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Clinical and Microbiological Evaluation of Long Term Clarithromycin in the Treatment of Chronic Rhinosinusitis

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The overall aim of the present study was to examine the effect of long-term, low-dose clarithromycin treatment of a population with chronic sinusitis who did not respond to sinus surgery and traditional conservative therapy. Thirty nine patients with persistent symptoms of chronic sinusitis were studied. They had all been treated with systemic steroids and long-term antibiotics other than macrolides. A nasal swab was performed at each visit for microbiological evaluation and the microorganisms were identified by using standard bacteriological identification procedures. All patients were treated with Clarithromycin 500 mg 2x daily with other routine medication of chronic rhinosinusitis. Twenty six patients responded to the treatment (66.6%). There were no significant statistical differences between non-responders and responders in defined parameters at study commencement. After 3 months of treatment, endoscopes nasal examination scoring improved ($p<0.05$). In the Visual Analog Scale (VAS) scoring, the most significant change was in nasal obstruction ($p<0.05$). According to the results of microbiological investigation, *Staphylococcus aureus* was the most prevalent organism isolated from patients followed by *Pseudomonas aureginosa* and coagulase negative staphylococcus. At 3 months, the number of positive cultures were reduced with no *S. aureus* isolated. The results of present study suggest that long-term, macrolide antibiotic therapy is effective in the majority of surgical failures of chronic sinusitis. We recommend a minimum treatment period of 3 months to evaluate the efficacy of the treatment.

Key words: Clinical, microbiological, clarithromycin, chronic rhinosinusitis

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INTRODUCTION

Chronic maxillary sinusitis is defined as sinusitis lasting longer than 12 weeks (Winstead, 2003). Suggestive history as above may include chronic facial pressure (maxillary region), headache, rhinorrhea, postnasal drip, decreased sense of smell, or dental pain. Confirmatory findings on the physical examination include intranasal edema, purulence, or rhinorrhea. Antibiotics should be chosen after cultures are obtained endoscopically if possible (Nagi and Desrosiers, 2005). CT scanning should be obtained to confirm clinical suspicion of chronic sinusitis. Medical therapy is the first-line treatment of chronic sinusitis. It should consist of a 3 to 6 week course of oral antibiotics (e.g., fluoroquinolones or macrolides, a broad-spectrum penicillin class drug with beta lactamase inhibitor), steroids and nasal saline irrigations. The key to breaking a cycle of recurrent or chronic sinusitis is the aggressive combination of antibiotics with therapies directed at predisposing conditions for a length of time adequate to allow for healing of upper respiratory tract mucosa with recovery of local immune defense (Gillespie and Osguthorpe, 2004). Some consensus is apparent on the idea that antibiotic therapy for chronic sinusitis should be based on culture results. This is based on the increase in antibiotic resistances that have been increasing consistently throughout the decades (Brook, 2005). The maxillary tap is the gold standard for culture diagnosis; this method is highly uncomfortable to the awake patients (Parida and Bhagat, 2005). New generation macrolides such as Clarithromycin and azithromycin achieve excellent mucosal levels but should be considered backup drugs. Azithromycin appears to be more potent against *Haemophilus influenzae*, whereas Clarithromycin may be slightly better against intermediate resistant *Streptococcus pneumoniae* (Scadding, 2004). Prolonged use of low-dose macrolides in patients with chronic rhinosinusitis was found to be effective even when the identified bacterial pathogen was not sensitive to first line agents. The observation that macrolides antibiotics were steroid-sparing in patients who had steroid-dependent asthma has been present for decades (Scadding, 2004). An interesting aspect of the pharmacokinetics of macrolide antibiotics is their extensive tissue uptake and intracellular accumulation (Cervin and Wallwork, 2005; Krouse, 2005). The overall aim of the present study was to examine the effect of long-term, low-dose Clarithromycin treatment of a population with chronic sinusitis who did not respond to sinus surgery and traditional conservative therapy, including systemic and topical steroids as well as long-term antibiotic treatment with agents other than macrolides. The specific aims were to determine clinical outcome and microbiological changes.

