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Evaluation of endoscopic sinus surgery for chronic sinusitis: Post-operative erythromycin therapy*

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SUMMARY

We discuss the results of endoscopic endonasal sinus surgery for chronic pan-sinusitis characterized by nasal polyposis, especially the effects of post-operative long-term administration of low-dose erythromycin (EM) therapy. The subjects analysed in this retrospective study are surgical cases who had initially been operated for chronic pan-sinusitis. They are classified into one group who has received a post-operative long-term, low-dose EM regimen and into another group who has not received this treatment. The groups have been compared with respect to: (1) the degree of improvement in the post-operative subjective symptoms; (2) post-operative objective findings of the ethmoidal sinus and the ostium of the frontal sinus; and (3) the degree of improvement in the maxillary sinus lesion. Better improvement is achieved in subjective symptoms and objective findings in the EM group than in the non-EM group.

Key words: chronic sinusitis, endoscopic sinus surgery, post-operative result, erythromycin

INTRODUCTION

About 45 years have passed since Takahashi's method of endonasal sinus surgery (Takahashi, 1950) was first employed by our department as an approach to chronic sinusitis, and it is about 13 years since our department started to employ endoscopy. We have previously reported (Moriyama et al., 1992) that the post-operative results of the endoscopic approach are superior to the naked-eye (non-endoscopic) approach in the treatment of chronic sinusitis. However, it is also true that there are some cases in which even the endoscopic endonasal approach fails to achieve improvement. These cases include "no change" cases and part of "mild improvement" cases, in terms of a clinical evaluation rating. Unsatisfactory results are seen with nasal discharge and post-nasal discharge in terms of objective symptoms and with persistence of maxillary sinus lesions and recurrence of ethmoidal sinus lesions, in terms of subjective findings. Thus, one of the current problems which endoscopic endonasal sinus surgery is confronted with, is the existence of a group of patients exhibiting insufficient healing. In order to cope with the problem, we have been striving to improve surgical techniques, for instance through the improvement of forceps, et cetera. In addition, we have contrived a means of improving post-operative drug therapy, i.e. we have administered erythromycin (EM) - which has recently been drawing much attention as a drug for treating pan-bronchiolitis (Kudo et al., 1987) - after endoscopic endonasal surgery of chronic sinusitis, in a low dose for a long period. This has resulted in excellent efficacy and these results, along with a brief discussion, are reported in this paper.

MATERIAL AND METHODS

Surgical method

Via the middle nasal meatus, the anterior and posterior ethmoidal sinuses are completely opened to make a single cavity (the mucosa is retained whenever possible), followed by restoration of good communication with the frontal sinus (i.e., through widening of the nasofrontal duct). The lamellae in the ethmoidal sinus are sufficiently resected using forceps to make the surface as smooth as possible. Again via the middle nasal meatus, the maxillary fontanelle is removed to achieve sufficient communication with the maxillary sinus (middle meatus antrostomy). In short, we create as wide a communication route as possible between the ethmoidal sinus and both the frontal and maxillary sinuses in order to facilitate ventilation and drainage, thereby aiming to normalize the diseased mucosa and achieve permanent curing of the sinusitis. However, for patients with severe mucosal lesions (such as polyps) in the maxillary sinus, we excise the lesions via the opening created by the middle meatus antrostomy, using a 70°-oblique endoscope and special forceps, taking care not to expose the bone surface. If deemed necessary, we open the sphenoidal sinus, but this treatment is required in only about 10% of the cases. Last, the posi-

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tion of the middle nasal concha is corrected so that the olfactory cleft opens properly. In addition, any existing nasal deformities (nasal septum deviation, hypertrophy of the inferior turbinate, et cetera) are surgically treated and corrected.

Administration of erythromycin

For the past several years, we have been using erythromycin (EM) with the patients' consent after endoscopic endonasal surgery of chronic pan-sinusitis. So far, the administration period of EM has been three months at the shortest and six months at the longest. With the objective of preventing infections, ordinary antibiotics (such as penicillins) are administered for two weeks after the operation, and then EM administration is started by the oral route. Usually, we administer a daily dose of 600 mg (t.i.d.) for 1–2 months, 400 mg (b.i.d.) for 1–2 months, and 200 mg (once a day) for 1–2 months. If the severity of the pathological lesion is not extreme, administration is stopped after three months.

