

## Mupirocin Ointment Effect on Polyposis Recurrence After Sinus Surgery

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### Abstract

#### Introduction:

Staphylococcus aureus is an identified pathogen involved in the recurrence of symptoms in patients with chronic rhinosinusitis with nasal polyps. We investigated the effectiveness of a topical ointment of mupirocin applied in the nasal vestibule in lessening symptom recurrence and improving the efficiency of functional endoscopic sinus surgery.

#### Materials and Methods:

Patients with chronic rhinosinusitis, nasal polyps, and a positive nostril culture for Staphylococcus aureus were included in a clinical trial. The right nostril was determined as the intervention group (applying mupirocin ointment) and the left as the control group (applying vitamin A ointment). Lund-Mackay radiological scores and Lund-Kennedy endoscopic scores were examined at the time of diagnosis and six months later.

#### Results:

Among 60 patients with chronic rhinosinusitis with nasal polyps, 91.6% were positive for nostril Staphylococcus aureus. Comparing the average of the diagnostic radiological and endoscopic scores with the follow-up values in both groups indicated a significant improvement after surgery (P-value=0.001, 0.001). However, there was no significant difference in the radiological and endoscopic score improvements between the study and control groups (P-value > 0.56, 0.74).

#### Conclusion:

Nasal mupirocin administration following endoscopic sinus surgery cannot significantly prevent symptom recurrence in chronic rhinosinusitis with nasal polyps.

**Keywords:** Chronic rhinosinusitis, Nasal polyps, Mupirocin, Staphylococcus aureus

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## Introduction

Chronic rhinosinusitis (CRS), a common complaint worldwide, is an inflammatory disease of the paranasal sinuses lasting 12 weeks or longer. It can be classified according to the presence of a nasal polyp (NP) to CRS with NP (CRSwNP) and CRS without NP. Approximately 20-30% of patients with CRS suffer from CRSwNP, followed by reduced mortality, quality of life, and increased cost of living and patient care (1-3). Although the etiology of CRS has not yet been determined, it is believed that the defects in the mucosal barrier, the lack of the individual's immune system, different nasal bacterial biofilms, and the colonization of pathogenic bacteria, especially gram-positive ones, are important causes. So far, no specific genetic role has been considered for the disease (4).

Previous studies have shown the association of colonized *Staphylococcus aureus* in meatus and sinuses with symptom recurrence in patients with CRSwNP. Applying medical treatments of nasal irrigation, topical antibiotics, corticosteroids, and functional endoscopic sinus surgery (FESS) in more severe cases would be beneficial in reducing symptoms. Nonetheless, the complaint recurrence occurred in 55-70% of the patients, and 7% required surgical reintervention (4-7). Among antibiotics, mupirocin has significant anti-staphylococcal activity. By inhibiting bacterial protein and RNA synthesis (8), this antibiotic is very effective against methicillin-sensitive strains and methicillin-resistant *Staphylococcus aureus* colonized in nasal cavities and sinuses (9). This study aimed to investigate the effectiveness of topical mupirocin in the nasal vestibule in lessening the recurrence of symptoms and improving the efficiency of FESS in patients with CRSwNP.

## Materials and Methods

This study is a double-blind case-controlled clinical trial among Caucasian patients with a standardized diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) -according to the American Academy of Otolaryngology- who were referred to the otolaryngology clinics of Firoozgar General Hospital and Rasool General Hospital, Tehran, Iran, between 2020-2022.

After receiving study approval from the Institutional Review Boards (IRCT code

76431) at Iran University of Medical Sciences (IR.IUMS.FMD.REC.1399.290) and patient contents, all baseline characteristics, diagnostic studies, radiological findings, and treatment details were collected from patient files.

**Inclusive criteria:** All candidates for sinus surgery diagnosed with CRSwNP who had not received optimal benefits from a four-week course of oral antibiotics were enrolled in the first step of the study. Bilateral vestibular swab samples for *Staphylococcus aureus* were taken from all individuals. Then, patients with culture-proven *Staphylococcus aureus* were enrolled in the second step of the study.

