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Clinical and Rhinoscintigraphic Evaluation of Oral Macrolides in the Management of Sinonasal Polyposis

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Aim: To document the efficacy of low-dose long-term oral macrolide treatment in the management of sinonasal polyposis. The study was designed prospectively in a group of patients with sinonasal polyposis and negative history of surgery.

Materials and Methods: Ten patients were administered roxithromycin (RXM) 150 mg/day single oral dose for eight weeks. All patients underwent Tc-99m rhinoscintigraphic evaluation of mucociliary activity and endoscopic evaluation before and after the treatments. Response to treatment, in terms of rhinoscintigraphic and endoscopic improvement, was assessed.

Results: Of the 10 patients, 7 were male and 3 female, with an average age of 46 years (27-74). Following treatment, mucociliary transport time was significantly reduced ($P < 0.05$) and the polyps were clinically shrunk ($P < 0.05$).

Conclusions: It was determined that low-dose long-term oral macrolide treatment was effective in the management of sinonasal polyposis. Macrolides can be considered, as an alternative to or in conjunction with steroids, in the management of sinonasal polyposis.

Key Words: Sinonasal polyp, nasal polyp, nasal polyposis, macrolide, rhinoscintigraphy

Sinonazal Polipozis Tedavisinde Oral Makrolidlerin Yerinin Klinik ve Rinosintigrafik Olarak Değerlendirilmesi

Amaç: Düşük doz uzun süreli oral makrolid tedavisinin sinonazal polipoziste etkinliğini belirlemek. Çalışma, sinonazal polipozisli ve cerrahi hikayesi olmayan bir grup hastada prospektif olarak planmıştır.

Yöntem ve Gereç: On hastaya sekiz hafta boyunca günlük 150 mg roksitromisin verilmiştir. Tüm hastalara mukosiliar aktivitenin Tc-99m rinosintigrafik değerlendirilmesi ve tedavi öncesi ve sonrası endoskopik değerlendirme yapıldı. Tedaviye yanıt, rinosintigrafik ve endoskopik iyileşme ile değerlendirildi.

Bulgular: On hastanın 7'si erkek ve 3'ü bayandı. Ortalama yaş 46 (27-74) idi. Tedaviyi takiben mukosilier transport zamanı anlamlı derecede düşmüş ($P < 0.05$) ve polipler klinik olarak küçülmüştür ($P < 0.05$).

Sonuç: Düşük doz uzun süreli oral makrolid tedavisi sinonazal polipozisin tedavisinde etkilidir. Makrolidlerin, sinonazal polipozis tedavisinde bir alternatif olarak veya steroidlerle bir arada kullanımı düşünülebilir.

Anahtar Sözcükler: Sinonazal polip, nazal polip, nazal polipozis, makrolid, rinosintigrafi

Introduction

Sinonasal polyposis (SNP) represents an important clinical problem, with several local and/or systemic manifestations, and its prevalence ranges from 0.2 to 4.3% in the general population. SNP is considered to result from a chronic inflammation, and is characterized by edematous masses of mucosa prolapsing into the nose. Multiple factors, local and/or systemic, can play a role in the etiology. It can sometimes be associated with systemic diseases such as asthma, cystic fibrosis, primary ciliary dyskinesia, aspirin sensitivity, and allergy. Major symptoms are nasal obstruction, increased secretions, loss of smell, and headache, which may result in significantly reduced quality of life (1-5).

Management includes medical treatment and/or surgery, and can be quite challenging in some patients. Disease extension and systemic status are important in making the treatment decision. Medical treatment with various combinations is considered in both pre- and postoperative periods. Topical and/or systemic steroids are usually preferred. Endoscopic surgery is complementary but recurrences are frequent in the long-term.

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Therefore, even the best surgery should be followed by postoperative medical treatment (1-7).

In the search for alternative medical treatments, oral macrolides have been increasingly reported to reduce nasal polyps due to their anti-inflammatory effects (8,9). The aim of this study was to document the therapeutic effects of oral macrolides in SNP. We utilized rhinoscintigraphy to assess the mucociliary activity and endoscopic examination to evaluate clinical response.

Materials and Methods

Patients

The study involved 10 adult patients with SNP. The patients who had systemic and/or infectious diseases, history of nasal or systemic steroid application in the last 3 months, or history of sinonasal operations were excluded.

The study was designed prospectively in a single institution and was approved by the ethical committee. The patients received 150 mg/day oral single dose of roxithromycin (RXM) for 8 weeks. Clinical and rhinoscintigraphic improvement profiles were utilized to evaluate the success rates.

