and a power value of 0.8, this calculation enabled us to have approximately 35 study patients in each study group.

All data are presented as mean ± SD. The age, preoperative, pretreatment and posttreatment TWSNOT-22 scores, endoscopic score, mean MCA_2, smell threshold, and UPSIT-TC score were compared between two groups using Mann–Whiney *U* test. The gender, polyp and atopic status, and bacterial culture rates were compared using χ^2 test. In addition, pre and posttreatment outcomes were compared within the erythromycin and intranasal steroid group using Wilcoxon signed-rank test and McNemar test. All computations were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Two-tailed *p*-values < 0.05 were considered statistically significant.

3. RESULTS

3.1. Patients

One-hundred patients with persistent rhinosinusitis after FESS were included in the study. Seventy-two patients completed the study, with 35 in the erythromycin group, and 37 in the intranasal steroid group. The flow chart of enrollment and analyses is demonstrated in Fig. 1. In the erythromycin group, there were 15 males and 20 females aged 20 to 67 years, with a mean of 45.6 years. In the intranasal steroid group, there were 16 males and 21 females aged 24 to 67 years, with a mean of 49.4 years. The clinical characteristics of study subjects are listed in Table 1.There were no significant differences in gender or age between the two groups ($p = 1$ and 0.267, respectively). In addition, the prevalence of nasal allergy or asthma was not different between two groups ($p = 0.161$ and 0.233). More patients in the erythromycin group had nasal polyps before FESS ($p = 0.005$). Nevertheless, fewer patients had eosinophil-dominant nasal polyps in erythromycin group when compared to those of intranasal steroid group ($p = 0.002$).

3.2. Preoperative, pretreatment, and posttreatment clinical characteristics

There were no significant differences in the TWSNOT-22 score, mean MCA_2, smell threshold, UPSIT-TC score, or bacterial culture between the two groups either preoperatively, before treatment or after treatment (Table 2). The endoscopic score was significantly higher in the erythromycin group preoperatively and before treatment ($p = 0.002$ and 0.001, respectively) but was not shown to be significantly different between the two groups after treatment. Clinical presentations of representative cases at different timing from each group are shown in Fig. 2.

3.3 Comparison between preoperative and pretreatment clinical characteristics

Both TWSNOT-22 score and endoscopic score significantly decreased after surgery in the erythromycin group while the mean MCA_2 significantly increased. The saccharine transit time improved in 15 (42.9%) patients. In the intranasal steroid group, TWSNOT-22 score, smell threshold, and endoscopic score significantly decreased after surgery. The saccharine transit time improved in 15 (40.5%) patients.

3.4. Comparison between pretreatment and posttreatment clinical characteristics

Comparison of the clinical characteristics before and after treatment is shown in Table 3. In patients who were administered with erythromycin, there was no significant difference in the TWSNOT-22 score, mean MCA_2, UPSIT-TC score, or bacterial culture rate after treatment; however, the endoscopic score and smell threshold significantly decreased. The saccharine transit time improved in 24 (64.9%) patients. In patients who had taken the intranasal steroid, there was no significant difference in the TWSNOT-22 score, smell threshold, UPSIT-TC score, or bacterial culture rate after treatment. However, the endoscopic score significantly decreased, while the mean MCA_2 significantly increased. The saccharine transit time improved in 13 (35.1%) patients. The improvement rate of saccharine transit time was significantly higher in the erythromycin group ($p = 0.009$).

