Effects of Preoperative Clarithromycin Administration in Patients with Nasal Polyposis

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ABSTRACT

Objective: *In recent years, various investigators have shown considerable interest in the use of macrolide antibiotics for treatment of chronic rhinosinusitis and nasal polyposis. The aim of this study was to evaluate the clinical effects of preoperative long-term, low-dose clarithromycin administration in patients with nasal polyposis.*

Methods: *Eighty nasal polyp patients (42 non-atopic and 38 atopic) were included in this prospective, non-placebo controlled investigation and randomized equally to either the combined clarithromycin-surgical or surgical group. Forty patients received 500 mg of clarithromycin daily for eight weeks, and, after evaluation, they were treated by functional endoscopic sinus surgery (FESS). The other 40 patients were treated only surgically. The nasal symptom scores and endoscopic scores after macrolide treatment/surgical treatment, and after six and 12 months of follow-up were evaluated.*

Results: *After clarithromycin therapy, we found improvement in symptom scores in 25/40, and improvement in endoscopic scores in 19/40 patients. We found no significant difference in nasal symptom score between allergic and non-allergic patients regarding the outcome to macrolide (*$p = 0.352$*) or surgical treatment (*$p = 0.396$*). When we compared differences between endoscopic scores at the time points of 12 months and six months postoperatively (ESt12 minus ESt6), we found statistically lower differences in the clarithromycin-surgery group than in the surgery group (*$p = 0.006$*).*

Conclusion: *Preoperative clarithromycin administration postponed nasal polyp relapse after FESS. Allergies have no influence on the clinical efficacy of clarithromycin therapy and on the efficacy of FESS.*

Keywords: Clarithromycin, long term, low dose, nasal polyposis, surgical procedures

Efectos de la Administración de Claritromicina Preoperatoria en Pacientes con Poliposis Nasal

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RESUMEN

Objetivo: *En los últimos años, varios investigadores han mostrado un interés considerable en el uso de antibióticos macrólidos para el tratamiento de la rinosinusitis crónica y la poliposis nasal. El objetivo de este estudio fue evaluar los efectos clínicos de la administración preoperatoria de dosis bajas de claritromicina a largo plazo en pacientes con poliposis nasal.*

Métodos: *Ochenta pacientes con pólipos nasales (42 no atópicos y 38 atópicos) fueron incluidos en esta investigación prospectiva controlada sin placebo, e igualmente aleatoria para el grupo de combinación cirugía/claritromicina, o el grupo quirúrgico. Cuarenta pacientes recibieron 500 mg de claritromicina diariamente durante ocho semanas, y luego de la evaluación, fueron tratados mediante cirugía endoscópica nasosinusal (CENS). Los otros 40 pacientes fueron tratados sólo quirúrgicamente. Se evaluaron las puntuaciones de los síntomas nasales y las puntuaciones endoscópicas después del tratamiento quirúrgico/macrólido, y después de seis y doce meses de seguimiento.*

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Resultados: *Después de la terapia de claritromicina, hallamos una mejoría tanto de las puntuaciones de síntoma en 25/40, como de las puntuaciones endoscópicas en 19/40 pacientes. No encontramos diferencias significativas en la puntuación de los síntomas nasales entre los pacientes alérgicos y no alérgicos con respecto al resultado del tratamiento con macrólidos (*p = *0.352) o el tratamiento quirúrgico (*p = *0.396). Cuando comparamos las diferencias entre las puntuaciones endoscópicas en los momentos correspondientes a los 12 meses y seis meses postoperatoriamente (ESt12 menos ESt6), hallamos diferencias estadísticamente inferiores en el grupo de cirugía-claritromicina con respecto al grupo de cirugía (*p = *0.006).*

Conclusión: *La administración preoperatoria de la claritromicina retrasó la recaída del pólipo nasal después del tratamiento mediante CENS. Las alergias no tienen ninguna influencia sobre la eficacia clínica de la terapia con claritromicina, ni sobre la eficacia de la CENS.*

Palabras claves: Claritromicina, a largo plazo, dosis baja, poliposis nasal, procedimientos quirúrgicos

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INTRODUCTION

Nasal polyps develop usually in the anterior ethmoidal area and appear as grape-like structures, often in relation to inflammatory condition, but the exact aetiology is still under debate. Many histological studies have found higher numbers of inflammatory cells, especially eosinophils, neutrophils and lymphocytes in nasal polyp lamina propria compared to healthy nasal mucosa (1). Oxidative stress and chronic persistent inflammation are the main factors in the development of nasal polyps and inflammatory triggers include bacterial, fungal and viral infection, allergy and environmental pollution (2−4). Therefore, the results of previous investigations showed that allergy does not modify the symptoms and endoscopic finding of nasal polyposis (3, 4).