Subjects

The subjects analysed in this retrospective study were adult patients who had been operated on for the first time all by the same surgeon using endoscopic endonasal sinus surgery for chronic pan-sinusitis during the period from 1985–1991. All patients had pathological lesions in both the ethmoidal and maxillary sinuses (and also the frontal sinus in many patients), and at least one year had passed since the operation. Their ages ranged from 15 to 70 years, with a mean age of 36.2 years. They were classified into one group consisting of 57 patients who had received a post-operative long-term, low-dose EM regimen (EM group) and another group consisting of 92 patients who had not received such a regimen (non-EM group). EM was administered with the patients' consent. Both groups were compared with respect to the criteria described in the following section. The pre-operative severity of the lesions in the EM group and non-EM group are compiled in Table 1. On the basis of the findings of tomography and CT, the severity of lesions in the ethmoidal and maxillary sinuses was rated into three grades: mild (+: slight hypertrophy of the mucosa), moderate (++: moderate mucosal hypertrophy), and severe (+++: entirely opaque).

Table 1. Severity of pathological changes before surgery.

erythromycin group (57 cases, 105 sides)		non-erythromycin group (92 cases, 144 sides)
	ethmoidal change	
35.2% (37 sides)	+++	34.0% (49 sides)
41.9% (44 sides)	++	38.2% (55 sides)
22.9% (24 sides)	+	27.8% (40 sides)
0%	-	0%
	maxillary change	
24.8% (26 sides)	+++	32.6% (47 sides)
41.0% (43 sides)	++	39.6% (57 sides)
34.2% (36 sides)	+	27.8% (40 sides)
0%	-	0%

+++: marked; ++: moderate; +: mild; -: none

Ethmoidal lesions were somewhat more severe in the EM group (polyps were present in 92 of 105 sides) than in the non-EM group. Maxillary lesions in the EM group tended to be rather milder than those in the non-EM group, but there were no significant differences between the two groups.

In the present study, patients with typical allergic diseases, such as asthma, as well as chronic sinusitis were excluded. Subjects in whom pre-operative tests revealed eosinophilia or a high serum IgE level, and to subjects manifesting allergic symptoms (e.g., sneezing), the anti-allergic drugs - such as azelastine, which blocks degranulation, as well as EM - were concomitantly administered, but patients receiving systemic or local steroidal drugs were excluded.

Evaluation methods

Both the EM- and non-EM groups were compared with respect to: (1) the degree of improvement in the post-operative subjective symptoms; (2) post-operative objective findings of the ethmoidal sinus and the ostium of the frontal sinus; and (3) the degree of improvement in the maxillary sinus lesions. Follow-up observations are still continuing at regular intervals, but the most recent findings are presented in this report. The shortest period from the operation was one year for some patients, while the longest follow-up period was more than five years.

The subjective symptoms were analysed based on the results of a questionnaire to the subjects with respect to nasal obstruction, nasal discharge, post-nasal discharge, heavy-head feeling, and overall improvement. Each item was rated by a four-grade system (+++; ++; +; -). An improvement by at least two grades from pre-operative rating to post-operative rating (i.e., +++/+, +++/-, or ++/-) was defined as "good improvement"; an improvement by one grade (i.e., +++/++, ++/+, or +/-) was defined as "fair improvement"; no change in rating as "no change", and aggravation of existing symptom(s) or appearance of symptom(s) not seen before operation was defined as "aggravated".

The findings obtained from the post-operative ethmoidal sinus were used to classify the patients into three groups: (1) those in which the sinus was almost normal; (2) those in which the sinus was covered with oedematous and/or polypoid mucosa; and (3) those in which the sinus had many polyps. The findings obtained from the post-operative frontal ostium were also used to classify the patients into three groups: (1) those in which sufficient communication was retained after opening of the sinuses; (2) those in which communication was seen, although the ostium had been narrowed by oedematous mucosa; and (3) those in which the ostium had been obstructed with polyps, et cetera.

Post-operative maxillary sinus lesions were graded into four groups from "severe" to "almost normal" (i.e., +++, ++, +, and -) based on the X-ray findings. Post-operative improvement in lesions by at least two grades was rated as "good improvement"; post-operative improvement by one grade as "fair improvement"; and absence of improvement was rated as "no change".