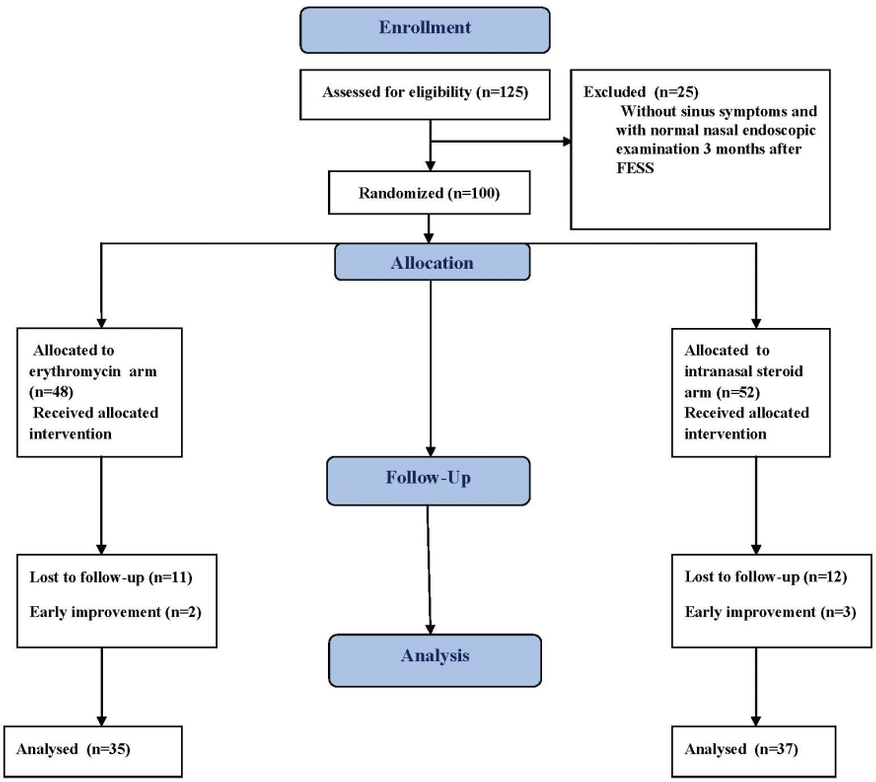

Fig. 1 Flow chart from enrollment to analysis.

Table 1

Characteristics of study subjects

Group	Erythromycin N = 35	Intranasal steroid N = 37	*p*
M/F	15/20	16/21	1[a]
Age (mean, SD)	45.63 ± 13.22	49.35 ± 12.24	0.267[b]
Nasal polyps, N, %	21 (60%)	10 (27%)	0.005[a,*]
Eosinophilic polyps, N, %	4 (11.4%)	8 (21.6%)	0.002[c,*]
Nasal allergy	16 (45.7%)	11 (29.7%)	0.161[a]
Asthma	2 (5.7%)	0	0.233[c]

[a]χ^2 test.
[b]Mann–Whitney *U* test.
[c]Fisher's exact test.
*$p < 0.05$.

4. DISCUSSION

Despite FESS having achieved a good success rate in the management of CRS, a group of post-FESS patients still required continuous medical treatment.[2] Several mechanisms have been postulated to explain the persistence of disease in these patients, including immunologic responses to bacterial or fungal pathogens, persistence of bacteria, and persistent neutrophilic inflammation.[5] Topical steroid treatment has been used to decrease the risk of recurrence after FESS, but the effect on patients was not uniform.[5,6]

Since 1984, long-term, low-dose erythromycin treatment was found to be effective for diffuse panbronchiolitis.[15] Nowadays, long-term, low-dose macrolide treatment has been widely used to treat CRS as well. It has been stated that macrolides may reduce inflammation and biofilm formation by preventing bacterial colonization.[16] In addition to antimicrobial property, macrolides have been shown to have immunomodulatory effects similar to those of steroids. The British society for allergy and clinical immunology (BSACIs) guidelines from the United Kingdom for the management of rhinosinusitis and nasal polyposis state that the effects of macrolide therapy is comparable to that of the FESS.[17] Several studies have investigated whether long-term, low-dose macrolide treatment assisted in the postoperative care of CRS patients but the outcomes were variable (Table 4).[2,6,17,18] Several factors may influence the results. One possible reason was that the FESS itself has a strong positive treatment effect on CRS, in that the additional effect of macrolide treatment was difficult to be clarified.[6]

Our results showed that patients' symptoms significantly improved at 3 months after FESS, indicating FESS is effective in the treatment of CRS. In addition, 2-month nasal irrigation after FESS could very well play a role also. When erythromycin treatment further improved the endoscopic score, smell threshold, and saccharine transit time in patients with persistent rhinosinusitis after FESS, it seemed that long-term, low-dose erythromycin treatment might be beneficial, although there was no placebo group included in this study. Nevertheless, there was no significant improvement in SNOT-22 scores after erythromycin treatment. When it is in terms of items associated with nasal symptom, there was a tendency of reducing nasal discharge and postnasal dripping after erythromycin treatment. Nakamura et al.[17] reported that 6 months of macrolide treatment demonstrated better effect than 3 months treatment. Whether extension of treatment period helps to improve subjective outcome needs further investigation We also found that intranasal steroid use increased mean MCA_2 significantly after treatment in addition to endoscopic score. Nevertheless, there were no significant differences in nasal obstruction score before and after intranasal steroid treatment. In our results, patients who received erythromycin rather than intranasal steroid had better improvement in olfaction after treatment. Improvement of olfaction from macrolide might be related to its antiinflammatory effects. Further investigation is necessary for understanding the mechanism of macrolide on olfaction.