Nasal endoscopic examination was used for the clinical assessment of polyps and rhinoscintigraphy for evaluating the mucociliary activity. Both studies were performed before and after the treatment in all patients. Improvement in SNP-related symptoms was also evaluated in each patient.

Nasal examination: Diagnostic nasal endoscopy was done with topical anesthesia in sitting position with a rigid endoscope (4 mm, Storz-wide angle 0°). No decongestion or local anesthesia was used. The mass of the polyps in each nostril was assessed and the patients were staged according to the system of Lund and Mackay (10) (Table 1).

Rhinoscintigraphy: A gamma camera (Elscint SPX-6, Haifa, Israel) with a low-energy high-resolution collimator was used. Patients were positioned sitting in front of the gamma camera, with the involved nostril touching the collimator. Tc-99m MAA (macroaggregated albumin) (1.85 MBq; 50 µCi) was insufflated into the nostril while the patients held their breath. A spray applicator (nominal ejection volume, 50 µl) with a 2% aqueous solution of propylene glycol was used. The acquisition was immediately started, storing 30-second

Table 1. Special features of all patients before and after treatment.

Sex	Age	Pre-treatment Stage	Post-treatment Stage	Pre-treatment MTT (minute)	Post-treatment MTT (minute)
M	27	2	1	56.50	30.10
F	30	2	2	25.70	20.50
M	56	2	2	47.50	18.87
M	29	3	2	15.10	14.98
M	74	3	2	39.20	19.90
F	36	2	2	46.00	32.30
F	37	2	2	134.0	11.40
M	65	2	2	18.50	09.97
M	64	2	2	21.70	12.60
M	42	2	1	60.10	36.50

M: male; F: female; n: number of patients; MTT: mucociliary transport time.

The stages according to nasal endoscopic findings were as follows:

Stage-0: No polyp.

Stage-1: Polyps are limited to the middle meatus.

Stage-2: Polyps beyond the middle meatus but not completely obstructing the nasal cavity.

Stage-3: Polyps completely obstructing the nasal cavity.

frames for a total of 15 minutes per study. Two radioactive markers were placed on the mastoid and external acoustic meatus and then recorded. If no activity appeared in the pharynx, late static images were obtained 1 hour after radiopharmaceutical insufflation.

Regions of interest were drawn in the nasal cavity and pharynx. With the aid of radioactive markers, the separation between the palate and the pharynx was identified; here the radioactivity appeared as a downward and backward inclined area at the "end" of the scintigraphic pattern. Time-activity curves were obtained from each region of interest. The exact time when the radioactivity entered the pharynx was individualized using external markers, sequential images, and time-activity curves. The length of the radioactivity path from the hyperactive area corresponding to the insufflated radiopharmaceutical to the end of the nasal activity was displayed directly by the computer, transforming the number of pixels into millimeters. Mucociliary transport time (MTT) was then calculated by dividing length by exact time.

Assessment

Clinical and rhinoscintigraphic outcomes were used in order to assess treatment results.

Clinical assessment: A nasal endoscopy-based staging system and a questionnaire on patient improvement status were used. The questionnaires were completed by the patients under the observation of a resident, and nasal endoscopies were performed by the authors (HK, ED, AE) at each visit after the treatment. Final data at the 8th week visit was used as the end point of symptom profile and stage. Six SNP-related symptoms were evaluated.

Rhinoscintigraphic assessment: MTT was used for evaluating mucociliary function. The examinations were done before and after the treatment.

Statistical Analysis

Data were analyzed with the use of nonparametric statistics. All data were reported as medians with the interquartile range unless otherwise stated. Paired comparisons within a group were analyzed with the Wilcoxon signed rank test. Group comparisons were analyzed with the Mann-Whitney U test. A *P* value of <0.05 (2-tailed) was considered significant. Statistical Package for the Social Sciences (SPSS) 11.0 for Windows software was used.

Results

Of the 10 patients, 7 were male and 3 female, with an average age of 46 years (27-74). Patients were staged endoscopically; 8 were in stage-2 and 2 were in stage-3 before the treatment. Eight patients were in stage-2 and 2 were in stage-1 after the treatment (Table 1). Four patients were downstaged, and the average of the stages was improved from 2.20±0.42 to 1.80±0.42 after the treatment ($P < 0.05$) (Table 2).

The average MTT was improved from 46.43±34.66 to 20.71±9.28 after the treatment ($P < 0.05$) (Table 3).

Nasal stuffiness was the most common complaint. The improvement scores for the most frequent symptoms were as follows: nasal stuffiness improved in 22.2%, nasal drainage in 71.4%, and postnasal drainage in 25% of patients (Table 4).