**Exclusive criteria:** Individuals who had polyposis in the context of fungal sinusitis, neoplasm, and autoimmune diseases were excluded from the study. Patients with CRSwNP with other causes whose endoscopic or radiologic scores on both sides of the nose and sinus were significantly different were excluded from the study, along with patients with negative cultures and insufficient information.

Lund-Mackay radiological score was used to report CT imaging findings. Based on this system, five sinuses on each side, including the frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid, are examined, and the opacification criteria within the sinuses are scored with a minimum score of 0 to a maximum of 2 (0= no abnormalities, 1= partial opacification and 2= total opacification) on each side. Occlusion of osteomeatal complex is also graded, which scores a minimum of 0 or a maximum of 2 (0= not occluded, 2= occluded) on each side. The sum of these scores in the maximum mode is 12 on each side and 24 in total (10,11). Follow-up CT imaging was repeated for all patients. The operating surgeon also performed a diagnostic rigid nasal endoscopy at each site. The Lund-Kennedy endoscopic score was applied to visually assess the polyp's size and distribution, edema, discharge, scarring, and crusting within the nasal and paranasal sinuses. Scores are graded on an ordinal scale from 0-2 for each side. Higher scores indicate worse observed disease (10,12). In order to investigate the recurrence of polyposis, nasal endoscopy with a zero-degree lens was conducted by one senior resident of laryngology who was unaware of which patients belonged to the control group. On the

day of the operation, second samples were taken from the patient's nostrils with a swab, and the culture was sent for staph aureus to ensure all enrolled individuals had a positive result for staph aureus. After surgery, standard treatment included nasal saline irrigation, fluticasone nasal spray, and oral antibiotic cephalexin routinely prescribed to all patients due to nasal tampons and to prevent toxic shock syndrome (13). The experimental medication was Mupirocin-Najo 2% topical ointment (Iran Najo Pharmaceutical Company, Tehran, Iran). Xerovit (vitamin A) sterile ophthalmic ointment 25000 IU (Sina Darou Laboratories Company, Tehran, Iran) was administered as a placebo. All pharmaceutical treatments were continued twice daily for six months from primary FESS until the follow-up endoscopy.

**Statistical analysis**

In the descriptive analysis of the results, continuous data were presented as mean (standard deviation), and categorical data were

presented as frequency and percentage. Univariate analysis methods of independent t-test, Wilcoxon signed-rank test, and logistic regression analysis were applied for parametric, non-parametric, and categorical data. For all analyses, two-tailed p-values <0.05 were considered significant. Statistical analysis was performed using SPSS (version 22).

**Results**

Out of 60 candidates for sinus surgery in the first step, 55 patients (91.6%) had positive cultures of *Staphylococcus aureus* in both nostrils.

Among these 55 patients, 24 individuals [15 males (81%)] with an average age of 44 ±14 years old were eligible for the second step of the study.

The rest were excluded due to the exclusion criteria or patients' lack of cooperation. Table 1 displays the demographic characteristics of patients.

**Table 1:** Demographic characteristics of patients

Characteristic	Total patients n=24
Sex (male), no (%)	15 (81)
Age at time of procedure, Year (Mean ± SD)	
Male	44 ± 15
Female	43 ± 14
Smoker, no (%)	
Male	4 /15 (26)
Female	1 / 9 (11)
Seasonal Allergy, no (%)	
Male	6 /15 (40)
Female	8 / 9 (88)
Asthma, no (%)	
Male	2 /15 (13)
Female	6 / 9 (66)
Samter's Triad, no (%)	
Male	1 /15 (6)
Female	2 /9 (22)
Revision FESS <sup>a</sup> , no (%)	
Male	5 /15 (33)
Female	2 / 9 (22)

<sup>a</sup> Functional endoscopic sinus surgery

According to the analysis, gender did not affect the radiological and endoscopic scores (p-

value=0.63, 0.14). Also, gender did not affect the radiological and endoscopic scores (p-

value=0.92, 0.56). The average Lund-Mackay radiological score in the study group was  $10.2 \pm 1.7$  and  $5.2 \pm 3.0$  before and after the procedure. The average Lund-Mackay radiological score was  $10.5 \pm 1.6$  and  $5.8 \pm 2.5$  before and after the procedure in the control group (Table 2,3). The

average Lund-Kennedy endoscopic score was  $4.5 \pm 1.1$  and  $2.5 \pm 1.5$  before and after the procedure in the study group. The average Lund-Kennedy endoscopic score was  $4.6 \pm 1.0$  and  $1.8 \pm 1.9$  before and after the procedure in the control group (Table 2, 3).

