

The Efficacy of Clarithromycin in Patients with Severe Nasal Polyposis

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Abstract- Although several treatments have been suggested for nasal polyposis, from medical to surgical, there is no standard guideline for the management of this disease. During recent years increasing attention has been directed toward the effects of macrolide antibiotics on chronic sinusitis and nasal polyposis. In this study, the efficacy of clarithromycin on severe nasal polyposis were examined. In a Prospective, before - after study, forty patients with severe nasal polyposis received clarithromycin 500 mg twice a day for 8 weeks. At the beginning and end of treatment, the severity of patients' symptoms (using subjective analogue scale), computed tomography (CT) scan and endoscopic findings were recorded. After treatment, the severity of nasal obstruction, smelling problems, Post Nasal Discharge and rhinorrhea decreased significantly ($P<0.05$). Furthermore, the degree of sinus opacification in CT scan and endoscopic findings showed significant improvement. Most patients completed their treatment course without significant side effects. Although a course of clarithromycin improved nasal symptoms, polyp size and CT findings, further studies with more patients are required to recommend this drug as a general treatment in nasal polyposis

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Introduction

During recent decades, our knowledge of the pathophysiological mechanisms of nasal polyposis has increased. At the same time, treatment of this disease has been improved by the introduction of topical intranasal steroids and endoscopic sinus surgery (1).

Nowadays, corticosteroids administered either topically or systemically, are the most effective medical treatment and most experts consider intranasal steroid as treatment of choice in nasal polyposis (2). In general, surgery is reserved for cases who have failed medical treatment, but in patients with severe polyposis, surgery is regarded mandatory for successful treatment. However, the timing and type of the surgical procedure is also still a controversial subject (1).

Unfortunately, surgery of polyposis may cause complications secondary of scar formation. Furthermore, recurrence of polyps after surgery is not an uncommon event and at least one third of patients will experience it (3). Although there is little doubt that systemic corticosteroids are effective in reducing polyp size and associated symptoms, but due to adverse effects, there

are limitations in the use.

Topical application of corticosteroids significantly reduces adverse effects, but complete remission of the polyps may be achieved in only 60-80% of patients (4). In fact, extensive polyposis and polyps within the sinuses are problems to treatment success with intranasal steroids. Additionally even topical intranasal corticosteroid therapy can lead to systemic absorption and detectable suppression of hypothalamo-pituitary-adrenal axis (5). Thus, looking for new therapeutic approaches is clearly needed.

Even though, there is no single etiological factor that can explain the pathogenesis of nasal polyposis, the increased presence of inflammatory mediators indicates that chronic persistent inflammation is a common major factor in polyposis patients irrespective of etiology (6).

In the past decade, increasing interest has been shown in macrolide antibiotics in chronic sinusitis and nasal polyposis because of their effects on the immune system. Although there are a few studies that have demonstrated positive effects in chronic sinusitis and nasal polyposis (7-9), the debate concerning their therapeutic effects has been intense, and the need for

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more studies has been emphasized.

To gain insights into the unclear questions regarding macrolides treatment in nasal polyposis, this study was designed to evaluate the effect of a course of clarithromycin on nasal symptoms, endoscopic findings, and sinus opacification in CT scan in patients with severe nasal polyposis.

Patients and Methods

We conducted a prospective, before-after study in nasal polyposis patients who referred to otolaryngology clinic of Amiralam hospital, Tehran University of medical sciences between 2009 and 2011. All nasal polyposis patients were asked to fill in a questionnaire in which they rated their overall symptoms on a Visual Analogue Scale (VAS). Only patients with score 7 or more were included. Nasal polyposis was defined as the presence of visible bilateral polyps in anterior rhinoscopy or nasal endoscopy. We excluded patients with sinonasal symptoms of less than 1 year duration, patients with history of previous surgery or with evidence of allergic fungal sinusitis. We also excluded patients who had received oral or topical steroids or antibiotics during the past month.