Discussion

SNP is the most incapacitating benign disease of the nose, and its treatment is a subject of debate among clinicians and researchers. It is a multifactorial disease, and the current information about the cause and pathogenesis is inadequate for its cure. Several hypotheses have been put forward in the etiology, including systemic, local and genetic factors. Aspirin intolerance, epithelial cell defects/gene deletions, cystic fibrosis and ciliary dyskinesia, inhalant or food allergies, and altered Na+ absorption are all considered to be

Table 2. The stages before and after treatment (n: number of patients).

Stage	Pre-treatment		Post-treatment	
	n	%	n	%
0	0	0	0	0
1	0	0	2	20
2	8	80	8	80
3	2	20	0	0
Median (min-max)	2 (2-3)		2 (1-2)	
Mean (mean±SD)	2.20±0.42		1.80±0.42	

Table 3. Mucociliary transport time before and after treatment.

Mucociliary Transport Time			
Mean ± SD		Median (min-max)	
Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
42.60 ± 34.66	19.38 ± 9.28	42.60 (15.10-134)	19.38 (9.97-36.50)

Table 4. Pre-treatment and post-treatment symptoms and their improvement rates (n: frequency of patients' symptoms).

Symptoms	Pre-treatment		Post-treatment		Improvement	
	n	%	n	%	n	%
Nasal drainage	7	70	2	20	5	71.4
Postnasal drainage	4	40	3	30	1	25
Nasal stuffiness	9	90	7	70	2	22.2
Headache	9	90	8	80	1	11.1
Facial pain	5	50	5	50	0	0
Smell disorders	5	50	5	50	0	0

involved. Local mucosal and environmental factors are also important, resulting in alteration of aerodynamics with trapping of pollutants and epithelial disruptions (2,7,11-13). The other possible mechanism involves bacterial colonization of the nasal cavity, causing synthesis and release of enterotoxins that act as superantigens to stimulate the local immune system (14). In fact, the presence of inflammatory mediators is a prominent and common factor in SNP, indicating that chronic persistent inflammation is undoubtedly a major factor irrespective of the etiology (2,4,7,11-13).

Although the origin of polyps is not well understood, nasal polyps are well described in terms of cell types and cytokine content. Accumulation of eosinophils, neutrophils, plasma and mast cells, macrophages, and lymphocytes is a frequent finding, and there is much evidence on the activity and pathogenic role of these cells (2,13). A series of cytokines such as interleukin (IL)-1 , IL-3, IL-4, IL-5, IL-6, and IL-8, transforming growth factor-beta (TGF-beta), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokines such as eotaxin, RANTES and adhesion molecules (E-Selectin and P-Selectin, VCAM-1) are considered to be involved in the formation of polyps (2,8,13). The arachidonic acid pathway may also play a role in the initiation of polyposis, as well as the elevated 5-lipooxygenase activity (15).

Most authors agree that SNP management should be primarily based on medical treatment followed by complementary endoscopic sinus surgery in persistent cases (1-7). The aim of the medical treatment is to reduce polyp size, relieve symptoms, facilitate operative procedure and prevent recurrences. Systemic and/or intranasal (topical) steroids are the main medications used. Topical steroids can be used long-term either alone in mild cases or combined with systemic steroids and/or surgery in more severe cases (1,2,4,6). The efficacy of systemic steroids is well-known, but their usage is limited because of their potential adverse effects even in a healthy population. They are contraindicated and hazardous in a wide spectrum of diseases such as hypertension, diabetes mellitus, obesity, osteoporosis and glaucoma. Systemic effects of topical steroids are very rare, and use of these drugs does not cause dystrophy or atrophy of the nasal mucosa, but they are associated with some local side effects such as burning sensation, epistaxis, and oral candidiasis. Because of their wide

safety margins, these drugs have been used more than systemic steroids in clinical practice (6,16).

Macrolides have been used for decades as an important chemotherapeutic agent in the treatment of infectious diseases (8,9). The intracellular accumulation of macrolides altering the host cell functions has recently triggered a new interest in their therapeutic potential in clinical settings other than infections (17). A growing body of experimental and clinical evidence indicates that macrolide antibiotics possess distinct salutary properties that promote and sustain the reparative process in the chronically inflamed upper and lower respiratory tract (17,18). Potential effects of macrolides are to decrease the virulence of bacteria and suppress the production of bacterial toxins and biofilm formation. On the host site, they inhibit the activation of pro-inflammatory genes, increase apoptosis and degranulation of neutrophils, improve mucociliary transport and reduce goblet cell secretion (8). Many investigators have reported that anti-inflammatory effects of macrolides compete with their anti-bacterial effects (19). These distinct effects are expressed at lower doses, usually after a relatively prolonged period (weeks) of treatment, and in the absence of identifiable, viable pathogens. Long-term low-dose administration of macrolide antibiotics is not associated with increased incidence of adverse events, relevant bacterial resistance, or immunosuppression (8,18).