MATERIALS AND METHODS

In total 39 patients without immunodeficiency and with persistent symptoms of chronic sinusitis after one or several functional endoscopic sinus surgical procedures were invited to enter into the study. Informed consent was obtained from each patient. They were recruited consecutively from the outpatient clinic at the ENT department at Imam Khomeini Hospital, Ahwaz, Iran, during year 2007. All patients had previously endoscopic sinus surgery and all patients had patent middle meatus antrostomy. They had all been treated with systemic steroids and long-term antibiotics other than macrolides. Despite of this, they still had symptoms of chronic sinusitis as defined by the American Academy of Otolaryngology-Head and Neck Surgery. The patients were 24 men and 15 women with mean age of 41±8.2 years. Symptoms were registered using a Visual Analog Scale (VAS) of from 0 to 10, where 0 is no discomfort and 10 is the worst possible discomfort. The symptoms registered were headache, nasal obstruction, Post Nasal Discharge (PND) or sticky secretion, sense of smell and general well-being. Using a slide ruler graded from 0 to 10, the patient indicates the subjective scoring for each of the listed symptoms before treatment and at 3 months. The nasal passages were assessed by the use of a 0-degree rigid endoscope. Nasal inflammation was noted as either absent (0 points), mild (1 point), moderate (2 points), or severe (3 points). At the first visit before treatment, all the above mentioned procedures were performed. In addition, a nasal swab was performed at each visit for microbiological evaluation, blood tests for liver function, because macrolide antibiotics have been found, in rare instances, to cause a reversible increase in liver transferase levels. The swabs for microbiological investigation were transferred to thioglycollate broth (Merck, Germany) and incubated for 24 h at 37°C. The subcultures were made on preliminary differential culture media as blood agar, chocolate agar, McConcky agar and Mannitol salt agar (Merck, Germany) and incubated overnight at 37°C observing standard microbiological procedures. 'the grown colonies were then identified using conventional biochemical tests (Forbes *et al*., 2007). The patients were treated with Clarithromycin 500 mg 2x

daily with other routine medication of chronic rhinosinusitis. Clinical and microbiological tests were repeated at 3 months and the patients' symptoms and culture results were evaluated. Data were analyzed with the use of nonparametric statistics. Statistical SPSS (version 13) software was used. Paired comparisons within a group were analyzed with the Wilcoxon signed rank test. Between-group comparisons were analyzed with the Mann-Whitney U-test. A p-value of <0.05 was considered significant. The study was approved by the Ethics Committee of the Department of Otorhinolaryngology-Head and Neck Surgery, Ahwaz Jondishapour University of Medical Sciences.

RESULTS

Twenty six patients responded subjectively to the treatment (66.6%). At inclusion into the study, there were no significant statistical differences between the non-responders and the responders in parameters including age, gender and symptom score. In the results of non-responder group although they did not experience any change in symptoms, motivating them to continue treatment, there was a trend of improvement in one symptom. There was a tendency for improvement in symptom scoring for PND or sticky secretion ($p = 0.081$). However, all other symptoms remained unchanged. All data were expressed as median in non- responder group before treatment and at 3 months of clarithromycin (Table 1). In the results of responder group at 3 months endoscopic nasal examination scoring improved ($p<0.05$). In the VAS scoring, the most significant change was in nasal obstruction ($p<0.05$). There also was a significant improvement in headache, nasal obstruction and PND or sticky secretion. There was a trend to improvement in general well-being, but no significant changes were seen in the sense of smell (Table 2). In all patients (responders and non-responders groups) from all of symptoms only headache and nasal obstruction were statistically significant after three months treatment. According to the results of microbiological investigation, *Staphylococcus aureus* was the most prevalent organism isolated from patients followed by *Pseudomonas aeruginosa* and coagulase negative staphylococcus before treatment commencement. At 3 months, the number of positive cultures were reduced and no patient was positive for *S. aureus* (Table 3). The positive cultures did not seem to influence the improvement experienced by the patients. Three patients had a persistent growth of the same bacteria throughout the treatment period and four patients had positive cultures at all times, however the species were varied.