There have been many reports regarding the pharmacological actions of macrolide antibiotics in treatment of chronic rhinosinusitis and nasal polyposis (5, 6). Those actions include suppression of proliferation of nasal polyp fibroblasts, shrinkage of nasal polyps, supression of production of inflammatory mediators, such as interleukin (IL)-8, IL-1β and 'regulated on activation, normal T-cell expressed and secreted' (RANTES), breakup of bacterial biofilms, supression of secretion of mucin, promotion of ciliary movement, *etc* (5, 6).

For many years, nasal polyposis was managed by a combination of medical and surgical interventions. Of these, glucocorticoids (nasal or short-term oral) and functional endoscopic sinus surgery (FESS), have proven to be the medical and surgical treatment of choice. On the other hand, the present study has been designed to assess the effects of pre-surgical long-term clarithromycin administration and to compare this combined medical and surgical therapy with solely endoscopic surgical treatment in patients with nasal polyposis.

SUBJECTS AND METHODS

Eighty patients with nasal polyposis (42 non-atopic and 38 atopic) were selected for participation in the study and were randomized equally into either the combined clarithromycin-surgical or surgical group. This prospective, non-placebo controlled study was performed in accordance with the Declaration of Helsinki. The protocol and methods of the study were approved by the Ethics Committee of the Medical Faculty of the Military Medical Academy, Belgrade, Serbia. Written informed consent was obtained from all patients. The diagnosis of nasal polyposis was based on the presence of bilateral polyps in the nasal cavities on endoscopic examination and on the computed tomography (CT) presence of bilateral areas of opacification in the ethmoidal labyrinths in accordance with the current European guidelines (7). The exclusion criteria were the presence of unilateral nasal polyps, aspirin sensitivity, bronchial asthma, systemic diseases affecting the nose (sarcoidosis, primary ciliary dyskinesia, Wegener's granulomatosis, cystic fibrosis, Churg-Strauss syndrome), pregnancy, lactation and children under 18 years of age. None of the patients had any acute upper and lower respiratory tract infections, use of antibiotics, antihistamines, systemic or topical corticosteroids and montelukast within three weeks before the inclusion. All subjects with history of paranasal sinus surgery before enrolment were excluded.

The atopic status was evaluated on the basis of clinical criteria, medical history of allergic rhinitis, positive skin-prick tests and positive serological test. Skin-prick tests were performed on the volar part of the forearm with a standard battery of common aeroallergens: birch, timothy, mugwort (*Artemisia vulgaris*), dog, cat, horse, mite (*Dermatophagoides farinae, Dermatophagoides pteronyssinus*), molds (*Alternaria alternata, Aspergillus fumigatus, Cladosporium herbarum*), *Olea europaea, Parietaria judaica, Plantago lanceolata, Platanus acerifolia*). Negative (0.9% natrium-chloridum solution) and positive (1 mg/mL histamine dihydrochloride solution) controls were also included with each skin-prick tests. Reactions were read after 15 minutes and a test was considered positive if the diameter of wheal was greater than 3 mm with respect to the negative control. Total serum IgE level was measured by enzyme-linked immunosorbent assay (ELISA) kit (Elitech Diagnostics,

Salon-de-Provence, France) and an ELISA reader (Spectra III, Austria). Venous blood was collected and centrifuged, and the serum stored at -70 °C until testing. Subjects were considered allergic if they had a serum IgE level > 100 IU/mL.

Forty patients with nasal polyps, 22 non-allergic and 18 allergic, received 500 mg/day oral single dose of the 14-membered ring macrolide antibiotic clarithromycin for eight weeks. There was no concomitant medication used during the macrolide therapy. The exclusion criteria for long-term low-dose macrolide treatment were: pregnancy, lactation, macrolide hypersensitivity, younger than 18 years, liver and gastrointestinal dysfunction.