Erythromycin (EM) is the original macrolide molecule, and clarithromycin (CAM), RXM and azithromycin (AZM) are new semi-synthetic derivatives of EM. *In vitro* studies also support the view that there are no major differences in anti-inflammatory efficacy. The higher incidence of gastrointestinal side effects of EM suggests that newer macrolides, with better absorption and fewer side effects, can be preferred (8). The anti-inflammatory effects of RXM, CAM and AZM were compared in an experimental rat study. When rats were given a prophylactic dose of RXM, it suppressed the edema produced by injecting carrageenin into the paw with effects almost equal to those seen with the nonsteroidal anti-inflammatory drug nimesulide. However, AZM and CAM showed only slight anti-inflammatory effects (20).

These evidences suggest that macrolides can be effective in treating chronic rhinosinusitis (CRS) and SNP. In a clinical study, EM was found to improve MTT and decrease secretions in CRS and SNP (8). Our findings were also parallel to the results of this study.

In the human nose, the mucous flow is predominantly posterior towards the nasopharynx, streaming above and below the tubal opening. Nasal mucociliary transport is disturbed in a variety of conditions that affect the activity of the cilia. If there is a defect associated with pooling of the mucus or with squamous metaplasia, normal mucociliary transport will be lost at this site. SNP is edematous swelling of the nasal mucosa. The ciliated surface can undergo squamous metaplasia. When the mucociliary blanket is preserved, the mucous moves in the normal fashion, but with pedunculated swelling of the mucosa, the direction of the mucous flow may be changed. Patients with SNP have disturbed mucociliary function (21). MTT is a highly reproducible parameter and can be used to compare the therapy results (22).

Various well-established methods to study the ciliary activity of nasal mucosa are available. Direct methods such as stroboscopy, roentgenography, and photoelectron techniques are performed to assess the ciliary activity and the frequency of ciliary beat, but they are expensive and unsuitable for routine studies. Indirect methods use soluble, insoluble, or radioactive substances to assess nose-to-pharynx transport times. Saccharine and vegetal-carbon powder testing is the easiest and most inexpensive technique to evaluate nasal ciliary function (22). However, gamma scintigraphy (rhinoscintigraphy) provides the most physiological information about the deposition, dispersion and clearance of particles in the nose. It follows the movement of many particles once they have been deposited in the nasal cavity, rather than the movement of individual particles or the passage of a substance in solution such as saccharin (21). Thus, it appears to accomplish some significant goals in the research on the ciliary system of the nasal mucosa. However, the equipment is expensive, the patient has to remain in a room suitable for radioactive materials and the subject is exposed to the radiation. Various radiopharmaceuticals (colloidal solutions, resin particles, and albumin microspheres) labeled with ^{51}Cr or I-131 have been proposed for rhinoscintigraphy. Tc-99m MAA is preferred by most authors because it is cost-effective and has more suitable physical characteristics and does not allow radiation burden. MTT has been calculated as a mean 5.3 mm/min (range 3.3-8.2 mm/min) by rhinoscintigraphy (22).

In our study, we used Tc-99m MAA to compare the therapeutic effects of RXM objectively. The test was

successfully applied in all patients without any complication, and we were able to obtain satisfactory data. We determined that MTT decreased from 42.60 ± 34.66 to 19.38 ± 9.28, which revealed a significant improvement. We also used endoscopic evaluation to monitor the clinical response of the disease. We observed significant clinical improvement in accordance with the findings of rhinoscintigraphy. After the treatment, the stages were downgraded from 2.20 ± 0.42 to 1.80 ± 0.42.

Our findings were parallel to those in the literature, which revealed the efficacy of RXM in the medical treatment of SNP. The drawback of this study is the limited number of patients. Nevertheless, it is still possible to recommend that macrolides be considered in the treatment of SNP. Further studies with a higher number of patients should be designed to study preoperative and postoperative treatment alternatives. With the information available, we believe that macrolides are good treatment alternatives in the management of SNP, either in conjunction with steroids or as a replacement.

In conclusion, RXM was used in this study in the medical treatment of SNP. After RXM treatment, polyp size decreased, symptoms improved and mucociliary transport increased (MTT decreased). It was seen that a low-dose macrolide treatment was effective in the treatment of SNP. It is believed that macrolides can be an alternative to nasal and systemic steroids in the management of SNP, especially in patients in whom steroid use is contraindicated.

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