The study was approved by the institutional research ethics committee, and 43 patients, who participated to study, were informed about objectives of the study, drug benefits and complications and completed informed consent forms. For all patients, the epidemiologic data were collected, including the age, sex, drug intolerance and possible side effects.

The severity of symptoms (nasal obstruction or congestion, smelling disturbance, headache and facial pain, nasal discharge, post nasal discharge (PND) were assessed with the Symptom Score Instrument (10), which uses a 0-10 visual analogue scale (VAS). On a 10 cm vertical line patients rated their symptoms ranging from 0 "no symptoms" to 10 "the most severe condition".

Endoscopic physical findings were scored based on the Lildholdt staging system (11) where

1=small polyps not reaching the upper edge of the inferior turbinate, 2= polyps reaching between the upper and lower edges of the inferior turbinate and 3= large polyps reaching below the lower edge of the inferior turbinate. Each side of the nose was graded separately, and scores from each side was added to determine the overall score of every patient.

The pretreatment CT scans of all patients were graded based on Lund-Mackay scoring system. This imaging scoring system considers sinus mucosal

thickening, extent of sinus opacification and obstruction of osteomeatal complex and a total score of 0 to 24 can be obtained (12).

After primary assessment, patients received clarithromycin 500 mg twice a day for 8 weeks. This dose was chosen based on previous studies in the literature (9,13). All patients were monitored weekly for their compliance and possible complications. At the end of treatment patients underwent endoscopy and CT scan again and their subjective score (VAS), endoscopic staging and CT scan score compared before and after treatment. For dealing with inter-observation variability, assessing before and after intervention was performed by one ENT specialist. We followed the patients for three months after the treatment course, and nasal endoscopy was repeated at that time.

For statistical calculation, paired *t*-test was used in the assessment of pre and post treatment values, and Wilcoxon signed rank test was performed during the evaluation of qualitative data. The statistical significance level was established at $P < 0.05$.

Results

During the study period, 43 patients with severe nasal polyposis were enrolled. Three of the patients were excluded from the study due to gastrointestinal disturbances and drug intolerance (in 2 patients) or loss of follow up (in one patient) so the data of 40 patients were evaluated. Patients' ages ranged from 17 to 64 years with Mean age 40.7 ± 16.4 years. Twenty-three (57.5%) of patients were male, history of smoking was positive in eight (20%) patients; five patients (12.5%) had asthma and two patients (5%) had a history of hypersensitivity to NSAIDs.

The mean of subjective analogue scale (VAS) scores before and after treatment were shown in table 1. After the treatment, the severity of all symptoms decreased considerably, however, the difference between before and after treatment scores was statistically significant for nasal obstruction, smelling problems and rhinorrhea. The largest improvement after treatment was noted for nasal obstruction and rhinorrhea, and most patients reported subjective improvement of their symptoms. None of the patients had aggravation of symptoms after treatment.

Mean of Lund-Mackay score before treatment was 20.37 ± 3.5 (range: 13-24) that changed to 14.24 ± 4.5 (range: 6-24) after treatment. This improvement was statistically significant ($P < 0.001$), however, the average score remained high, and a clear CT scan was not seen in any patient.

Table 1. Results of Subjective Analogue Scale Scores before and after treatment.

Symptom	Before Treatment	After Treatment	Mean Reduction of the Score	P- Value
Nasal obstruction	8.9+/- 0.5	4.8+/- 3.6	4.1+/- 3.1	0.001
Smelling disturbance	9.3 +/- 0.5	6.3 +/- 3.2	3.0 +/- 2.7	0.045
Headache and facial pain	4.2 +/- 3.3	2.3 +/- 1.6	1.9+/- 1.7	0.111
PND	5.4 +/- 2.4	3.6 +/- 2.2	1.8+/- 0.2	0.141
Rhinorrhea	7.3 +/- 2.2	2.9+/- 2.4	4.9+/- 0.7	0.001

In three patients, the Lund-Mackay score did not decrease in the score was observed (Table 2). have any change after treatment, but in others, a

Table 2. Changes of Lund-Mackay score after treatment.