Although erythromycin was the first drug in a class of antibiotics, and was used to treat infections caused by Gram-positive bacteria,[19] it has been reported that long-term, low-dose

Table 2

Comparison of preoperative, pretreatment, and posttreatment clinical characteristics between the erythromycin and intranasal steroid groups (data presented with mean ± SD)

	Erythromycin	INS[a]	*p*	Erythromycin	INS	*p*	Erythromycin	INS	*p*
Group	**Preoperative**			**Pretreatment**			**Posttreatment**		
TWSNOT-22 score	40.4 ± 18.6	40.5 ± 22.3	0.884[a]	27.8 ± 18.7	23.3 ± 18.6	0.195[a]	27.6 ± 22.9	21.5 ± 18.2	0.284[a]
Endoscopic score	6.7 ± 2.3	5.0 ± 2.1	0.002[a,*]	5.7 ± 1.4	4.7 ± 1.4	0.001[a,*]	4.4 ± 1.7	4.0 ± 1.6	0.384[a]
MCA_2	0.41 ± 0.17	0.47 ± 0.22	0.295[a]	0.48 ± 0.19	0.48 ± 0.20	0.919[a]	0.52 ± 0.23	0.60 ± 0.27	0.206[a]
Smell threshold	−3.50 ± 3.30	−2.65 ± 2.65	0.388[a]	−4.20 ± 3.44	−4.32 ± 3.19	0.691	−5.06 ± 3.50	−4.67 ± 3.19	0.703[a]
UPSIT-TC score	19.8 ± 9.6	17.7 ± 7.4	0.456[a]	20.4 ± 8.5	19.8 ± 8.6	0.668[a]	21.2 ± 9.1	21.4 ± 6.1	0.835[a]
Bacterial culture rate	31.4%	27.0%	0.691[b]	38.6%	32.4%	0.551[b]	32.9%	32.4%	1[b]

[a]Mann-Whitney *U* test.

[b]χ^2 test.

*$p < 0.05$.

INS, Intranasal steroid; MCA_2 = second minimal cross-sectional area; TWSNOT-22 = Taiwanese version of the 22-item sino-nasal outcome test; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test.

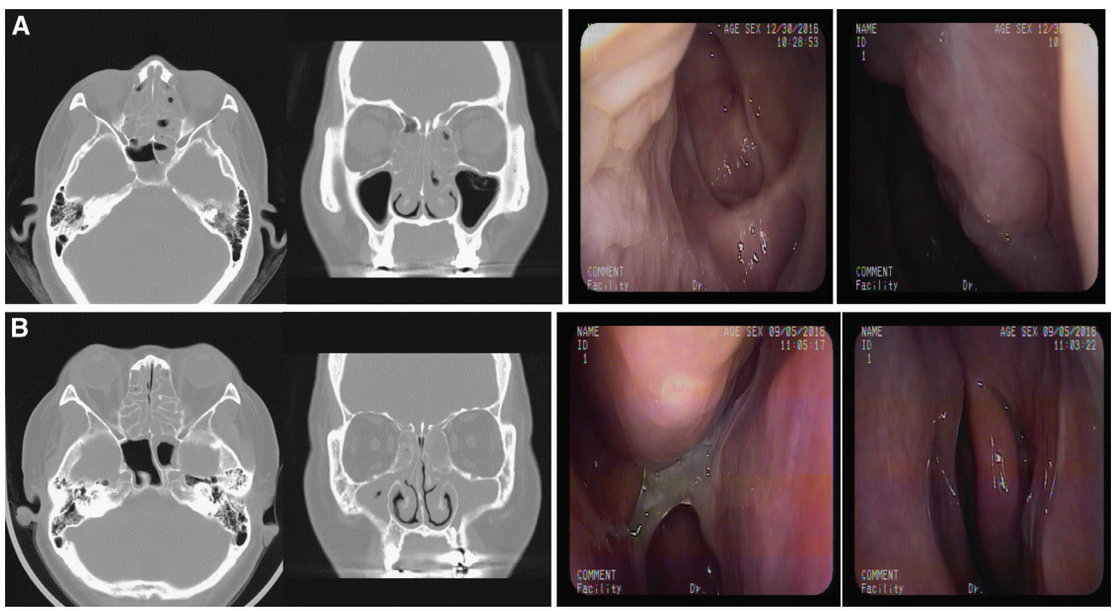

Fig. 2 Two representative cases of chronic sinusitis with nasal polyps after functional endoscopic sinus surgery, nasal irrigation, and 3 months of erythromycin (A) and intranasal steroid (B) treatment. Preoperative CT and posttreatment endoscopic pictures were shown.

