

## Original Research Article

# Long term oral azithromycin versus functional endoscopic sinus surgery in patients suffering from chronic rhinosinusitis: a comparative study

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### ABSTRACT

**Background:** Chronic rhinosinusitis (CRS) is defined as inflammation of the nasal cavity and paranasal sinuses. Azithromycin, a macrolide antibiotic, a well-established class of anti-bacterial agents, which also have anti-inflammatory properties. The present study was designed to compare the role of azithromycin with surgical management in patients with chronic-rhinosinusitis.

**Methods:** The study population included 60 adult patients with symptomatic CRS refractory to 3 weeks of medical therapy. The patients were divided in two groups with 30 patients in each group. One group of patients received oral Azithromycin as main treatment for 12 weeks while the other group of patients underwent sinonasal surgery. Symptom scoring and endoscopic scoring were done previous to the treatment and at 1 month and 3-month follow-ups.

**Results:** A good subjective as well as objective outcome in terms of symptom improvement was obtained with in patients with chronic rhinosinusitis with Surgical intervention as compared to those patients who received long term oral Azithromycin.

**Conclusions:** We advocate that patients suffering from chronic sinonasal disease should be initially targeted with maximal medical therapy using an oral macrolide for at least 3 months. After this patient should be assessed and surgery considered in those cases refractory to medical therapy.

**Keywords:** Chronic rhinosinusitis, Macrolide, Azithromycin, FESS

### INTRODUCTION

Chronic rhinosinusitis (CRS) is defined as inflammation of the nasal cavity and paranasal sinuses. It is a multifactorial illness caused by air pollution, viruses, bacteria, fungi, genetic factors, immunodeficiency and anatomic abnormalities within the sinus system each of these play a contributory role in disease. Because of the multifactorial nature of the disease, it is often difficult to define a precise cause of illness in an individual patient.<sup>1</sup> It causes significant physical symptoms, negatively affects quality

of life (QOL), and can substantially impair daily function. It is fairly well accepted that rhinosinusitis is one of the most common reasons that an individual seeks medical care, resulting in high direct medical costs, including the costs of an office visit, diagnostic tests (such as cultures and laboratory or radiological investigations), antibiotics or other pharmaceuticals, procedures or surgery and hospitalization. Immunoglobulin deficiencies whether transient or permanent, diminish the body's ability to combat infection. Allergic reaction can lead to obstruction of the sinus ostia, preventing mucus outflow. Ostial

obstruction results in a reduction in oxygen tension, changes in mucociliary transport, and a transudation of fluid into the sinuses.<sup>2</sup> The ostiomeatal complex or ethmoid sinus area is believed to be a major focus for the initiation of CRS. It has long been recognized that persistent infection within the ethmoid sinuses is usually the reason for failure of therapy directed at any other paranasal sinuses.<sup>3</sup> Obstruction of the area generally leads to secondary blockage of other sinuses.<sup>4</sup>

Anatomic factors occasionally play a significant role in rhinosinusitis. Septal spur or deviation, hypertrophic or paradoxical middle turbinate and concha bullosa have been identified as anatomic abnormalities that can affect outflow of the sinus and result in rhinosinusitis.<sup>4</sup> CRS is an extremely common medical condition and one of the most common reason for attendance of an otolaryngologic clinic. Surgery in the form of Functional Endoscopic Sinus Surgery (FESS) is the procedure of choice for patients who fail to respond to medical treatment.<sup>5</sup>

Hyperplastic changes in mucosa associated with increased secretions in nose and paranasal sinus are typical. The infiltrate contains lymphocytes, plasma cells, neutrophils, and eosinophils.<sup>6</sup> This leads to hyperplastic and hypertrophic changes of nasal and sinus mucosa which causes narrowing of the drainage route from the openings of paranasal sinuses, leading to polypoidal changes in the area. Excessive secretions disturb mucociliary clearance leading to subsequent bacterial infections. Obstruction of sinus ostia creates a negative pressure and hypoxic environment within the sinus, and leads to inflammation and an ideal culture medium within sinus cavity.<sup>7</sup> Thus, maintaining a patent ostium is very important in reversing sinus disease.<sup>8</sup>

