



## Original Article



## Efficacy of Long-Term Low-Dose Macrolide Therapy in Preventing Early Recurrence of Nasal Polyps after Endoscopic Sinus Surgery

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### ABSTRACT

Long-term low-dose macrolide therapy has been shown to reduce eosinophilic inflammation and delay early recurrence of nasal polyps following endoscopic sinus surgery (ESS). **Objective:** To compare the efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. **Methods:** This randomized controlled trial was conducted in the Department of ENT, Sir Ganga Ram Hospital, Lahore, from October to December 2025. Male and female patients aged 15–75 years diagnosed with nasal polyps and undergoing ESS were included. Patients already receiving antibiotics or macrolides, those with multiple facial fractures, or those with neurological or psychological disorders were excluded. Preoperatively, Sino-Nasal Outcome Test (SNOT), Lund-Kennedy endoscopic score, and Lund-Mackay CT score were recorded. Postoperatively, Group A received clarithromycin 250 mg once daily for three months in addition to standard therapy, while Group B received standard postoperative treatment alone. Outcomes were reassessed at 8 and 12 weeks, and recurrence of nasal polyps was evaluated after three months. **Results:** Mean SNOT scores showed significant improvement in the macrolide group compared to controls at both 8 and 12 weeks ( $p < 0.05$ ). Similarly, Lund-Mackay and Lund-Kennedy scores demonstrated significantly greater reductions in the macrolide group than in the non-macrolide group ( $p < 0.05$ ). Recurrence of nasal polyps was observed in 12% of patients receiving macrolide therapy compared to 32% in the control group. **Conclusions:** Three-month low-dose clarithromycin therapy (250 mg/day) is a safe and effective adjunct to ESS, significantly improving clinical, endoscopic, and radiological outcomes while reducing early recurrence of nasal polyps.

### INTRODUCTION

A chronic inflammatory disease that affects the sinuses and nasal canal, chronic rhinosinusitis affects 8% of Asians. Endoscopic sinus surgery plus typical post-operative medications, such as antibiotics, intranasal corticosteroids, mucolytic agents, oral hormones, and nasal irrigation, can cure chronic rhinosinusitis in 75% to 98% of cases; however, about 10% of patients still do not experience the desired clinical outcomes [1, 2]. Chronic rhinosinusitis has recently been treated with long-term, low-dose macrolide therapy [3]. Patients with other chronic inflammatory airway illnesses, including chronic rhinosinusitis without polyps, have reported the anti-inflammatory effects of macrolides, particularly

clarithromycin. The literature contains conflicting views on the effectiveness of clarithromycin for individuals with chronic rhinosinusitis and sinonasal polyposis, and there are no national prospective studies evaluating the drug's efficacy in treating chronic rhinosinusitis within our population [4]. The absence of evidence in systematic reviews is reflected in the inconsistent guidelines about the inclusion of antibiotics in basic medical care. A fivefold difference in intervention rates can be explained by insufficient evidence to substantiate the role of surgery [5]. After endoscopic sinus surgery, "long-term" low-dose clarithromycin (250 mg/day) can reduce eosinophilic inflammation and stop nasal polyps from relapsing too



soon [6, 7]. When compared to baseline, macrolide therapy can dramatically improve endoscopic and CT scores in patients with chronic rhinosinusitis. To verify the effectiveness and safety of macrolides in the treatment of chronic rhinosinusitis, further well-planned research is required [1]. One study in Iraq found that the Lund-Mackay score decreased from  $20.53 \pm 2.16$  to  $5.90 \pm 2.81$  with macrolide, from  $19.55 \pm 3.14$  to  $8.45 \pm 2.76$  without macrolide ( $p < 0.05$ ), and the Lund-Kennedy score decreased from  $18.13 \pm 1.36$  to  $4.30 \pm 0.65$  with macrolide and from  $17.52 \pm 1.46$  to  $4.48 \pm 0.79$  without macrolide ( $p > 0.05$ ). These findings were reported in an Iraqi study [8]. With macrolide, regrowth is seen in 11% of cases, but 32% of cases without macrolide exhibit regrowth or recurrence of nasal polyps [9].