**Table 2:** Comparing clinical findings in the both groups

Characteristic	Before procedure			After procedure		
	Study n=24	Control n=24	p-value	Study n=24	Control n=24	p-value
<b>Total Lund-Mackay Radiological Score,</b> (Mean $\pm$ SD)	10.2 (1.7)	10.5 (1.6)	0.56	5.2 (3.0)	5.8 (2.5)	0.56
<b>Sinus scores,</b> (Mean $\pm$ SD)			0.56			0.56
Maxillary	1.6 (0.4)	1.7 (0.4)		1.0 (0.5)	1.1 (0.6)	
Anterior ethmoids	1.9 (0.2)	1.9 (0.2)		1.0 (0.6)	1.0 (0.6)	
Posterior ethmoids	1.8 (0.3)	1.9 (0.2)		0.8 (0.6)	0.9 (0.6)	
Sphenoid	1.3 (0.7)	1.4 (0.6)		0.9 (0.8)	1.2 (0.7)	
Frontal	1.5 (0.7)	1.6 (0.7)		1.0 (0.8)	1.1 (0.7)	
Ostiomeatal complex	2 (0.0)	2 (0.0)		0.4 (0.7)	0.3 (0.7)	
<b>Total Lund-Kennedy Endoscopic Score,</b> (Mean $\pm$ SD)	4.5 (1.1)	4.6 (1.0)	0.91	2.5 (1.5)	1.8 (1.9)	0.74
<b>Polyposis,</b> no (%)			1			0.35
None	0	0		12 (50)	11 (46)	
Confined to middle meatus	3 (13)	3 (13)		12 (50)	11 (46)	
Beyond middle meatus	21 (87)	21 (87)		0	2 (8)	
<b>Discharge,</b> no (%)			0.59			0.92
None	1 (4)	0		7 (29)	7 (29)	
Clear and thin	15 (62)	15 (62)		13 (54)	12 (50)	
Thick and purulent	8 (34)	9 (37)		4 (17)	5 (21)	
<b>Edema,</b> no (%)			0.74			0.68
Absence	0	0		8 (34)	7 (29)	
Mild	17 (71)	18 (75)		14 (58)	13 (54)	
Severe	7 (29)	6 (25)		2 (8)	4 (17)	
<b>Scarring,</b> no (%)			1			0.68
Absence	23 (96)	23 (96)		21 (87)	20 (83)	
Mild	1 (4)	1 (4)		3 (13)	4 (17)	
Severe	0	0		0	0	
<b>Crusting,</b> no (%)			1			0.74
Absence	23 (96)	23 (96)		17 (71)	18 (75)	
Mild	0	0		7 (29)	6 (25)	
Severe	1 (4)	1 (4)		0	0	