RESULTS

The degrees of improvement in the subjective symptoms are shown in Figure 1. The improvement in nasal obstruction are good in both the EM- and non-EM groups. The incidences of non-EM group patients showing "good improvement" in rhinorrhoea and post-rhinorrhoea was 59.3% and 50.6%, respectively. The corresponding incidences in the EM group were 78.9% and 66.7%, respectively, indicating clearly better results ($p < 0.05$; Wilcoxon two-sample test). With regard to overall improvement, as well, the EM group tended to show a higher improvement rate ($p < 0.01$; Wilcoxon two-sample test) and, in particular, the improvement rates in rhinorrhoea and post-rhinorrhoea were significantly higher in the EM group.

With regard to ethmoidal sinus lesions, nearly normal findings were recorded in 81.9% of the EM group, while the corresponding incidence in the non-EM group was 70.3%, indicating a considerable difference as might be expected (Figure 2). In addition, the incidence of a pathological mucosa, such as oedematous mucosa and polyps, was clearly lower in the EM group.

The findings of the frontal sinus ostium were in agreement with the findings of the ethmoidal sinus. The "patent" cases were seen in 78.1% of the EM group, which was clearly higher than the 60.8% in the non-EM group (Figure 3). Similarly, the incidence of mucosal lesions, such as polyps, was also lower in the EM group.

The degree of improvement in maxillary sinus lesions as evaluated by X-ray findings was "good improvement" in 72.4%, "fair improvement" in 23.8%, and "no change" in 3.9% in the EM group, while it was 55.9%, 36.5% and 6.8%, respectively, in the non-EM group (Figure 4). Thus, clearly better results were obtained in the EM group than in the non-EM group.

Changes in the bacterial flora harbouring in the maxillary sinus were found in a small number of patients who were on low-dose long-term EM therapy after endonasal operation. In patients with a severe lesion in the maxillary sinus, *Staphylococcus aureus* was detected during endonasal surgery and persisted for more than two months after surgical intervention, but the maxillary mucosal lesion improved markedly in some of them. From patients whose maxillary lesion was mild, *Staphylococcus epidermidis* and *Corynebacterium* were isolated during surgery, and these were still detected two months after surgery, but the maxillary sinus had been cured. In other patients, bacteria were isolated during endonasal operation, but two months post-operatively the maxillary mucosa had normalized and the bacteria had disappeared.

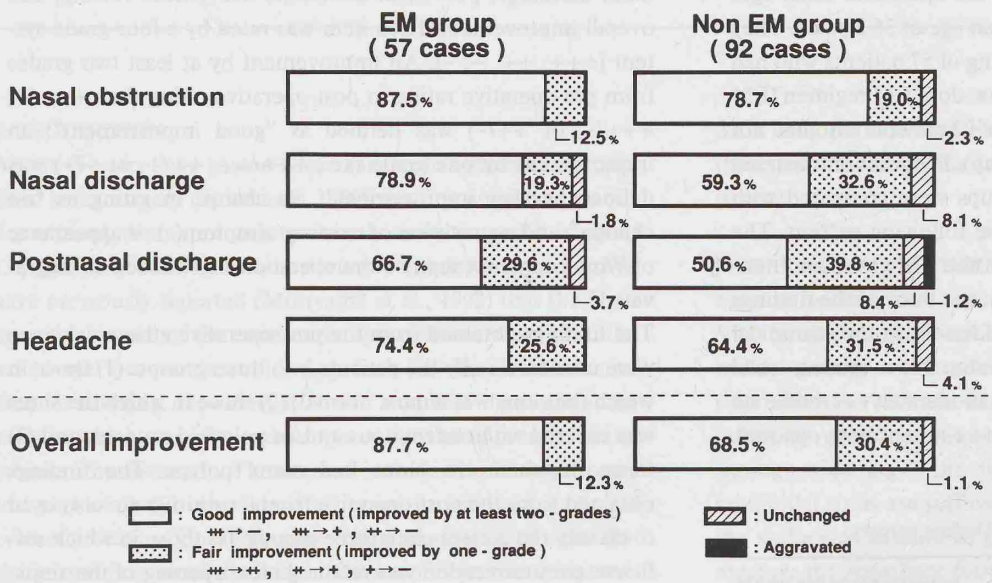

Figure 1.
Rate of improvement in subjective symptoms.