Pretreatment Lund-Mackay Score	Frequency	Post-treatment Lund Mackay Score	Frequency
13	3	8	1
		9	1
		12	1
14	1	10	1
		16	1
17	2	12	1
		13	1
		9	1
18	6	14	1
		8	1
		11	1
20	5	12	1
		16	2
		18	1
		6	1
		10	1
		16	1
22	7	17	1
		18	1
		9	1
		11	1
		12	1
		15	1
		16	1
		18	1
23	2	20	1
		14	1
		19	1
24	12	8	1
		10	1
		12	1
		15	1
		16	2
		18	2
		20	2
		24	2

Table 3. Nasal Endoscopic Staging before and after treatment.

Pre-treatment endoscopic staging	Frequency	Post-treatment endoscopic staging	Frequency
Stage I	2	Stage I	2
Stage II	23	Stage I	17
		Stage II	6
		Stage III	0
Stage III	15	Stage I	0
		Stage II	12
		Stage III	3

Comparison of endoscopic staging of polyps before and after treatment is shown in Table 3. After treatment in twenty- nine patients, a clear decrease in polyp size occurred while 11 patients did not show any improvements but in no patient the size of polyps increased. A polyp free nasal cavity was not seen in any of our cases. Although complete clearance of polyps using clarithromycin was not achieved in any patient, 72% of patients showed an objective improvement. The differences were statistically significant at a *P* value <0.001.

Three months after completion of treatment, patients underwent endoscopic examination again. Three of the patients underwent endoscopic sinus surgery before 3 months follow-up and three of them did not return for reexamination visit. Among 23 patients who showed decreasing polyp size after treatment and returned for follow-up, two showed signs of polyp re growth within three months. Other patients remained stable over the follow-up period.

Except in two patients in whom the drug was discontinued because of severe gastrointestinal disturbances, almost all patients tolerated the treatment well and completed therapy with no major adverse event.

Discussion

This study was developed to gain more insight into the effects of clarithromycin in severe nasal polyposis. We enrolled only severe cases because these patients present a notable problem for treatment success especially with topical intranasal corticosteroids. Since subjective symptom score is the only tool currently validated to assess the severity in chronic sinusitis (2), we selected severe polyposis patients based on the VAS score. According to total severity VAS score, the disease can be divided into mild (VAS 0-3), moderate (VAS> 3-7) and severe (VAS > 7-10) (2).

Macrolide therapy can favorably modify the clinical symptoms of patients with a range of upper respiratory inflammatory conditions such as chronic sinusitis, diffuse panbronchitis, and cystic fibrosis (7). Although the therapeutic effects of the drugs are reported to be due, in part, to their anti- inflammatory activities rather than decreasing the virulence of colonizing bacteria (14), the precise mechanisms underlying macrolide therapy has not yet been fully elucidated.

Macrolides have been reported to normalize accumulation and activation of polymorphonuclear leukocytes especially neutrophils at the site of airway inflammation (13). Macrolides decrease mucosal secretion along the respiratory tract (15), inhibit vascular growth factor¹⁶and have a suppressive effect on nitric oxide production from fibroblasts (17).

Other effects of macrolides include increasing mucociliary movement, accelerating neutrophils apoptosis and thereby reducing injury products from these cells¹, and reduction of interleukin-8 and interleukin-1beta production suggesting that macrolides block cytokine-mediated neutrophil recruitment¹⁶.

It is well-known that bacterial infection is very common in patients with nasal polyposis (1), and coagulase positive *S. aureus* can be found in the middle meatus of nearly 70% of polyposis patients³. There is increasing knowledge that point to bacteria as a factor in the initiation or modification of nasal polyposis (18). So reducing virulent bacteria may be one of the mechanisms by which macrolides can influence polyposis.