Table 1: Prevalence of clinical symptoms in non- responders group

CRS criteria	Pretreatment (median)	3 months (median)	p-value
Endoscopy	2.0	2.0	0.070
±Headache	7.2	7.0	0.800
±Nasal obstruction	6.7	6.1	0.140
±PND	7.0	5.3	0.081
±Sense of smell	5.4	5.1	0.310
±General well- being	4.8	4.5	0.350

Pnd: Post Nasal Secretion, Endoscopy scoring is on scale from 0 to 3, where 0 is no inflammation and 3 is severe inflammation. ±Symptoms are expressed on a visual analog scale from 0 to 10 where 0 indicates no symptoms and 10 as possible symptoms

Table 2: Prevalence of clinical symptoms in responders group

CRS criteria	Pretreatment (median)	3 months (median)	p-value
Endoscopy	3.0	0.5	0.0021
±Headache	2.3	1.6	0.0050
±Nasal obstruction	1.8	0.1	0.0060
±PND	3.6	2.1	0.0380
±Sense of smell	5.0	3.2	0.3200
±General well- being	2.9	1.7	0.0410

Table 3: Incidence of isolated bacteria in initial cultures and 3 months after treatment

Organism type	Before treatment	3 months
S. aureus	12	0
P. aeruginosa	3	2
GNS	2	1
**H. influenza*	2	1
Moraxella catarrhalis	1	1
Enterobacter spp.	0	1

* nontypeable; GNS: Coagulase Negative Staphylococci

DISCUSSION

Chronic sinusitis is a common health problem that leads to frequent visits to primary care physicians and to ear, nose and throat Specialists in all over the world. It contributes to a significant amount of health care expenditure due to direct costs arising from physician visits and antibiotics, as well as indirect costs related to missed days at work and a general loss of productivity due to a decrease in life-quality of those affected (Scadding, 2004). Due to this, present study was undertaken to examine the effect of long-term, low-dose Clarithromycin treatment of a population with chronic sinusitis. 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. This was recently shown with *Pseudomonas aureginosa*, where erythromycin, at concentrations below that required for an antibacterial effect, suppressed the production of toxic lectins as well as protease and hemolysin. Besides, it was also shown that the bacteria in antibiotic-treated patients had reduced virulence in mice (Sofer *et al*., 1999). Macrolides downregulate the excessive immune and inflammatory

responses observed in these conditions while promoting tissue repair (Hatipoglu and Rubinstein, 2007). Animal studies, as well as in vitro data, support this view. In the guinea pig trachea, it was shown that the oral administration of Clarithromycin (5 mg kg^{-1}) or Erythromycin (10 mg kg^{-1}) inhibited lipopolysaccharide-induced goblet cell hypersecretion (Tamaoki *et al*., 1997). Furthermore, studies of experimental pulmonary infections suggest that macrolides accelerate apoptosis of neutrophils, thus reducing the possibility for prolongation of the inflammatory response (Chin *et al*., 1998). Some *in vitro* evidence for anti-inflammatory effects has been found when studying inflammatory cells. Macrolides seem to affect degranulation of neutrophils and eosinophils, thus interfering with the release of cytotoxic substances. Prolonged use of low-dose macrolides in patients with chronic rhinosinusitis was found to be effective even when the identified bacterial pathogen was not sensitive to this agent. This management has also been found to decrease the size of nasal polyps (Denburg and Keith, 2004). There also is evidence for a direct interaction between macrolides and the intracellular regulation of pro-inflammatory mediators. An interesting aspect of the pharmacokinetics of macrolide antibiotics is their extensive tissue uptake and intracellular accumulation. Macrolides accumulate in inflammatory cells at concentrations up to several hundred-fold higher than concentrations in extracellular fluid. The macrolide antibiotics decrease cytokine production (IL-5, IL-8, GM-CSF, TGF-β, IL-6, IL-8, TNF-α), altered structure and function of biofilm, reduced expression of cell surface leukocyte adhesion molecules, accelerate neutrophil apoptosis, impaired neutrophil oxidative burst, decrease secretion and improve mucociliary clearance and Inhibited release of elastase, protease, phospholipase C and eotaxin A by *P. aeruginosa* (Denburg and Keith, 2004). The present study shows that long-term treatment with Clarithromycin is effective in some cases of chronic sinusitis with surgical failure. All of our patients had previously undergone sinus surgery, most of them on several occasions. They had also been treated both systemically and locally with steroids as well as long-term treatment of antibiotics other than macrolides. In these patients, chronic sinusitis had a severe impact on their quality of life. As an alternative to systemic steroids, a patient taking macrolides seems to be less troubled by side effects, especially the mood swings, restlessness and weight gain that seem to trouble patients on systemic steroids. Present study postulated that in the non-allergic patient who has chronic sinusitis despite adequate surgery, long-term Clarithromycin therapy is a valid alternative. We recommend a minimum treatment period of 3 months to evaluate the efficacy of the treatment.

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