Table 3

Comparison of pretreatment and posttreatment clinical characteristics in the erythromycin and intranasal steroid groups

Group	**Erythromycin**			**Intranasal steroid**		
	N = 35			**N = 37**		
Patient number	**Pretreatment**	**Posttreatment**	***P*[a]**	**Pretreatment**	**Posttreatment**	***P*[a]**
TWSNOT-22 score, (mean, SD)	27.8 ± 18.7	27.6 ± 22.9	0.701[a]	23.3 ± 18.6	21.5 ± 18.2	0.248[a]
Rhinological symptom scores of SNOT-22 (mean, SD)						
Need to blow nose	1.49 ± 1.38	1.23 ± 0.97	0.148[a]	1.59 ± 1.32	1.54 ± 1.39	0.876[a]
Sneezing	1.25 ± 1.17	1.26 ± 1.17	0.821[a]	1.14 ± 1.00	0.76 ± 0.96	0.034[a,*]
Runny nose	1.37 ± 1.24	1.49 ± 1.46	0.552[a]	0.97 ± 1.01	1.05 ± 1.00	0.526[a]
Postnasal discharge	1.83 ± 1.54	1.97 ± 1.65	0.508[a]	1.92 ± 1.40	1.78 ± 1.36	0.419[a]
Thick nasal discharge	2.06 ± 1.35	1.60 ± 1.56	0.061[a]	1.51 ± 1.47	1.32 ± 1.27	0.407[a]
Blockage/congestion of nose	1.46 ± 1.34	1.86 ± 1.38	0.848[a]	1.41 ± 1.21	1.24 ± 1.3	0.3[a]
Endoscopic score	5.7 ± 1.4	4.4 ± 1.7	<0.001[a,*]	4.7 ± 1.4	4.0 ± 1.6	0.006[a,*]
MCA_2	0.48 ± 0.19	0.52 ± 0.23	0.134[a]	0.48 ± 0.20	0.60 ± 0.27	0.002[a,*]
Smell threshold	−4.20 ± 3.44	−5.06 ± 3.50	0.044[a,*]	−4.32 ± 3.19	−4.67 ± 3.19	0.408[a]
UPSIT-TC score	20.4 ± 8.5	21.2 ± 9.1	0.596[a]	19.8 ± 8.6	21.4 ± 6.1	0.125[a]
Bacterial culture rate	38.6%	32.9%	0.593[b]	32.4%	32.4%	1[b]

[a]Wilcoxon signed-rank test.

[b]McNemar test.

*$p<0.05$.

MCA_2 = second minimal cross-sectional area; TWSNOT-22 = Taiwanese version of the 22-item sino-nasal outcome test; UPSIT-TC = traditional Chinese version of the University of Pennsylvania Smell Identification Test.

Table 4

Previous studies investigated macrolide therapy after functional endoscopic sinus surgery

Study	Subjects	Numbers	Study design	Treatment	Assessment	Results
Amali A, et al. 2015[2]	CRS after FESS	66 (22 azithromycin and 44 placebo)	A double blind, randomized, placebo-controlled trial	Azithromycin 250 mg/d, INS, plus saline irrigation vs placebo, INS, plus saline irrigation for 3 mo	SNOT-22	Long-term low-dose azithromycin in combination with the conventional therapy could statistically reduce the recurrence rate of CRS symptoms after FESS
Haxel BR, et al. 2014[6]	CRS after FESS	58 (29 erythromycin and 29 placebo)	A double-blind, placebo-controlled trial	Erythromycin 25 mg/d vs placebo for 3 mo	SNOT-20, olfaction, saccharin transient time, endoscopy	Only the nasal endoscopy score showed a statistically significant improvement in the erythromycin group compared to the placebo group
Nakamura Y, et al. 2013[17]	CRS after FESS	110 (44 3-mo and 66 6-mo' clarithromycin)	Randomized assigned	Clarithromycin 200 mg/d for 3 or 6 mo	Subjective symptom score and endoscopy	6-mo treatment group showed significantly lower VAS scores in rhinorrhea and postnasal drip, and lower endoscopic score at 12 mo after surgery
Varvyanskaya A, et al. 2014[18]	CRS with polyps after FESS	66 (22 in each group)	Randomized assigned	Clarithromycin 250 mg/d for 12, 24 wk, or no clarithromycin. All patients received mometasone furoate 400 μg/d	SNOT-20, acoustic rhinometry, saccharin transient time, endoscopy, CT, nasal ECP level	Significant improvement of all parameters except acoustic rhinometry and VAS in both 12 wks' and 24 wks' clarithromycin groups as compared to the control

CRS = chronic rhinosinusitis; CT = computed tomography; ECP = eosinophil cationic protein; FESS = functional endoscopic sinus surgery; SNOT = sino-nasal outcome test; VAS = visual analogue score.