Azithromycin belongs to macrolide group of antibiotics. Macrolide antibiotics, are well established class of antibacterial agents, which are active against many species of Gram-positive and some Gram-negative bacteria. Besides their antibacterial activity, these compounds have anti-inflammatory actions.<sup>9-11</sup> It has been reported that macrolides reduce the inflammatory process by inhibition of inflammatory cell migration, modulation of oxidative burst and inflammatory cytokine production.<sup>12-14</sup> In this regard, the anti-inflammatory action associated with antimicrobial action of macrolides, is responsible for the clinical effectiveness of these agents against the disease. There is cumulating evidence that macrolides alter the natural history of chronic sinusitis, which is characterized by elevated levels of inflammatory mediators example-granulocyte macrophage colony stimulating factor [GM-CSF], interleukin [IL] -3, and interleukin [IL]-8. Macrolides may inhibit the vicious cycle of cytokine production, neutrophil recruitment, and impaired mucociliary function at the site of inflammation, thereby interrupting the prolonged inflammation of chronic sinusitis.<sup>15-17</sup>

Surgery in the form of Functional endoscopic sinus surgery (FESS) is the procedure of choice for patients who fail to respond to medical treatment. It is surprising that the definition pathophysiology microbiology and consequently the treatment of CRS have remained a source of debate. as consequence a wide range of medical and surgical therapies have been used to treat CRS. The documentation of medical treatment of CRS is deficient in literature. On the other hand, sinus surgery is classified into conventional and endoscopic sinus surgery, with endoscopic sinus surgery largely replacing conventional sinus procedures. The high success rate, the low incidence of complications, and the technologic advances in optical instrumentation and imaging techniques for endoscopic sinus surgery, in presence of poor documentation of the medical therapy has made endoscopic sinus surgery the primary therapy for CRS.<sup>18</sup>

To address this deficiency the present study was designed to evaluate and compare surgical and medical treatment with oral Azithromycin in chronic sinonasal diseases.

### ***Mechanism of action of Azithromycin***

Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, and thus inhibits translation of mRNA. Nucleic acid synthesis is not affected.<sup>19</sup> Besides their antimicrobial effects, macrolides are

thought to have anti-inflammatory or immunomodulatory capacities based on the blockage of the production of cytokines, such as interleukin-8 (IL-8) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), combined with the effects on neutrophil migration and adhesion, and modulation of synthesis and secretion of mucus.<sup>20,21</sup>

### **METHODS**

A prospective study was conducted at a tertiary care center from November 2011 to March 2013. The study included 60 adult patients with symptomatic CRS refractory to 3 weeks of medical therapy. The patients were divided in two groups with 30 patients in each group. One group of patients received oral Azithromycin as main treatment (AZM group) for 12 weeks along with steroid spray and oral levocetizine. The other group of patients underwent Functional endoscopic sinus surgery (Surgical group) and received post-operative steroid spray and levocetizine for 8 weeks after surgery. Symptom scoring was done using visual analogue scoring (VAS). Endoscopic scoring was carried out according to a template that graded mucosal colour (0, normal; 1, abnormal), mucosal swelling (0, no swelling; 1, mild swelling; 2, severe swelling), nasal secretions (0, normal; 1, abnormal) and polyps (0, absent; 1, mild; 2, severe).<sup>22</sup> Postnasal drip (0, absent; 1, present). These values were recorded prior to the treatment and at 1 month and 3-month follow-up after the treatment.

**Patients/subjects**

A total of sixty cases, 18-60 years of age and of both sexes were included in the study. Sample size was calculated using the Cochran’s formula.

**Inclusion criteria**

Patients with symptoms of chronic rhinosinusitis persisting for more than 12 weeks. Not responding to medical line of treatment with amoxicillin and decongestants.

**Exclusion criteria**

Patients who underwent previous FESS. Gross nasal polyps on clinical Examination. Patients with gross clinical abnormality like deviated nasal septum, septal spur. Pregnant or Lactating females. Patients suffering from hypertension and diabetes. Systemic diseases affecting nose (example- Wegener’s granulomatosis, sarcoidosis, primary ciliary dyskinesia, cystic fibrosis, acute upper or lower respiratory tract infection). Patients on systemic corticosteroids. Asthmatic patients.

Ethical approval: The study was approved by the Medical Division of the University Board of Studies, University of Delhi, New Delhi, India.