Functional endoscopic sinus surgery was performed on all patients from the first study group in whom we found nasal polyps of different sizes after clarithromycin therapy and on 40 nasal polyp patients from the second study group (20 non-allergic and 20 allergic). Surgery was done by the same rhinologist, under general anaesthesia, without any medical preoperative procedure. The surgical procedure always included uncinectomy, anterior ethmoidectomy and exploration of the posterior ethmoids. If the posterior cells were involved, we also performed a posterior ethmoidectomy, and in some cases, sphenoidotomy. The maxillary sinus ostium was enlarged and hipertrophical mucosa from the frontal recess was removed. If the septal deviation and concha bullosa were present, we performed the septoplasty (according to the Cottle procedure), and a resection of the lateral portion of the pneumatized middle concha, before the uncinectomy and anterior ethmoidectomy. Glove finger packs were applied in the middle meatus and broad spectrum antibiotics were prescribed for four days after the operations. Nasal washing with saline solution was carried out three times daily for two weeks. Operative findings and complications were recorded in every case. The diagnosis of nasal polyposis was confirmed by histopathological analysis.

The same rhinologist examined, treated and followed-up all the patients. In the clarithromycin-surgical study group, the patients were asked to assess their symptoms associated with nasal polyps (nasal obstruction, rhinorrhoea, anosmia, sneezing and itching) before clarithromycin treatment, within the seven days after clarithromycin treatment, within the two weeks after the surgical treatment, after six months, and, finally, after 12 months. In the surgical group, the patients were evaluated four times: before surgery, within the two weeks after the surgical therapy, after six months and after 12 months. The symptoms were scored from 0 to 3: 0 for no symptoms, 1 for mild symptoms, 2 for moderate symptoms, and 3 for severe symptoms, resulting in a maximum nasal symptom score of 15, as previously described (8).

Endoscopic examination was performed in a sitting position with a rigid endoscope (0° and 30°; Storz, Tuttlingen, Germany). In the clarithromycin-surgery group, each patient had five examinations: before starting the clarithromycin administration, within the seven days after clarithromycin treatment, within the two weeks after endoscopic surgical treatment, after six months, and after 12 months. In the surgery group, the subjects were examined four times: before surgery, within the two weeks after the surgical intervention, after six months, and after 12 months. The nasal polyp size scores were made on the basis of the endoscopic findings, according to Malm (9): 0 = no polyposis; 1 = mild polyposis (small polyps that do not reach the upper edge of the inferior turbinate); 2 = moderate polyposis (medium-sized polyps between the upper and lower edges of the inferior turbinate); 3 = severe polyposis (large polyps that reach the lower edge of the inferior turbinate). The maximum endoscopic score is six bilaterally. Improvement in endoscopic score after clarithromycin treatment was defined as observed shrinkage of nasal polyps giving a minimum score improvement of two, bilaterally, after therapy.

Findings from CT scans were evaluated only at the start of the study according to the Lund-Mackay score (10). Further assessments of mucosal status were not made using new CT, because it was not in accordance with the decision of the local Ethics Committee. The mucosal abnormalities were graded as 0 (no abnormality), 1 (partial opacification), or 2 (total opacification) of the frontal, maxillary, anterior ethmoid, posterior ethmoid and sphenoid sinus, bilaterally. The ostiomeatal complexes were scored bilaterally as 0 (not occluded) or 2 (occluded). The maximal CT grading score is 24.

The primary end point was determined to be the endoscopic finding, precisely endonasal presence of bilateral nasal polyps, 12 months after the surgical treatment. Our expectation was that at the time point of one year after the FESS, we will find 35% lower number of patients with endoscopic evidence of nasal polyps in the clarithromycin-surgery group than in the surgery group. Accordingly, a power analysis predicted simple sizes of 40 patients in each group would be required to raise the power of the study of 80%. The type I error (α level) was set to 0.05. For calculation of participants number in each group, the G*Power 3.1.2. programme was used. Data are expressed as mean ± standard deviation (SD). Paired comparisons within a group were performed using the paired two sample *t*-test. Comparison between the groups were analysed using the Chi-squared test and Mann-Whitney U-test. *P*-values < 0.05 were considered significant. The analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc., Chicago, USA).

