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 and secretion, and inflammatory cells migration and adhesion 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). Although FESS has shown to have a good success rate, postoperative mucosal inflammation requires continuous management after surgery. Therefore, it has been emphasized that postoperative care is very important toward a successful outcome of FESS. Many measures, procedures, and medications have been advocated for use in postoperative care, including nasal saline irrigation and topical steroids.

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. In some clinical trials, the use of macrolides exhibited improvements in symptoms, endoscopic findings, and saccharine transit time in CRS patients. 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. A few studies had reported positive effects from macrolide therapy for refractory CRS patients after FESS. Macroline 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. Any patient with a history of immunodeficiency or previous sinus surgery was not eligible for enrollment. After surgery, all subjects received nasal irrigation for 2 months, through the use of a Sanvic SH903 pulsatile irrigator.
The MCA2 of the right and left nasal cavity was averaged to give a mean MCA2 (cm²). The clinically significant difference was set as a difference of 2.3. Sample size and statistical analysis

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.

3.2. Preoperative, pretreatment, and posttreatment clinical characteristics

There were no significant differences in the TWSNOT-22 score, mean MCA2, 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 MCA2, 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 MCA2, 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 MCA2, 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).
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. 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. Topical steroid treatment has been used to decrease the risk of recurrence after FESS, but the effect on patients was not uniform.

Since 1984, long-term, low-dose erythromycin treatment was found to be effective for diffuse panbronchiolitis. 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. 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. 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). 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.

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. 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 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, improvement of olfaction from macrolide might be related to its anti-inflammatory 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, it has been reported that long-term, low-dose

![Flow chart from enrollment to analysis.](image)

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of study subjects</th>
<th>Erythromycin</th>
<th>Intranasal steroid</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td><strong>N = 35</strong></td>
<td><strong>N = 37</strong></td>
<td>( p )</td>
</tr>
<tr>
<td>M/F</td>
<td>15/20</td>
<td>16/21</td>
<td>1*</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>45.63±13.22</td>
<td>49.35±12.24</td>
<td>0.267*</td>
</tr>
<tr>
<td>Nasal polyps, N, %</td>
<td>21 (60%)</td>
<td>10 (27%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Eosinophilic polyps, N, %</td>
<td>4 (11.4%)</td>
<td>8 (21.6%)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Nasal allergy</td>
<td>16 (45.7%)</td>
<td>11 (29.7%)</td>
<td>0.161*</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 (5.7%)</td>
<td>0</td>
<td>0.233*</td>
</tr>
</tbody>
</table>

*\( \chi^2 \) test.  
*Mann–Whitney U test.  
*Fisher’s exact test.  
*p < 0.05.
Table 2
Comparison of preoperative, pretreatment, and posttreatment clinical characteristics between the erythromycin and intranasal steroid groups (data presented with mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Erythromycin</th>
<th>INS*</th>
<th>p</th>
<th>Erythromycin</th>
<th>INS*</th>
<th>p</th>
<th>Erythromycin</th>
<th>INS*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWSNOT-22 score</td>
<td>40.4 ± 18.6</td>
<td>40.5 ± 22.3</td>
<td>0.884a</td>
<td>27.8 ± 18.7</td>
<td>23.3 ± 18.6</td>
<td>0.196a</td>
<td>27.6 ± 22.9</td>
<td>21.5 ± 18.2</td>
<td>0.264a</td>
</tr>
<tr>
<td>Endoscopic score</td>
<td>6.7 ± 2.3</td>
<td>5.0 ± 2.1</td>
<td>0.002**</td>
<td>5.7 ± 1.4</td>
<td>4.7 ± 1.4</td>
<td>0.001**</td>
<td>4.4 ± 1.7</td>
<td>4.0 ± 1.6</td>
<td>0.384a</td>
</tr>
<tr>
<td>MCA</td>
<td>0.41 ± 0.17</td>
<td>0.47 ± 0.22</td>
<td>0.295a</td>
<td>0.48 ± 0.19</td>
<td>0.48 ± 0.20</td>
<td>0.919a</td>
<td>0.52 ± 0.23</td>
<td>0.60 ± 0.27</td>
<td>0.206a</td>
</tr>
<tr>
<td>Smell threshold</td>
<td>−3.50 ± 3.00</td>
<td>−2.65 ± 2.65</td>
<td>0.388a</td>
<td>−4.20 ± 3.44</td>
<td>−4.32 ± 3.19</td>
<td>0.691</td>
<td>−5.06 ± 3.50</td>
<td>−4.67 ± 3.19</td>
<td>0.703a</td>
</tr>
<tr>
<td>UPSIT-TC score</td>
<td>19.8 ± 9.6</td>
<td>17.7 ± 7.4</td>
<td>0.456a</td>
<td>20.4 ± 8.5</td>
<td>19.8 ± 8.6</td>
<td>0.668b</td>
<td>21.2 ± 9.1</td>
<td>21.4 ± 6.1</td>
<td>0.835a</td>
</tr>
<tr>
<td>Bacterial culture rate</td>
<td>31.4%</td>
<td>27.0%</td>
<td>0.691a</td>
<td>38.6%</td>
<td>32.4%</td>
<td>0.551b</td>
<td>32.9%</td>
<td>32.4%</td>
<td>1b</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.
**χ2 test.
* p < 0.05.
INS, Intranasal steroid; MCA = 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

<table>
<thead>
<tr>
<th>Group</th>
<th>Erythromycin</th>
<th>Intranasal steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>N = 35</td>
<td>N = 37</td>
</tr>
<tr>
<td>TWSNOT-22 score, (mean, SD)</td>
<td>27.8 ± 18.7</td>
<td>23.3 ± 18.6</td>
</tr>
<tr>
<td>Endoscopic symptom scores of SNOT-22 (mean, SD)</td>
<td>1.49 ± 1.38</td>
<td>1.54 ± 1.39</td>
</tr>
<tr>
<td>Need to blow nose</td>
<td>1.25 ± 1.17</td>
<td>1.26 ± 1.17</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1.37 ± 1.24</td>
<td>1.49 ± 1.46</td>
</tr>
<tr>
<td>Runny nose</td>
<td>1.83 ± 1.54</td>
<td>1.97 ± 1.65</td>
</tr>
<tr>
<td>Postnasal discharge</td>
<td>2.06 ± 1.35</td>
<td>1.60 ± 1.56</td>
</tr>
<tr>
<td>Thick nasal discharge</td>
<td>1.46 ± 1.34</td>
<td>1.86 ± 1.38</td>
</tr>
<tr>
<td>Blockage/congestion of nose</td>
<td>5.7 ± 1.4</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td>MCA</td>
<td>0.48 ± 0.19</td>
<td>0.52 ± 0.23</td>
</tr>
<tr>
<td>Smell threshold</td>
<td>−4.20 ± 3.44</td>
<td>−5.06 ± 3.50</td>
</tr>
<tr>
<td>UPSIT-TC score</td>
<td>20.4 ± 8.5</td>
<td>19.6 ± 8.6</td>
</tr>
<tr>
<td>Bacterial culture rate</td>
<td>39.6%</td>
<td>32.4%</td>
</tr>
</tbody>
</table>

*Wilcoxon signed-rank test.
**McNemar test.
* p < 0.05.
MCA = 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.
macrolide treatment did not change the bacteriology.\textsuperscript{14} 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.\textsuperscript{13} 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 polyps still requires further investigation. Second, it has been assumed that macrolides may produce a better effect on CRS 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 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 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.
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. 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.

ACKNOWLEDGMENTS

This study was approved by the Ethics Committee of Taichung Veterans General Hospital.

REFERENCES