**Table 3:** Comparing clinical findings in the both groups

Characteristic	Study group n=24			Control group n=24		
	Before Procedure	After Procedure	p-value	Before Procedure	After Procedure	p-value
<b>Total Lund-Mackay Radiological Score, (Mean ± SD)</b>	10.2 (1.7)	5.2 (3.0)	0.001	10.5 (1.6)	5.8 (2.5)	0.001
<b>Sinus scores, (Mean ± SD)</b>			0.001			0.001
Maxillary	1.6 (0.4)	1.0 (0.5)		1.7 (0.4)	1.1 (0.6)	
Anterior ethmoids	1.9 (0.2)	1.0 (0.6)		1.9 (0.2)	1.0 (0.6)	
Posterior ethmoids	1.8 (0.3)	0.8 (0.6)		1.9 (0.2)	0.9 (0.6)	
Sphenoid	1.3 (0.7)	0.9 (0.8)		1.4 (0.6)	1.2 (0.7)	
Frontal	1.5 (0.7)	1.0 (0.8)		1.6 (0.7)	1.1 (0.7)	
Ostiomeatal complex	2 (0.0)	0.4 (0.7)		2 (0.0)	0.3 (0.7)	
<b>Total Lund-Kennedy Endoscopic Score, (Mean ± SD)</b>	4.5 (1.1)	2.5 (1.5)	0.001	4.6 (1.0)	1.8 (1.9)	0.001
<b>Polyposis, no (%)</b>			0.06			0.69
None	0	12 (50)		0	11 (46)	
Confined to middle meatus	3 (13)	12 (50)		3 (13)	11 (46)	
Beyond middle meatus	21 (87)	0		21 (87)	2 (8)	
<b>Discharge, no (%)</b>			0.84			0.42
None	1 (4)	7 (29)		0	7 (29)	
Clear and thin	15 (62)	13 (54)		15 (62)	12 (50)	
Thick and purulent	8 (34)	4 (17)		9 (37)	5 (21)	
<b>Edema, no (%)</b>			0.40			0.40
Absence	0	8 (34)		0	7 (29)	
Mild	17 (71)	14 (58)		18 (75)	13 (54)	
Severe	7 (29)	2 (8)		6 (25)	4 (17)	
<b>Scarring, no (%)</b>			0.007			0.02
Absence	23 (96)	21 (87)		23 (96)	20 (83)	
Mild	1 (4)	3 (13)		1 (4)	4 (17)	
Severe						
<b>Crusting, no (%)</b>			0.11			0.07
Absence	23 (96)	17 (71)		23 (96)	18 (75)	
Mild	0	7 (29)		0	6 (25)	
Severe	1 (4)	0		1 (4)	0	

Following functional endoscopic sinus surgery, both groups' average Lund-Mackay radiological and endoscopic scores decreased significantly ( $p = 0.001, 0.001$ ) (Table 3). Regarding comparing radiological and endoscopic findings between the two groups of study and control, there was no significant difference in sinus opacification and ostiomeatal complex occlusion before or after the procedure between the study and control groups ( $p = 0.56, 0.56$ ). Also, there was no significant difference in the distribution of the frequency of polyps, the intensity of edema, secretion, scar, and crust before or after the procedure between the two groups before or after the procedure ( $p = 0.91, 0.74$ ) (Table 2).

### Discussion

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease

of the nasal mucosa and paranasal sinuses associated with significant morbidity and reduced health-related quality of life (13-16).

Functional endoscopic sinus surgery with 5% minor complications is one of the greatest treatment options for CRSwNP (16). Surgery reduces the disease burden and increases the effectiveness of postoperative medical treatment, such as nasal irrigation, topical corticosteroids, and antibiotics, improving the FESS outcome in CRSwNP (17). However, in the long-term, the revision rate for endoscopic sinus surgery resulted in symptom recurrences of more than 20% to 60% during 18 months to 4 years of follow-up (18).

Several studies have investigated factors for the successful prognosis of endoscopic sinus surgery. The association of *Staphylococcus aureus* with chronic rhinosinusitis with nasal polyps has also been investigated. The

prevalence of *Staphylococcus aureus* in the nasal sinuses of healthy people was reported to be 26-33%, and the rate in CRSwNP patients is up to 67%. It has been established that patients with CRSwNP are long-term carriers of nasal staph aureus. In addition, the higher prevalence of *Staphylococcus aureus* in the nasal cavity or sinus of patients with CRSwNP, the more unsatisfactory results after sinus surgery as recurrence of polyposis (6,10,19,20). Out of 60 enrolled individuals in the current study, 55 (91.6%) were reported positive for *Staphylococcus aureus* in the nasal vestibule of both sides, as we expected.

To this point, in order to detect *Staphylococcus aureus* in previous studies, samples were prepared from the nasal cavity or sinuses (6,19). In this study, instead of the nasal cavity or sinus, we prepared cultures from the nasal vestibule of patients with CRSwNP to check the frequency of this bacteria in the nostrils. According to our findings in the first stage, the frequency of *Staphylococcus aureus* in the nasal vestibule of patients with CRSwNP was significantly higher than in healthy individuals (91.6% vs 33%) (6). The influence of vestibular *Staphylococcus aureus* on the unsatisfying results following FESS is remarkable and should be considered. We hypothesized by decreasing vestibular *Staphylococcus aureus* colonies, and we might enhance the post-surgery outcomes as it has already been established in other parts of the nose cavity and sinuses.