RESULTS

No statistically significant differences between the clarithromycin-surgery and surgery groups were found in the baseline data of male/female ratio, age, number of allergic patients, nasal symptom score, endoscopic score, CT score and total serum IgE levels (Table 1). However, when we

divided our patients according to the atopic status, we found significantly higher concentrations of IgE in atopic patients, than in the non-atopic ones [338.25 ± 55.87 *vs* 77.61 ± 28.83] ($p = 0.007$).

Table 1: Baseline data

Parameters	Clarithromycin-surgery	Surgery
Patients	40	40
Age* (years)	44.28 ± 13.05	43.30 ± 12.16
Men/women	26/14	25/15
Non-allergic/allergic	22/18	20/20
Nasal symptom score*	12.53 ± 2.34	12.18 ± 1.99
Nasal endoscopic score*	5.08 ± 0.97	4.78 ± 0.86
Lund-Mackay CT score*	16.24 ± 3.26	15.87 ± 2.95
Total serum IgE (IU/ml)*	188.63 ± 57.25	165.97 ± 60.27

*mean ± standard deviation. CT: computed tomography

In the group of patients primarily treated with clarithromycin, the mean nasal symptom score improved from 12.53 ± 2.34 before to 9.60 ± 4.26 after antibiotic therapy ($p < 0.0001$). We found improvement of nasal symptoms in 25 (15 non-atopic and 10 atopic) of 40 patients (62.5%). After FESS, nasal symptom score decreased to 3.76 ± 1.30 ($p < 0.0001$). However, in the postoperative period, we found a tendency of symptom score increase from 5.44 ± 2.57 after six months to 7.23 ± 3.90 after 12 months (Fig. 1).

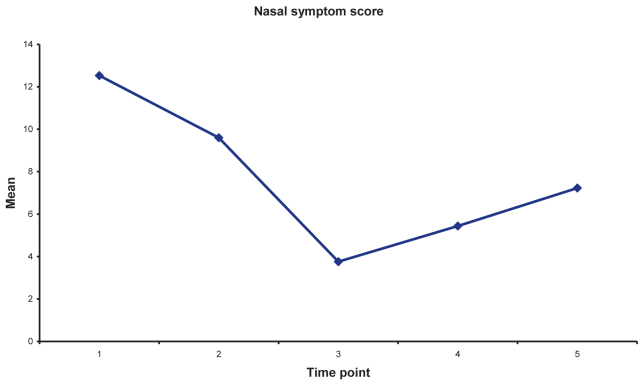

Fig. 1: Mean nasal symptom scores in clarithromycin-surgery group at different time points: at the start of the study (1), after clarithromycin administration (2), after endoscopic sinus surgery (3), six months after surgical treatment (4) and 12 months after surgical treatment (5).

In the group of only surgically treated patients, nasal symptom score decreased from 12.18 ± 1.99 before to 4.10 ± 1.00 after endoscopic sinus surgery ($p < 0.0001$). In the period after surgery, nasal symptom score increased from 6.03 ± 2.18 after six months to 7.60 ± 4.02 after 12 months (Fig. 2). We found no significant difference in nasal symptom score between allergic and non-allergic patients regarding the outcome to macrolide oral ($p = 0.352$) or surgical treatment ($p = 0.396$).

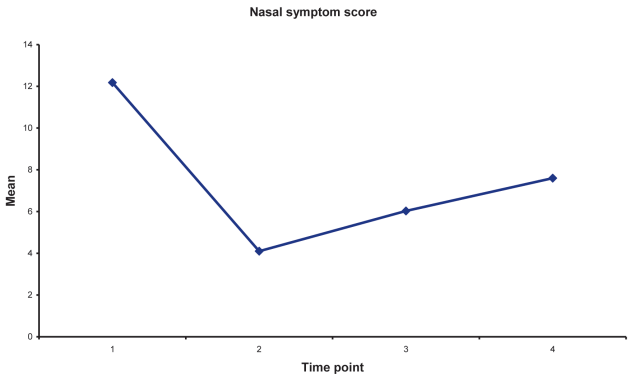

Fig. 2: Mean nasal symptom scores in surgery group at different time points: at the start of the study (1), after endoscopic sinus surgery (2), six months after surgical treatment (3) and 12 months after surgical treatment (4).