The purpose of this study was to compare the results of endoscopic sinus surgery and long-term low-dose macrolide therapy for nasal polyps. According to research, using low-dose macrolides over an extended period of time can lower the chance that nasal polyps will return following sinus surgery. There hasn't been any prior research in this area, and there isn't much local data in the literature to support our decision to add a macrolide for longer-term treatment. As a result, we intend to carry out this investigation. The study's findings will assist us in obtaining local magnitudes, which will enable us to apply the conclusions in a local context. This will enable us to enhance our procedures. Even after endoscopic surgery and conventional postoperative treatment, nasal polyp recurrence is still a serious clinical complication. Even though it is long-term and low doses of macrolide have demonstrated potential anti-inflammatory effects, the evidence on its effects in the prevention of postoperative polyp recurrence is inconsistent and limited, especially in local populations. The study aimed to compare the effectiveness of low-dose macrolide long-term treatment in preventing early recurrence of nasal polyps after endoscopic sinus surgery.

## METHODS

The ENT Department at Sir Ganga Ram Hospital in Lahore conducted this randomized controlled experiment registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT07316959) from October to December 2025 after getting ethical approval (260/Proposal-ENT/ERC). A sample size of 100 cases, 50 in each group, was determined using the WHO calculator, with a 5% significance level, 80% study power, and the percentage of recurrence, which is 11% with macrolide and 32% without it, following endoscopic sinus surgery [9]. Both male and female patients between the ages of 15 and 75 who have been diagnosed with nasal polyps, a persistent swelling and inflammation of the nose brought on by chronic rhinosinusitis, are having endoscopic sinus

surgery. Patients who were already taking antibiotics or macrolides, had multiple facial fractures, had ASA III or IV, or had neurological or psychological conditions were not included. One hundred patients who met the inclusion criteria were enrolled through the ENT wards following ethical review board permission. Written informed consent was obtained. Additional demographic data were recorded, including name, age, sex, duration of symptoms, domicile, socioeconomic level, history of diabetes, hypertension, smoking, allergic rhinitis, nasal polyps in the family history, and ASA status. Before surgery, the SNOT, Lund-Kennedy score, and Lund-Mackay score were recorded. The procedure's duration was recorded. Following surgery, patients were split into two groups at random using a lottery. For three months, patients in group A received Macrolide (clarithromycin 250 mg) once a day in addition to their usual prescription drugs. Following surgery, participants in group B received their usual prescriptions. Patients were evaluated for SNOT, Lund-Kennedy score, and Lund Mackay score at 8 and 12 weeks of therapy. Patients were also checked for nasal polyp recurrence after three months, if it was detected on a CT scan twelve weeks after surgery.

SPSS version 25.0 was used to examine the data that was gathered. The mean and standard deviation of quantitative factors, such as age, symptom duration, operative time, SNOT, Lund-Kennedy score, and Lund-Mackay score, were displayed. The frequency and percentage of qualitative characteristics, such as recurrence, gender, ASA, residence, socioeconomic position, and history (diabetes, hypertension, smoking, allergic rhinitis, and family history of nasal polyps), were displayed. The Lund-Kennedy, Lund-Mackay, and mean SNOT scores for both groups were compared using the t-test, and recurrence was evaluated using chi-square. A p-value significance level of  $\leq 0.05$  was used.