Table 5

Bacteriology of patients in the erythromycin group (70*)

	Before FESS	Pretreatment	Posttreatment
Species	**No. of isolates**		
Aerobic and facultative bacteria			
Gram-positive			
Staphylococcus aureus	7	9	6
Coagulase-negative staphylococci	6	1	4
Streptococcus pneumoniae	3	3	3
Corynebacterium spp.	1		1
Moraxella catarrhalis	2		
Gram-negative			
Haemophilus influenza	1	4	4
Pseudomonas aeruginosa		6	2
Citobacter koseri		2	2
Enterobacter cloacae	1		
Nonfermentative Gram-negative bacillus	1	1	1
Total aerobic and facultative bacteria	22	26	23
Anaerobic bacteria			
Gram-positive			
Propionibacterium acnes		2	
Peptostreptococcus magnus	1		
Peptostreptococcus micros	1	1	
Gram-negative			
Fusobacterium nucleatum			2
Fusobacterium varium	1		
Total anaerobic bacteria	3	3	2
Total bacterial isolates	25	29	25

*Number of specimens.
FESS = functional endoscopic sinus surgery.

Table 6

Bacteriology of patients in the intranasal steroid group (74*)

	Before FESS	Pretreatment	Posttreatment
Species	**No. of isolates**		
Aerobic and facultative bacteria			
Gram-positive			
Staphylococcus aureus	2	14	15
Coagulase-negative staphylococci	5	1	4
Streptococcus pneumoniae		1	2
Corynebacterium spp.	2		1
Moraxella catarrhalis		1	
Gram-negative			
Haemophilus influenza		2	2
Klebsiella pneumonia	3	1	
Pseudomonas aeruginosa		1	2
Citobacter koseri	4	2	1
Enterobacter cloacae		1	
Proteus mirabilis	2		
Acinetobacter baumannii	2		
Total aerobic and facultative bacteria	20	24	26
Anaerobic bacteria			
Gram-positive			
Propionibacterium acnes		1	2
Peptostreptococcus magnus		1	
Peptostreptococcus micros	2		
Gram-negative			
Capnocytophaga sp.			1
Fusobacterium sp.	1		
Total anaerobic bacteria	3	2	3
Total bacterial isolates	23	26	29

*Number of specimens.
FESS = functional endoscopic sinus surgery.

macrolide treatment did not change the bacteriology.[16] Our bacteriological results had similar findings (Tables 5 and 6).

There are some limitations in this study. First, we did not divide the patients into groups of those with and without nasal polyps, because the number of patients was too small. Long-term, low-dose macrolide therapy has been reported to prevent any relapse of nasal polyps after FESS.[17] More patients with nasal polyps were enrolled in the erythromycin group than those in the intranasal steroid group, which might affect the interpretation of our results. However, none of the patients were observed with a recurrence of nasal polyps while beginning either erythromycin or intranasal steroid treatment. In addition, we found that less eosinophilic polyps in our erythromycin group. Whether macrolide therapy has a better effect on treating persistent rhinosinusitis after FESS in patients with nasal polyps still requires further investigation. Second, it has been assumed that macrolides may produce a better effect on CRS patients with a low level of serum immunoglobulin E (IgE) or atopy, although this remains controversial.[17,20–22] In this study, we did not measure IgE levels, eosinophil count, or eosinophil cationic protein contents. However, there were no significant differences in having allergic rhinitis or asthma between two study groups. Whether a low IgE level or atopy has an impact

on the effect of macrolides on persistent rhinosinusitis after FESS also requires further study.

In conclusion, our study showed that long-term, low-dose erythromycin treatment decreased the endoscopic score, smell threshold, and saccharine transit time in patients with persistent rhinosinusitis after FESS. On the contrary, intranasal steroids also helped postoperative care of CRS, especially in decreasing the endoscopic score and increasing MCA_2. It seemed that erythromycin treatment was beneficial in the management of postoperative persistent rhinosinusitis, but whether the effect of macrolides was better than intranasal steroids still requires further investigation. Furthermore, whether nasal polyps, atopy, or IgE levels influence the effect of long-term, low-dose erythromycin on CRS patients with persistent rhinosinusitis after FESS also require further investigation.

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