In the postoperative period, no difference regarding the increase of nasal symptom score was found between atopic and non-atopic patients in both the clarithromycin-surgery group ($p = 0.778$) and surgery group ($p = 0.063$).

When we compared differences between nasal symptom score at the time point of 12 months and at the time point of six months (NSSt12 minus NSSt6), we found no statistical differences between clarithromycin-surgery group (NSSt12-NSSt6 = 2.93 ± 2.63) and surgery group [NSSt12-NSSt6 = 1.58 ± 3.66] ($p = 0.069$).

Endoscopic score

In the group of patients treated by clarithromycin, after antibiotic administration, we found nasal polyps of different sizes in all 40 patients. However, shrinkage of nasal polyps was observed in 19 (10 non-allergic and nine allergic) patients (47.5%). The average endoscopic score improved from 5.08 ± 0.97 before to 4.03 ± 1.70 after clarithromycin therapy ($p < 0.0001$). Therefore, we observed that clarithromycin treatment was more effective in reducing the size of smaller polyps compared with bigger ones (Table 2). After surgical treatment, endoscopic score was minimized to 0. In the post-surgery period, endoscopic score was found to be continuous in growth: six months after FESS, we found nasal polyps in 11 (5 non-allergic and 6 allergic) patients (27.5%); after 12 months, nasal polyps were observed endoscopically in 14 (7 non-allergic and 7 allergic) patients (35%). In this period, endoscopic score increased from 1.29 ± 1.76 (after six months) to 2.31 ± 2.53 [after 12 months] (Fig. 3).

In the surgery group, average endoscopic score dramatically decreased from 4.78 ± 0.86 to 0. However, in the post-surgery period, endoscopic score increased from 1.38 ± 1.44 (after six months) to 2.73 ± 2.33 [after 12 months] (Fig. 4). Six months postoperatively, we found nasal polyps in 20 (10 non-atopic and 10 atopic) patients (50%), whereas 12 months after surgery, we found polyps in 25 (12 non-atopic and 13 atopic) patients (62.5%).

Table 2: Reduction in nasal polyp size score in non-allergic and allergic patients, comparing scores before (pre) and after (post) clarithromycin treatment

Non-atopic patients			Atopic patients		
Patient	**Pre**	**Post**	**Patient**	**Pre**	**Post**
1	6	2	1	6	4
2	6	6	2	4	2
3	4	2	3	4	2
4	6	4	4	6	6
5	6	6	5	6	6
6	4	2	6	4	2
7	4	4	7	5	4
8	6	5	8	5	2
9	6	4	9	4	2
10	6	6	10	6	6
11	4	2	11	6	4
12	6	6	12	4	2
13	4	4	13	4	2
14	6	6	14	6	6
15	6	6	15	6	6
16	4	2	16	6	6
17	4	2	17	4	4
18	4	4	18	5	6
19	4	2			
20	6	6			
21	6	4			
22	4	4			

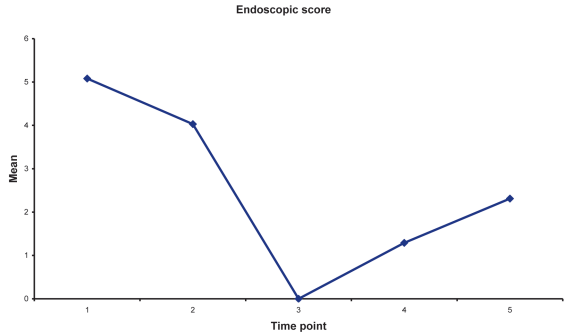

Fig. 3: Mean endoscopic scores in clarithromycin-surgery group at different time points: at the start of the study (1), after clarithromycin administration (2), after endoscopic sinus surgery (3), six months after surgical treatment (4) and 12 months after surgical treatment (5).

We found in the clarithromycin-surgery group a significantly lower percentage of patiens with the presence of nasal polyps than in the surgery group, six months postoperatively (27.5% *vs* 50%, $p = 0.034$; Chi-squared test), and 12 months postoperatively (35% *vs* 62.5%, $p = 0.029$; Chi-squared test). No differences regarding the growth of nasal polyps after FESS were found between allergic and non-allergic patients in both the clarithromycin-surgery group ($p = 0.510$) and in the surgery group ($p = 0.841$).