**Statistical analysis**

Paired t test was used to find out significant difference between symptomatic score before intervention and at 1 month and 3 months follow-ups. Unpaired t test was used for finding significant difference in the symptom scoring and endoscopic scoring between both the groups. Chi square test/fischer’s exact test was used for finding the significant difference for qualitative variable in endoscopic scoring in both the groups.

**RESULTS**

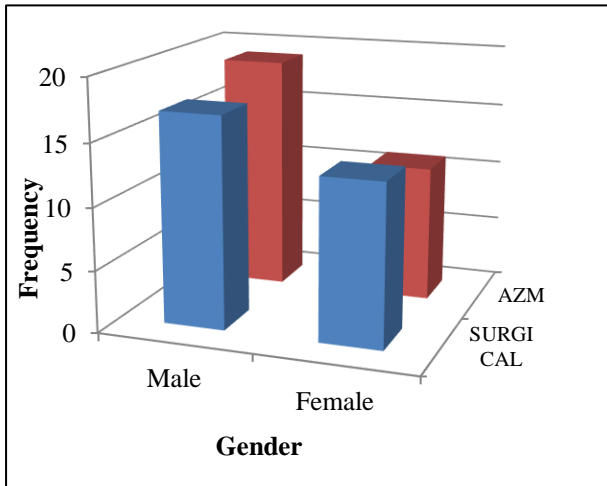
There were 70% males and 30% females in SURGICAL group (Figure1). In AZM group there were 60% males and 40% females. However, there is no significant difference between the sex distribution in the two groups (p=0.20840). All the cases in our study group were 18 years and above.

**Table 1: Comparison of total symptom score (VAS Scoring).**

Nasal symptoms	Surgical Group Mean (S.D)			AZM Group Mean (S.D.)		
	Pre-treatment	1 month	3 months	Pre-treatment	1 month	3 months
Nasal obstruction	5 (2.38)	2.1 (1.75)	1.70 (1.80)	4.37 (2.19)	2.60 (1.43)	2.97 (1.61)
Nasal discharge	6.47 (1.2)	3.27 (1.98)	2.80 (2.25)	6.43 (1.62)	3.10 (1.63)	4.5 (1.81)
Headache	6.67 (2.12)	2.87 (1.85)	2.80 (2.19)	6.90 (1.95)	4.47 (1.72)	4.17 (2.46)
Facial pain	3.87 (2.60)	1.97 (1.38)	1.73 (1.62)	3.70 (2.00)	2.5 (1.11)	2.6 (1.40)
Olfactory disturbance	2.10 (1.9)	1.27 (0.74)	1.27 (0.74)	3.17 (2.02)	1.43 (0.63)	1.33 (0.76)
Total symptom score	24.67 (6.24)	10.17 (7.00)	10.17 (7.00)	24.50 (4.85)	14.10 (3.30)	15.57 (3.92)

**Table 2: Comparison of endoscopic scoring.**

Endoscopic criteria		Surgical group		Azithromycin group	
		Pre-Treatment (% of patients)	3-month follow-up (% of patients)	Pre-Treatment (% of patients)	3-month follow-up (% of patients)
Mucosal colour	Normal	2 (6.67)	11 (36.67)	24 (80)	21 (70)
	Congested	28 (93.33)	19 (63.33)	6 (20)	9 (30)
	P value	0.0024		0.18	
Mucosal edema	Absent	1 (3.33)	10 (33.33)	22 (73.33)	17 (56.67)
	Mild	24 (80)	20 (66.67)	8 (26.67)	10 (33.33)
	Severe	5 (16.67)	(0)	(0)	3 (10)
	P value	0.009		0.03	
Secretions in Middle meatus	Absent	1 (3.33)	7 (23.33)	16 (53.33)	15 (51.72)
	Present	29 (96.67)	23 (76.67)	14 (46.67)	14 (48.27)
	P value	0.01		0.45	
Polyps	Absent	24 (80)	22 (73.33)	23 (76.67)	21 (70)
	Present	6 (20)	8 (26.67)	7 (23.33)	9 (30)
	P value	0.27		0.27	
Postnasal-drip	Absent	11 (36.67)	7 (23.33)	24 (80)	26 (86.67)
	Present	19 (63.33)	23 (76.67)	6 (20)	4 (13.33)
	P value	0.12		0.24	



**Figure 1: Sex distribution of cases.**

The mean age in surgical group was 24.7years ( $\pm 6.97$ ) while that in Azithromycin group was 26.03( $\pm 6.33$ ). Most common symptom in Surgical group was nasal discharge which was prevalent in all the patients. Nasal discharge and nasal obstruction were the most common symptom in AZM group. The least prevalent symptom was olfactory disturbance which was seen in only 33 % patients overall (Figure 2).