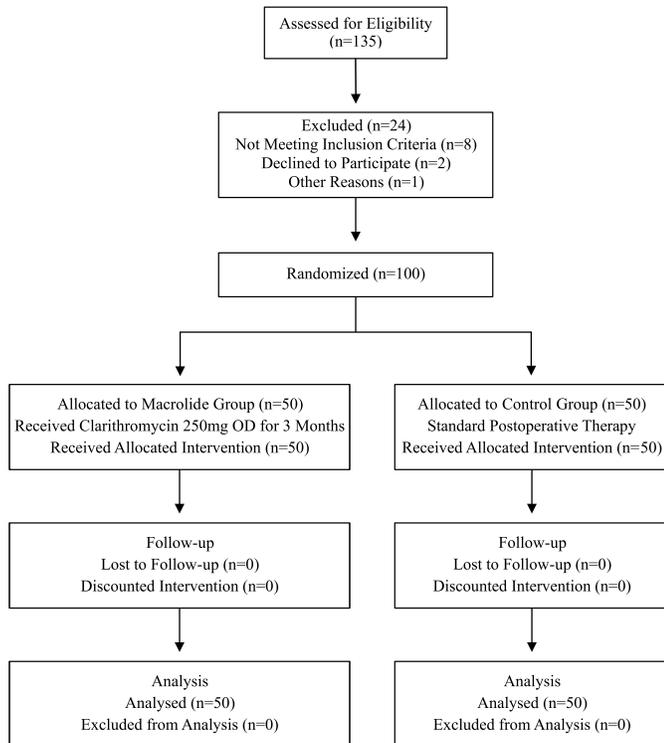


Figure 1: CONSORT Flow Diagram

## RESULTS

This study involved 100 patients. In Group A, 50 patients (31 men and 19 women) with a mean age of  $37.60 \pm 13.18$  years were examined. Group B consisted of 50 patients, with a mean age of  $39.62 \pm 13.30$  years, including 32 men and 18 women. The mean duration of symptoms in group A was  $6.66 \pm 1.99$  weeks, and in group B was  $6.70 \pm 1.79$  weeks. Mean operative time in group A was  $34.48 \pm 8.12$  minutes, and in group B was  $35.76 \pm 9.38$  minutes (Table 1).

Table 1: Distribution of Different Variables (n=100)

Variables	Group A (n=50), n (%)	Group B (n=50), n (%)
<b>Age (Years)</b>		
15-45	38 (76.0%)	33 (66.0%)
46-75	12 (24.0%)	17 (34.0%)
<b>Gender</b>		
Male	31 (62.0%)	32 (64.0%)
Female	19 (38.0%)	18 (36.0%)
<b>Duration of symptoms (weeks)</b>		
≤8	41 (82.0%)	42 (84.0%)
>8	09 (18.0%)	08 (16.0%)
<b>ASA status</b>		
I	27 (54.0%)	28 (56.0%)
II	23 (46.0%)	22 (44.0%)
<b>Operative time (min)</b>		
≤30	18 (36.0%)	18 (36.0%)
>30	32 (64.0%)	32 (64.0%)

<b>SES</b>		
Poor	14 (28.0%)	13 (26.0%)
Middle	28 (56.0%)	29 (58.0%)
Upper	08 (16.0%)	08 (16.0%)
<b>Residence</b>		
Rural	27 (54.0%)	25 (50.0%)
Urban	23 (46.0%)	25 (50.0%)
<b>Hypertension</b>		
Yes	11 (22.0%)	12 (24.0%)
No	39 (78.0%)	38 (76.0%)
<b>Diabetes mellitus</b>		
Yes	10 (20.0%)	11 (22.0%)
No	40 (80.0%)	39 (78.0%)
<b>Smoking</b>		
Yes	13 (26.0%)	18 (36.0%)
No	37 (74.0%)	32 (64.0%)
<b>Allergic rhinitis</b>		
Yes	08 (16.0%)	07 (14.0%)
No	42 (84.0%)	43 (86.0%)
<b>Family h/o nasal polyp</b>		
Yes	06 (12.0%)	06 (12.0%)
No	44 (88.0%)	44 (88.0%)