Finally, when we compared differences between endoscopic score at the time point of 12 months and at the time point of six months postoperatively (ESt12 minus ESt6), we found statistically lower differences in the clarithromycin-surgery group (ESt12-ESt6 = 1.05 ± 1.15) than in the surgery group [ESt12-ESt6 = 1.35 ± 1.19] ($p = 0.006$). So, our results suggest that preoperative use of clarithromycin postponed nasal polyp relapse after endoscopic sinus surgery.

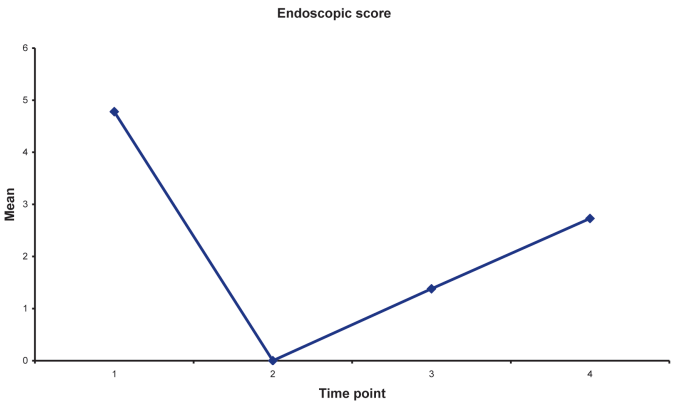

Fig. 4: Mean endoscopic scores in surgery group at different time points: at the start of the study (1), after endoscopic sinus surgery (2), six months after surgical treatment (3) and 12 months after surgical treatment (4).

In the surgery group, two patients suffered epistaxis on the fourth and on the sixth postoperative day. They were admitted for nasal packing and intravenous antibiotics for four days. Three patients developed nasal mucopurulent discharge and received courses of antibiotics, according to the antibiograms. Two patients developed synaechias between the middle turbinate and nasal septum. In the clarithromycin-surgery group, four patients reported a feeling of nausea on using macrolide antibiotic, but this feeling was tolerable, and the patients continued with therapy.

DISCUSSION

Long-term, low-dose administration of erythromycin, roxithromycin and clarithromycin has recently been reported to be very effective for patients with chronic upper respiratory tract inflammation. Ichimura *et al* (11) found that roxithromycin administered at 150 mg/day for at least eight weeks shrank the nasal polyp size in 52% of twenty investigated patients. Yamada *et al* (12) showed that clarithromycin administered at 400 mg/day for 8−12 weeks resulted in marked shrinkage of polyps in 40% of twenty patients. The results of the bacterial cultures suggest that the risk of selecting resistant bacteria is low after long-term, low-dose macrolide antibiotic treatment (13). In a small number of patients, the cultures were positive, but this was not always linked with an increase in symptoms, which could be due to the fact that in addition to the direct bacteriostatic effect of macrolides, they may in some cases reduce the virulence of bacteria without eradicating them (15). An interesting

evidence supporting macrolide use comes from Wallwork *et al* (14) in a placebo-controlled study of roxithromycin use in dosage of 150 mg daily for three months in twenty-nine patients with refractory chronic rhinosinusitis. The patients in the macrolide group demonstrated a significant improvement in subjective response, endoscopic findings and measured saccharine transit time compared to placebo. No macrolide resistant micro-organisms developed during treatment (14). Another investigation with thirty-three patients with chronic rhinosinusitis, performed by Videler *et al* (15), showed that sinonasal symptoms of patients treated with macrolides responded well in 76%, whereas nasal endoscopic findings responded well in 85% of patients at the end of the treatment. Ichimura *et al* (13) reported that the efficacy of macrolide therapy is not related to allergic symptoms. These results are not in accordance with results presented by Wallwork *et al* (14). Patients with low levels of total serum IgE showed significant improvements in symptom scores and endoscopic scores. Patients with high IgE levels showed no improvements in clinical scores (14). However, asthma and aspirin sensitivity were not the exclusion criteria for participation in Wallwork and co-authors' study. It is previously known that nasal polyposis in asthmatic and patients with aspirin sensitivity is an aggressive form of disease, mainly resistant to different modalities of corticosteroid and antibiotic therapy. Haruna *et al* (16) performed an investigation which included 68 patients with chronic rhinosinusitis and nasal polyps. The comparison of the findings of allergic examinations and the therapeutic efficacy of macrolides found no correlation between the presence of nasal allergies and the treatment efficacy (16). On the other hand, Bonfils and Malinvaud (17) showed that allergy does not modify the symptoms and endoscopic findings of nasal polyposis after surgical treatment. Our results showed that there was no relationship between the presence of atopy and clinical efficacy of clarithromycin treatment. Therefore, we found no significant influence of atopy on symptoms and endoscopic findings in the post-surgical period in both investigated groups (clarithromycin-surgery and surgery).