As the intent of this study was to determine the efficacy of clarithromycin in severe nasal polyposis, it was necessary to find methods to reliably assess the different aspects of the disease. A variety of methods may be used for measuring symptom severity in chronic rhinosinusitis patients. Although Sinonasal Outcome Test-22 (SNOT-22) has been shown to be the best available test for subjective classification (19), however,

its use is time consuming and rather complicated in a busy clinic. Using simpler methods like VAS scoring is more feasible and enables an accurate and repeatable evaluation of symptoms (10). The Lund-Mackay staging system is a simple assessment tool that was developed to facilitate treatment decisions and currently has been recommended for future outcome research (12). Nasal endoscopy is needed to reliably diagnose polyposis and to evaluate the efficacy of treatment. Among the different methods that have been proposed for endoscopic staging, the score system that was used in this study was found to be reproducible and simple to use and has been recommended for polyp scoring in the clinical setting (11).

The main goals in treatment of nasal polyposis are the relief of patients' symptoms and prevention of complications and disease recurrences (3). Before treatment, the major nasal complaints were nasal blockage and loss of the sense of smell. At the end of study, most nasal symptoms improved especially nasal obstruction, rhinorrhea and smelling disturbance.

The size of polyps in endoscopy clearly decreased after treatment. In fact in post-treatment endoscopy in nineteen patients (48%) the polyps were limited to the middle meatus. However, nasal polyps remained in all patients after treatment, and there was no case in which polyps disappeared completely. Regarding the large size of polyps in these patients, it is not surprising that small polyps persisted after treatment. In a similar study, roxithromycin 150 mg daily for at least 8 weeks administered to 20 patients with nasal polyposis associated with chronic sinusitis. After treatment, there was a 52% reduction in polyp size as measured by rhinoscopy. The combination of roxithromycin with azelastine (1 mg twice a day), in another 20 patients with polyps improved 68% of patients (8). In another study involving 20 patients with nasal polyposis and chronic rhinosinusitis, there was a significant decrease in polyp size in 40% of patients after 8–12 weeks of treatment with clarithromycin 400 mg/day (9).

This study shows that sinus opacification improvement after treatment with clarithromycin was statistically significant, but the Lund score still remained high. This provides additional evidence that findings in CT scan do not necessarily correlate with the severity of nasal symptoms because most patients had only mild symptoms after treatment. Recent studies have shown that Lund-Mackay scoring system measures a different aspect of chronic sinusitis comparing to subjective scoring systems and the extent of disease in CT scan does not correlate strongly with the severity of

symptoms (12).

Anosmia is a very disturbing symptom in patients with extensive nasal polyposis that severely affects the quality of life. Unfortunately, olfaction in many studies remains the most challenging function to re-establish, and the effect of intranasal steroids or surgery with or without steroids on olfaction is poor (1,20). In our patient population, smelling disorder improved significantly after treatment. Because we measured olfaction only subjectively, more precise objective tests are needed to determine the exact effects of macrolides on olfaction.

Because of its pilot nature, this study lacks a control group and therefore the data should be considered with this in mind. Unfortunately we are not sure about long term outcome of patients with polyposis after treatment with macrolides and recurrence of symptoms is a strong possibility. Although three months follow up showed favorable results, further investigation is needed to determine the long-term efficacy of this treatment. Furthermore, long term treatment with macrolides may induce bacterial resistance, which may limit this approach. Further studies to answer these questions are required. Currently, there is a great interest in the role of macrolides in sinusitis and polyposis as physicians looking for new methods to decrease steroid usage in patients with severe disease. In our opinion, it is obvious that supplementary controlled studies with more patients and longer follow up must be performed before macrolides can be recommended as a general treatment for all polyposis patients. But until that time, clarithromycin may be considered as an adjunct treatment in severe nasal polyposis.

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References

1. Holmström M, Holmberg K, Lundblad L, Norlander T, Stierna P. Current perspectives on the treatment of nasal polyposis: a Swedish opinion report. *Acta Otolaryngol* 2002;122(7):736-44.