The mean pre-treatment total symptom score in both the groups was comparable ( $p=0.454$ ). The total symptom score at 1 month follow-up in Surgical group was 11.47 ( $\pm 5.78$ ) while that in AZM group was 14.10 ( $\pm 3.30$ ), the difference between the two was statistically significant ( $p=0.017$ ), i.e. the improvement of total symptom score in Surgical group was significantly greater than that in the AZM group. At 3-month follow-up, the mean total symptom score was 10.17 $\pm 7$  in SURG group and 15 $\pm 3.92$  in AZM group, the difference between these two was also significant ( $p=0.0002$ ). In AZM group there is a rise in total symptom score at the 3-month follow-up, while in the Surgical group there is a fall in total symptom score. (Table 1, Figure 3)

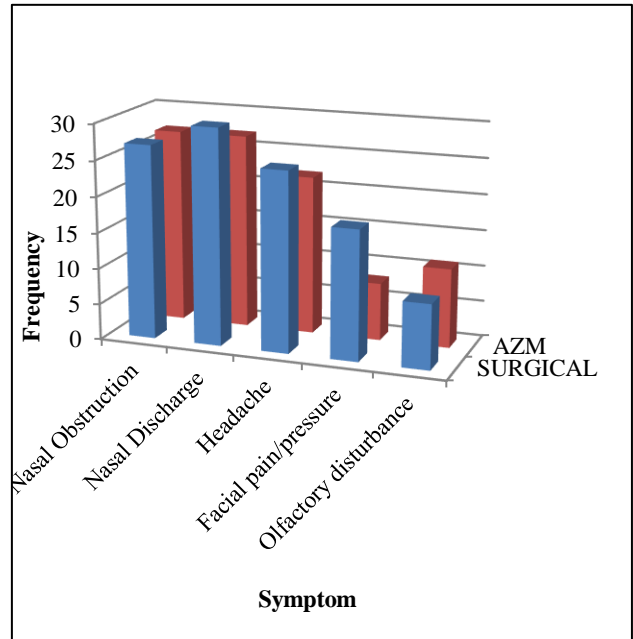
Nasal endoscopy was done of all the patients in both the groups at pre-treatment and at 3- month follow-up after the intervention. Mucosal colour, mucosal swelling/mucosal edema, discharge in middle meatus, post-nasal drip were the parameters seen on nasal endoscopy (Table 2)

**Mucosal colour:** There was significant improvement in SURGICAL group at 3-month follow-up ( $p=0.0024$ ), while in AZM group there was no significant improvement ( $p=0.18$ )

**Mucosal edema:** In SURGICAL group there was significant improvement in patients having severe mucosal edema ( $p=0.009$ ) while in AZM group there was no significant improvement, rather there was slight increase in mucosal edema at 3-month follow-up.

**Secretions in the middle meatus:** There was significant improvement in secretions in middle meatus in SURGICAL group ( $p=0.01$ ). While in AZM group there was no significant improvement ( $p=0.45$ )

**Polyps:** However, severe nasal polyp was the exclusion criteria, mild nasal polyposis patients were included. There was no significant improvement in both the groups.



**Figure 2: Frequency of symptoms.**

**Post nasal drip:** There was no significant improvement in post-nasal drip in both the groups, however improvement in SURGICAL group was more as compared to AZM group.

**DISCUSSION**

Chronic Sino nasal diseases remains an extremely common clinical condition, with an estimated lifetime prevalence of 12%. The optimal treatment strategies for CRS are yet to be determined. The common symptoms seen in our study were headache, nasal obstruction, and discharge.

Videler et al in Netherland studied, the use of long-term oral Azithromycin in patients of chronic rhinosinusitis.<sup>22</sup> This study was a double blind, randomized, placebo - controlled trial done in six tertiary referral centers of Netherland and was named as MACS (Macrolides in chronic sinusitis) study. Patients were treated with Azithromycin (AZM) or placebo. AZM was given for three days at 500 mg during the first week followed by 500 mg per week for the next 11 weeks. The patients were monitored until 3 months post-therapy. They observed no significant difference between AZM and placebo groups.