This study reported that the mean pre-operative SNOT score was  $76.38 \pm 5.00$  and after 8 weeks and 12 weeks was  $13.74 \pm 1.65$  and  $9.72 \pm 1.86$  with macrolide treatment while from  $77.95 \pm 5.25$ ,  $20.80 \pm 3.14$  and  $13.72 \pm 1.95$  without macrolide treatment ( $p < 0.05$ ), Lund-Mackay score was  $20.08 \pm 1.93$ ,  $5.88 \pm 1.00$  and  $3.72 \pm 0.81$  with macrolide while  $20.76 \pm 1.46$ ,  $11.32 \pm 0.96$  and  $7.86 \pm 0.99$  without macrolide ( $p < 0.05$ ) and Lund-Kennedy score was from  $16.68 \pm 1.41$ ,  $4.86 \pm 1.11$  and  $2.74 \pm 0.69$  with macrolide and  $16.54 \pm 1.37$ ,  $11.38 \pm 1.28$  and  $7.88 \pm 0.90$  without macrolide ( $p < 0.05$ ) (Table II).

Table 2: Comparison of the Outcome between Both Groups

Variables	Group A (n=50), Mean ± SD	Group B (n=50), Mean ± SD	p-value
Pre-Operative SNOT Score	$76.38 \pm 5.00$	$77.95 \pm 5.25$	0.128
After 8 Weeks SNOT Score	$13.74 \pm 1.65$	$20.80 \pm 3.14$	<0.001
After 12 Weeks SNOT Score	$9.72 \pm 1.86$	$13.72 \pm 1.95$	<0.001
Pre-Operative Lund-Kennedy Score	$16.68 \pm 1.41$	$16.54 \pm 1.37$	0.616
After 8 Weeks, Lund-Kennedy Score	$4.86 \pm 1.11$	$11.38 \pm 1.28$	<0.001
After 12 Weeks Lund-Kennedy Score	$2.74 \pm 0.69$	$7.88 \pm 0.90$	<0.001
Pre-Operative Lund-Mackay Score	$20.08 \pm 1.93$	$20.76 \pm 1.46$	0.049
After 8 Weeks, Lund-Mackay Score	$5.88 \pm 1.00$	$11.32 \pm 0.96$	<0.001
After 12 Weeks Lund-Mackay Score	$3.72 \pm 0.81$	$7.86 \pm 0.99$	<0.001

Recurrence was observed in 12% with macrolide, while 32% without macrolide, with statistically significant associations ( $p = 0.0158$ ) (Table 3).

**Table 3:** Comparison of the Recurrence between Both Groups

Resources	Group A (n=50), Frequency (%)	Group B (n=50), Frequency (%)	p-value
Yes	06(12.0%)	16(32.0%)	0.015
No	44(88.0%)	34(68.0%)	