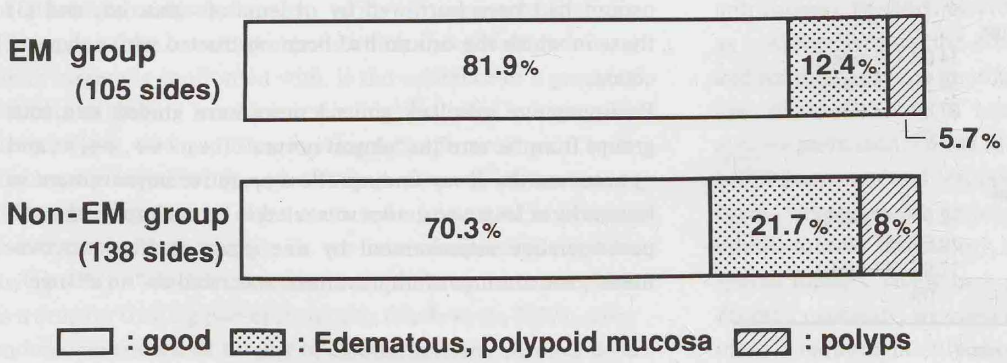

Figure 2.
Post-operative status of the ethmoidal sinus (243 sides).

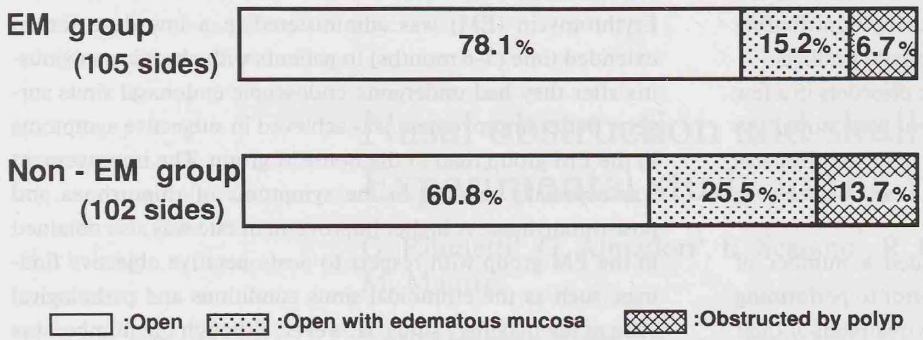

Figure 3.
Post-operative status of the nasofrontal duct (207 sides).

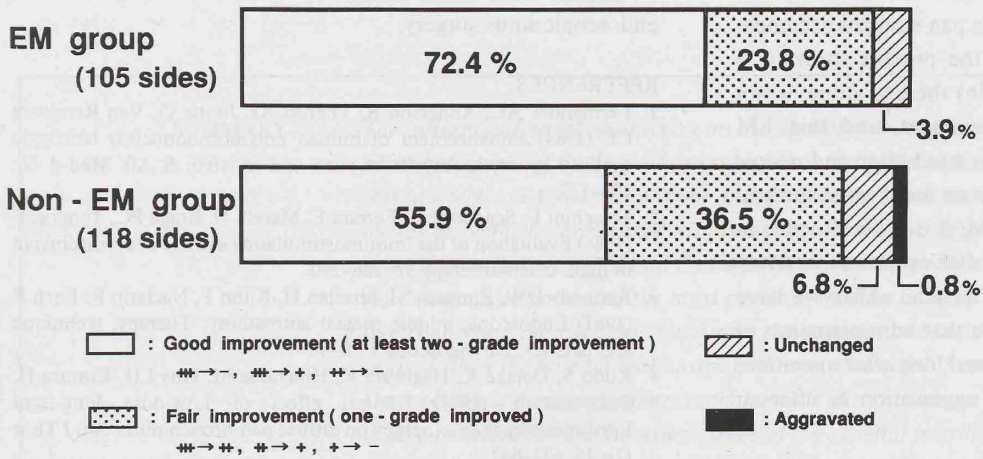

Figure 4.
Rate of improvement in the maxillary sinus (223 sides).

DISCUSSION

Compared to conventional surgical methods, endoscopic endonasal surgery for chronic pan-sinusitis achieves better results, but "marked improvement" has not been achievable in a small percentage of cases, including cases rated as "no change" and "worsening". In the past, such cases would be treated by Caldwell-Luc's surgery, which is a radical method. However, Caldwell-Luc's surgery has been reported to cause various post-operative problems, including strange feelings in the buccal region, neuralgia, development of maxillary sinus cysts, et cetera. Therefore, it is better to avoid this approach whenever possible. An even more serious problem with Caldwell-Luc's surgery is that it eliminates cavities that naturally exist in the paranasal sinuses. Even if surgical treatment is unavoidable, we should aim at achieving, whenever possible, a physiologically normal cure by retaining the original cavity structure of the paranasal sinuses. To improve the post-operative results of the endonasal approach, we must consider it from the following two aspects: (1) improvement in surgical method (Kennedy et al., 1987; Levine, 1990); and (2) improvement in post-operative drug therapy. The surgical method has been improved gradually thanks to the advance in optical instruments and as a result of improvements in forceps, et cetera. Regarding the second aspect, there has been little improvement in drugs for use after surgery for chronic sinusitis, in spite of the significant progress in developing antibiotics such as the third-generation cephalosporins. Therefore, in the present study, we decided to evaluate the efficacy of the macrolide antibiotic erythromycin – which has long been in use for treatment of diffuse pan-bronchiolitis – administered in a low dose for a long period.