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- Fokkens W, Lund V, Mullol J; European Position Paper on Rhinosinusitis and Nasal Polyps Group. EP3OS 2007: European Position Paper on Rhinosinusitis and Nasal Polyps 2007. A summary for otorhinolaryngologists. *Rhinology* 2007;45(2):97-101.
- Bachert C, Watelet JB, Gevaert P, VanCauwenberge P. Pharmacological management of nasal polyposis. *Drugs* 2005;65(11):1537-52.
- Tuncer U, Soyulu L, Aydogan B, Karakus F, Akcali C. The effectiveness of steroid treatment in nasal polyposis. *AurisNasus Larynx* 2003;30(3):263-8.
- Fowler PD, Gazis AG, Page SR, Jones NS. A randomized double-blind study to compare the effects of nasal fluticasone and betamethasone on the hypothalamo-pituitary-adrenal axis and bone turnover in patients with nasal polyposis. *Clin Otolaryngol Allied Sci* 2002;27(6):489-93.
- Pawankar R. Nasal polyposis: an update. *Curr Opin Allergy Clin Immunol* 2003;3(1):1-6.
- Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope* 2006;116(2):189-93.
- Ichimura K, Shimazaki Y, Ishibashi T, Higo R. Effect of new macrolide roxithromycin upon nasal polyps associated with chronic sinusitis. *Auris Nasus Larynx* 1996;23:48-56.
- Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. *Am J Rhinol* 2000;14(3):143-8.
- Toros SZ, Bölükbaşı S, Naiboğlu B, Er B, Akkaynak C, Noshari H, Egeli E. Comparative outcomes of endoscopic sinus surgery in patients with chronic sinusitis and nasal polyps. *Eur Arch Otorhino laryngol* 2007;264(9):1003-8.
- Johansson L, Akerlund A, Holmberg K, Melén I, Stiernä P, Bende M. Evaluation of methods for endoscopic staging of nasal polyposis. *Acta Otolaryngol* 2000;120(1):72-6.
- Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: How is it used and what does it predict? *Otolaryngol Head Neck Surg* 2007;137(4):555-61.
- MacLeod CM, Hamid QA, Cameron L, Tremblay C, Brisco W. Anti-inflammatory activity of clarithromycin in adults with chronically inflamed sinus mucosa. *Adv Ther* 2001;18(2):75-82.
- Keicho N, Kudoh S. Diffuse panbronchiolitis: role of macrolides in therapy. *Am J Respir Med* 2002;1(2):119-31.
- Ikeda K, Wu D, Takasaka T. Inhibition of acetylcholine-evoked Cl⁻ currents by 14-membered macrolide antibiotics in isolated acinar cells of the guinea pig nasal gland. *Am J Respir Cell Mol Biol* 1995;13(4):449-54.
- Matsune S, Sun D, Ohori J, Nishimoto K, Fukuiwa T, Ushikai M, Kurono Y. Inhibition of vascular endothelial growth factor by macrolides in cultured fibroblasts from nasal polyps. *Laryngoscope* 2005;115(11):1953-6.
- Asano K, Kamakazu K, Hisamitsu T, Suzaki H. Suppressing activity of macrolide antibiotics on nitric oxide production from nasal polyp fibroblasts in vitro. *Acta Otolaryngol* 2003;123(9):1064-69.
- Bachert C, Gevaert P, van Cauwenberge P. Staphylococcus aureus enterotoxins: a key in airway disease? *Allergy* 2002;57(6):480-7.
- Morley AD, Sharp HR. A review of sinonasal outcome scoring systems- which is best? *Clin Otolaryngol* 2006;31(2):103-9.
- Benítez P, Alobid I, de Haro J, Berenguer J, Bernal-Sprekelsen M, Pujols L, Picado C, Mullol J. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. *Laryngoscope* 2006;116(5):770-5.