More interestingly, our results showed that at the time point of six months postoperatively, there was 22.5% fewer number of patients with endoscopic evidence of nasal polyps in the clarithromycin-surgery group, whereas 12 months postoperatively, in this group, the number of nasal polyp patients was 27.5% fewer than in the surgery group. This suggests that the relapse-free period was significantly longer among patients who received clarithromycin before surgical treatment. Our explanation is that long-term, low-dose preoperative clarithromycin administration can decelerate nasal polyp growth for a long time after surgical treatment. The mechanisms of polyp shrinkage during macrolide treatment are not well known. Although the mechanism by which macrolides reduce inflammation has not yet been fully elucidated, there is some evidence to indicate that macrolides are not simply bactericidal. Nonaka *et al* (18) demonstrated that *in vivo* roxithromycin administration directly suppressed nasal polyp fibroblast proliferation, and that this effect on fibroblast growth was persistent, indicating that this antibiotic may prevent the progression of nasal polyps by inhibiting the development of fibrosis. Therefore, although roxithromycin did not directly suppress IL-8 production from nasal polyp fibroblasts, the reduction in the proliferation of fibroblasts suggests that roxithromycin can indirectly reduce the total levels of IL-8 in the nasal polyps and thereby play a role in regulating inflammatory cell recruitment (18). Park *et al* (19) showed that macrolides can inhibit nasal polyp fibroblast differentiation and collagen production in differentiated nasal polyp fibroblasts through their antioxidant effect. The results of previous investigations showed that long-term, low-dose macrolide treatment can decrease inflammatory mediator production in nasal/paranasal sinus mucosa. *In vitro* roxithromycin administration directly suppresses IL-6 and RANTES production from cultured nasal polyp fibroblasts *via* the inhibition of IL-6 and RANTES messenger RNA expression (6). Previous investigations performed by Perić *et al* (20, 21) demonstrated that after eight weeks treatment by 500 mg single oral dose of clarithromycin daily, RANTES and IL-8 levels in nasal secretion samples fell in both allergic and non-allergic patients with nasal polyposis. Eosinophilic cationic protein (ECP) and tumour necrosis factor (TNF)-α levels fell in non-atopic patients, whereas IL-6 and IL-1β concentrations fell in atopic patients with nasal polyps (20, 21). So, long-term, low-dose clarithromycin administration has similar anti-inflammatory and variable immunomodulatory effect in these patients. Interestingly, decreased levels of RANTES and IL-8, strong eosinophil and neurophil chemo-attractants, were associated with a reduction in polyp size in non-allergic and allergic patients (20, 21). Matsune *et al* (22) demonstrated the ability of clarithromycin and roxithromycin to suppress vascular endothelial growth factor (VEGF) production from cultured nasal polyp fibroblasts, as well as VEGF messenger RNA expression. These findings suggest an additional mechanism by which macrolide treatment might reduce persistent inflammation in patients with nasal polyps. According to our results and previous investigations, we suggest that preoperative long-term, low-dose clarithromycin treatment can reduce the production of inflammatory mediators and growth factors in the nasal/paranasal sinus mucosa for a long time after the end of antibiotic administration, implying postponement of nasal polyp growth and prevention of polyp relapse after endoscopic sinus surgery.

CONCLUSION

The results of this investigation show the efficacy of preoperative long-term, low-dose macrolide treatment in patients with nasal polyposis. These results suggest that preoperative clarithromycin administration delays nasal polyp relapse after endoscopic sinus surgery. Allergies have no influence on the clinical efficacy of clarithromycin therapy

and on the efficacy of endoscopic sinus surgery. No differences regarding the growth of nasal polyps after FESS were found between allergic and non-allergic patients pre-operatively treated with clarithromycin, as well as in only surgically treated patients.

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