## DISCUSSION

Low-dose long-term (LDLT) macrolide therapy is a lengthier course of treatment with a lower dose than what is used to treat a bacterial infection that comes on suddenly. In 1984, LDLT erythromycin was used for the first time in Japan to treat patients with diffuse panbronchiolitis [10, 11]. Through a variety of mechanisms, macrolides' immunomodulatory and anti-inflammatory potencies, as well as their antibacterial qualities, are believed to be useful in controlling these disorders [12, 13]. According to this study, the mean pre-operative SNOT score was  $76.38 \pm 5.00$ , and the Lund Mackay score was  $20.08 \pm 1.93$ ,  $5.88 \pm 1.00$ , and  $3.72 \pm 0.81$  with macrolide and  $20.76 \pm 1.46$ ,  $11.32 \pm 0.96$ , and  $7.86 \pm 0.99$  without macrolide ( $p < 0.05$ ). The Lund-Kennedy score was  $16.68 \pm 1.41$ ,  $4.86 \pm 1.11$ , and  $2.74 \pm 0.69$  with macrolide and  $16.54 \pm 1.37$ ,  $11.38 \pm 1.28$ , and  $7.88 \pm 0.90$  without macrolide ( $p < 0.05$ ). Recurrence was seen in 32% of cases without macrolide and 12% of cases with it. One study in Iraq found that the Lund-Mackay score decreased from  $20.53 \pm 2.16$  to  $5.90 \pm 2.81$  with macrolide, from  $19.55 \pm 3.14$  to  $8.45 \pm 2.76$  without macrolide ( $p < 0.05$ ), and the Lund-Kennedy score decreased from  $18.13 \pm 1.36$  to  $4.30 \pm 0.65$  with macrolide and from  $17.52 \pm 1.46$  to  $4.48 \pm 0.79$  without macrolide ( $p > 0.05$ ). These findings were reported in an Iraqi study [8]. After receiving clarithromycin for 8–12 weeks, 40% of the 20 CRSwNP patients saw a reduction in the size of their nasal polyps and a notable decrease in the amount of IL-8 in their lavage fluid; the remaining 60% exhibited no change [14]. Eight weeks of 500 mg of clarithromycin before surgery cut down on the number of polyps that came back six and twelve months after surgery [15]. SNOT-20 scores of CRSwNP patients improved following eight weeks of steroid monotherapy and low-dose clarithromycin combination therapy [16]. With LDLT clarithromycin, 52 CRSwNP patients experienced a significant decrease in their SNOT-20 and Lund-Kennedy endoscopic score after 12 weeks [17]. Furthermore, compared to those who did not improve on SNOT-20, 54% (28 of 52) exhibited lower levels of total IgE. Three months of 150 mg roxithromycin treatment resulted in significant improvements in mucociliary transit time, nasal endoscopy results, and sinus nasal symptoms (SNOT-20) in CRSsNP patients [18]. At three months, there were no significant differences between the two groups when looking at either the endoscopic results or the visual analogy ratings of symptoms. Clinical improvement was also observed in

CRSsNP patients after 8 weeks of erythromycin treatment [19]. Apart from severe polyposis, LDLT azithromycin exhibited no significant differences between the treatment and placebo groups in a mixed cohort of CRSwNPs (52.0%) and CRSsNPs [20]. A biomarker analysis showed that the overall symptom score was a good sign for predicting which patients with CRS would need macrolide therapy following surgery [21]. In the Netherlands, a pragmatic, multicentre RCT comparing endoscopic sinus surgery + medication to medication alone in adults with chronic rhinosinusitis and nasal polyps has been published since the start of the MACRO Program. Additionally, the study demonstrated increased efficacy with surgery; however, the mean difference between groups in SNOT-22 at 6 months did not reach the minimal clinically significant difference. Patients who had not responded to proper medical therapy were also enrolled in the trial. Medical therapy is any medical intervention, without standardization, that the participant's otorhinolaryngologist deems appropriate, such as systemic antibiotics, intranasal corticosteroids, and systemic corticosteroids [22].

In spite of evidence that low-dose long-term macrolide treatment is associated with better symptom scores, endoscopic results, and lower recurrence rates, the small sample size, heterogeneity of disease phenotypes, and absence of follow-up limit the ability to make certain conclusions about the long-term effectiveness and safety. Large multicentric randomized trials with prolonged follow-up and the use of biomarkers to select patients in future investigations should define responders better and improve the use of postoperative macrolides with concerns of antimicrobial resistance.

## CONCLUSIONS

Our study's findings supported the safety and effectiveness of a three-month low-dose (250 mg/day) clarithromycin treatment in preventing early recurrence of nasal polyps after endoscopic sinus surgery. This treatment was found to be substantially associated with an improvement in quality of life, as measured by SNOT-20, LMS, and LKS, and it can prevent an early recurrence of NP. Patient selection is essential to the successful administration of macrolide treatment in CRS. Particularly for CRS patients with comorbidities, our study advised using the macrolide at a low dose for three months after surgery.

## Authors' Contribution

Conceptualization: MSS

Methodology: MSS

Formal analysis: MSS, WJ

Writing and Drafting: WJ

Review and Editing: MSS, WJ

All authors approved the final manuscript and take responsibility for the integrity of the work.

## Conflicts of Interest

All the authors declare no conflict of interest.

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