In a review article published by Maina and his colleagues in 2018, the prominent role of *Staphylococcus aureus* biofilm and its superantigens in sinusitis with polyps was discussed. They stated that the formation of polyps in chronic sinusitis is secondary to stimulation of inflammatory pathway by cytokines produced as a result of activated T-helper type 2 lymphocytes, while T-helper type 1 lymphocytes play the principal role in chronic sinusitis without polyps (21). Also, in Cheng et al.'s (2017) study, the presence of enterotoxins and local allergy was related to the development of polyps. They stated that *Staphylococcus aureus* could be related to the pathogenesis of the disease through its type A and B superantigens (22). Mupirocin is a unique antimicrobial agent with antimicrobial activity against staphylococci and most streptococci but

less activity against other gram-positive and gram-negative bacteria. Mupirocin is the best topical antimicrobial agent against gram-positive bacteria, which binds to bacterial tRNA synthetase and inhibits bacterial protein and RNA synthesis (23,24). Intranasal mupirocin is a simple and effective strategy to eradicate MRSA nasal colonization (19,25).

Most of the previous studies have evaluated the effectiveness of mupirocin irrigation in patients with CRS (20,26), while in the present study, topical mupirocin ointment was prescribed through the nostrils that have been addressed by limited studies (27). Applying mupirocin as a topical ointment could be more convenient than using irrigation forms, thus raising patient cooperation over a long period. However, according to the current study, we did not discover any efficacy of administering mupirocin ointment through the nostrils of patients with CRSwNP in post-surgery results (26,28).

Considering that the case and control groups are both in the same patient, the variables related to the host were removed, and the groups were matched. So, the insignificant results cannot be attributed to group dissimilarities. In addition, employing two different scoring systems of Lund-Mackay radiological scores and Lund-Kennedy endoscopic scores in the current study to evaluate patients is ascendency in terms of validity, sensitivity, and providing additional information about secondary sinuses and ethmoid fossa (20). Carr et al. 2015 determined changes in microbiological culture resulting from pre and post-topical mupirocin treatment in CRS patients with refractory disease. Before treatment with mupirocin, culture results from symptomatic patients revealed common bacteria involved in CRS, which were characteristically gram-positive. After treatment with mupirocin, cultures from symptomatic patients changed significantly; before treatment, 19 cultures were gram-positive and three gram-negative versus nine gram-positive and 13 gram-negative after receiving mupirocin treatment. As a result, mupirocin alters the nasal microbiological flora by inhibiting *Staphylococcus aureus* growth. Pathogenic gram-negative bacteria and *Corynebacterium* development in the nasal cavity after endoscopic nasal surgery can be

associated with symptom recurrence (29,30). Kim and Kwon evaluated the effect of mupirocin irrigation on *Staphylococcus aureus* infection in chronic rhinosinusitis patients in a meta-analysis of 101 patients from 3 studies. They concluded that mupirocin is an effective treatment for resistant CRS with *Staphylococcus aureus* infection only for a short-term period. Moreover, the infection rate with *Staphylococcus aureus* increases again after six months (27). Therefore, the time-dependent mupirocin efficacy could explain the non-significant difference in the radiological and endoscopic between the control and mupirocin groups in the present study.

### Conclusion

Administration of mupirocin ointment twice a day in the nostrils of CRSwNP patients cannot significantly affect surgical outcomes following endoscopic nasal surgery. The use of mupirocin in these patients should be considered due to the possibility of the growth of gram-negative pathogenic bacteria. It is recommended that further studies with a larger sample size be conducted to compare mupirocin and other topical antibiotics in the prevention of relapse in CRSwNP patients. The effect of combining mupirocin with other effective antibiotics on gram-negative bacteria can also be evaluated in this context. Furthermore, it is recommended that different methods and dosages of mupirocin administration be investigated in future studies and that short-term, medium-term, and long-term results be compared.

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