Smith et al, at Portland, published in 2013 compared the medical management with the surgical management in patients of chronic Sino nasal diseases.<sup>23</sup> This study evaluated 1-year outcomes in patients with chronic rhinosinusitis (CRS) who were considered surgical candidates by study criteria and elected either medical management or endoscopic sinus surgery (ESS). Adult subjects with CRS who failed initial medical therapy were prospectively enrolled into a nonrandomized, multi-institutional cohort. Subjects were included in 1 of 3 cohorts: medically managed, surgically managed, or crossover (from medical to surgical). The primary outcome measure was disease-specific quality-of-life (QOL). Bivariate and multivariate analyses compared QOL improvement between both cohorts with 1 year of follow-up, patients electing Surgical intervention experienced significantly higher levels of improvement in outcomes compared to patients managed by medication alone. In addition, a crossover cohort who initially elected medical management experienced improvement in several outcomes after crossing over to Surgical intervention. Results in our study are also consistent with Smiths study in terms of improvement in overall symptom scoring, however follow-up in our study was short.

Maniakas and Desrosiers in 2014 retrospectively studied the effect of azithromycin as add-on therapy in high-risk post endoscopic sinus surgery patients who were showing disease recurrence after endoscopic sinus surgery despite topical corticosteroid therapy.<sup>24</sup> These patients showed response after addition of Azithromycin.

Amali et al studied sixty-six patients who were divided in two groups. One group received standard conventional treatment with fluticasone nasal spray, while the study group received standard treatment along with Azithromycin 250 mg once daily for 3 months. They concluded that treatment with low dose Azithromycin in combination with conventional standard treatment after surgery could significantly reduce the recurrence rate.<sup>25</sup>

#### **Comparison of outcomes in AZM group**

In AZM group we noticed significant improvement in VAS scoring for the five major symptoms i.e. nasal obstruction, nasal discharge, facial pain, headache and olfactory disturbance, when compared with the pre-treatment values on one month and 3 months follow-ups. In endoscopic scoring, however, no significant improvement was seen in any of the parameters at 3 months follow-up post-treatment.

Videler's study also showed improvement in visual analog score at three months follow-up but the difference was not significant when compared with placebo, in his study. The results of endoscopic scoring in our study were consistent with Veidlers study in that no significant improvement was seen in endoscopic scoring.

#### **Comparison of outcomes in surgical group**

In Surgical group the VAS score of all the five major symptoms i.e., nasal discharge, headache, facial pain and olfactory disturbances showed significant improvement at 1 month and 3 months follow-up after surgery. In endoscopic scoring also patients had significant improvement at 3 months follow-up when compared with their pre-treatment values.

#### **Comparison of outcomes surgical versus azithromycin groups**

On comparison between the two groups, the Surgical group had significantly better results in terms of VAS score as well as Endoscopic score, when compared to AZM group. This difference was statistically significant. Thus, Endoscopic sinus surgery remains the mainstay of treatment in patients of CRS.

#### **Limitations**

Lesser number of subjective and objective outcome measures and a short follow up period of three months were some limitations of our study. Further studies for evaluation of usefulness of long-term low dose Azithromycin and other macrolides is recommended. Other dosage schemes and different treatment periods with a longer follow-up period have to be evaluated to further define the role of long-term Azithromycin and other macrolides in the treatment for recalcitrant Chronic Sinonasal Disease.

#### **CONCLUSION**

Our observations suggest that a good subjective as well as objective outcome in terms of symptom improvement can be obtained with in patients with chronic rhinosinusitis with Surgical intervention as compared to those patients who received long term oral Azithromycin. There was significant subjective improvement in patients who received oral Azithromycin when compared with their pretreatment values. However, there was much improvement in surgical group when compared with AZM group. We advocate that patient that patients suffering from Chronic Sinonasal Disease should be initially targeted with maximal medical therapy using an oral macrolide for at least 3 months as good outcomes were achieved when compared with its pre-treatment values. After this patient should be assessed and surgery considered in those cases refractory to medical therapy.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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