As described in the Material-and-Methods section, there were no clear differences in the severity of pre-operative pathological lesions between the EM- and non-EM groups. Nevertheless, clearly better results were obtained in the EM group than in the non-EM group with respect to the improvement in both subjective symptoms and objective findings. In other words, the EM group achieved better results in terms of the state of healing of the ethmoidal lesions, findings of the frontal sinus ostium and the rate of improvement in the maxillary sinus lesions. Particularly marked improvement was seen in the EM group with regard to the subjective symptoms of rhinorrhoea and post-rhinorrhoea, and this indicates that EM has an action of suppressing secretion of mucus.

Many points remain unelucidated in relation to the action mechanism of EM. In addition to its primary anti-bacterial action, effects due to cell-activating actions, such as stimulation of migration of multinucleate leukocytes (Fermandes et al., 1984) and acceleration of active oxygen generation, effects due to activation of macrophages and lymphocytes, as well as effects based on enhancement of the activity of natural killer cells have been reported, but these are still hypothetical. It is surmised that various immunological actions (Van Rensburg et al., 1981; Fraschini et al., 1986) and suppression of mucus section (Satindra et al., 1990) as well as EM's primary anti-bacterial

action, are involved in improving physiological (i.e., mucociliary function) and morphological conditions, thereby contributing to improvement of nasal symptoms and endonasal findings.

With regard to side effects of EM, only gastric disorders in a few patients and numbness of hands in one patient were noted. As a whole, there were no side effects worthy of note, and EM was judged to be a drug that is highly safe and thus can be used over a longer period of time.

In the present study, the EM group included a number of patients to which we had administered EM prior to performing the operation and evaluated its efficacy in the treatment of their sinusitis. However, only very slight improvement in the symptoms of rhinorrhoea and post-rhinorrhoea was obtained. For the treatment of patients with to chronic pan-sinusitis accompanied by polyps, as those selected in the present study, it is thought that conservative (erythromycin) therapy alone, is not capable of achieving sufficient improvement, and that EM exerts much higher efficacy when it is used after endoscopic endonasal sinus surgery, as is evident from the present study.

Regarding time of administration of EM, it is most effective to start oral administration immediately after operation or when the patient has been discharged from hospital. Also, we have learned through our clinical experience that administration of EM is still efficacious even when it is used long after operation, for example when symptoms showed aggravation or after an revision surgery.

There have been reports describing that in patients undergoing EM therapy, the frequency of detection of pathogenic bacteria decreased, while that of non-pathogenic bacteria (so-called normal bacterial flora) increased. However, there have been very few reports of studies on changes in intrasinus bacterial flora in patients who received low doses of EM for a long period of time. It is predicted that low-dose long-term EM administration causes an increase in EM-resistant bacteria and a tendency toward diversification of bacterial species. To date, although we have not experienced any ill effects or a change in symptoms toward refractory ones due to the low-dose long-term EM therapy, the possibility remains that susceptibility to antibiotics other than EM decreases. Thus, there may be occasions in which it is necessary to take some precautions when administering this therapy for treatment of acute aggravation (infection) after endonasal operation.

CONCLUSION

Erythromycin (EM) was administered in a low dose for an extended time (3–6 months) to patients with chronic pan-sinusitis after they had undergone endoscopic endonasal sinus surgery. Better improvement was achieved in subjective symptoms in the EM group than in the non-EM group. The improvement was especially marked in the symptoms of rhinorrhoea and post-rhinorrhoea. A higher improvement rate was also obtained in the EM group with respect to post-operative objective findings, such as the ethmoidal sinus conditions and pathological state of the maxillary sinus. However, although the number was limited, there were cases in which nasal symptoms persisted or a complete cure was not achieved. These cases needed revision endoscopic sinus surgery.

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