ORIGINAL ARTICLE

The Role of the Macrolide in Preventing Recurrence of the Nasal Polyposis after Fess

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a heterogeneous, multifactorial inflammatory disease of the nose and Paranasal sinuses, Chronic rhinosinusitis (CRS) affects around 5–15% of the European and American population, which makes it a common health problem that makes significant costs for health systems and state economies, phenotype classification of CRS with polyposis (CRSwNP) and without polyposis (CRSsNP).
Methods: A prospective, comparative randomized study was done in ENT Center, Sulaymania Teaching Hospital and Middle East ENT Head and Neck Surgery private center from October 2018 to October 2019. Sixty Patients presented with (CRSwNP) refractory to the maximal medical treatment and listed for FESS with informed consent included in the current study. The patients were randomly divided into two groups, each group included 30 patients, Group A; were Macrolide (clarithromycin 250mg /d/ 3m) prescribed postoperatively, Group B; without Macrolide. Both groups were topographic data collected preoperatively and clinical assessment pre and post-operatively at 1, 3, 6 months done utilizing the Lund-Kennedy Score (LKS), Lund-Mackay Score (LMS) and Sino-Nasal Outcome Test (SNOT 20) scores.
Results: The study established ability of short term low dose Clarithromycin treatment after FESS, throughout improving of the Lund-Kennedy Score (LKS), Lund-Mackay Score (LMS) and Sino-Nasal Outcome Test (SNOT 20) scores in group A in comparison to the control group B.
Conclusion: 3 months post FESS macrolide is able to control the inflammatory condition and inhibit the recurrence of the nasal polyposis after FESS.
Keywords:Chronic rhinosinusitis, Nasal polyposis, Endoscopic sinus surgery, Clarithromycin

INTRODUCTION

Chronic rhinosinusitis (CRS) is a heterogeneous, multifactorial inflammatory disease of the nose and Paranasal sinuses, affects around 5–15% of the European and American population, which makes it a common health problem that makes significant costs for health systems and state economies[1,2].

Until now, there is noglobal uniform classification for this disease. Clinically, CRS in adults is defined as the presence oftwo or more symptoms, one of which should be nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), ± reduction or loss of smell, ± facial pain/pressure, for morethan 12 weeks. Secondary symptoms such as headache, fever, halitosis, cough, toothache, drowsiness, or ear pressure may also be present[3,4].

Recently, American and European guidelines need in addition to two main criteria, endoscopic and/or radiological evidence of chronic inflammation. According to, endoscopic examinations of the nasal cavity or radiological imaging, CRS can be distinguished into chronic rhinosinusitis with nasal polyps(CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP), This classification is stated asphenotype classification[5].

Nowadays, increasing evidence is available to suggest that there are various endotypes of CRS, with different pathophysiology's and different forms of inflammation within the phenotypes[1,5]. Endotypes of CRS may becategorized according to availability of the T helper cell type into(1) nontype Th2[2] moderate type Th2, and(3)severe type Th2 immune. Based on cytokines and mediators such as IL4, 5, 13. CRS endo-typingincludesa[1] type 2 cytokine-based[2] eosinophil-mediated[3], immunoglobulin E-based, and[4] cysteinyl leukotriene-based[6,7]. All types of CRS seem to be affected by inflammatory changes in the sinonasal mucosa, A Th2-mediated inflammatory process and eosinophil's is commonly found in CRSwNP, while both Th2- and Th1-mediated processes are found in CRSsNP[8,9,10].

CRSwNP associated diseases includes; CRSwNP with cystic fibrosis (CF), aspirin -Exacerbated Respiratory Disease (AERD), inhalation allergies, immunodeficiency syndromes, Wegener's granulomatosis, allergic fungal rhinosinusitis and asthma. In case of CF, nasal polyps are existed in about40%[11].The incidence of AERD among patients with CRSwNP is about 16%, while, conversely, more than 96% of AERD patients have nasal polyposis[12,13,14,15].

The cytokine profile of nasal polyps in AERD patients displays the typical components of a Th2 disease, as well as eosinophilia and significant up regulation of IL-4 and IL-5[16]. The number of eosinophils in nasal polyps was higher in allergic patients compared with the non-allergic group. Besides, it has been revealed that both IL- and the Th2 cytokines IL-4 and IL-5 are found. Only0.4-4.5 percent of patients with allergic rhinosinusitishave nasal polyposis[17,18].

The incidence of allergic fungal rhinosinusitis (AFRS) or eosinophilic fungal rhinosinusitis (EFRS) in patients with nasal polyposis is approximately 9–12% and displays Th2-mediated inflammation with variable levels of Th2 cytokines, AFRS-/EFRS-related nasal polyps show a higher level of IgEand IL-5[19,20].

Bronchial asthma is mainly associated with nasal polyps, roughly 30-71% of patients with CRSwNP also

suffer from bronchial asthma; conversely, about 7% of asthma patients have nasal polyps[21,22].Though, the correlation between asthma and CRSwNP is poorly understood as yet. Consequently, the incidence of asthma raises expressively based on this endotype classification in patients with CRSwNP. IL-5 remains the main factor determining the phenotype with nasal polyps and asthma[23].

Functional endoscopic sinus surgery (FESS) has been used for more than three decades in treating sinonasal conditions, was introduced by Messerklinger[24] and Wigand[25] in Europe, later on advocated in USA by Kennedy[26]. Utilizing either Mini or Full-House techniques in anterior-posterior or posterior-anterior fashion based on the extent of disease, anatomical configuration and surgeon's skills[27,28,29,30]. Advantages are claimed over conventional surgery: permitting a better view of the surgical field, a more accurate and thorough clearance of the inflammatory change, fewer complications and lower recurrence rates[31].

There is proof that a 3-month macrolide canprevent early recurrence of the nasal polyps, by which macrolide considered to contain anti-inflammatory and immune-modulatory capabilities which act through inhibition of cytokine production[32]. Macrolides have been shown torisemucociliary transport, diminish goblet cell secretion and cause enhanced apoptosis of neutrophils, altogether of which would diminish the symptoms of chronic inflammation[33].

PATIENTS AND METHODS

A prospective comparative randomized study was done in ENT Center, Sulaymania Teaching Hospital and Middle East ENT Head and Neck Surgery in Private center from October 2018 to October 2019.Ethical and scientific committee of Kurdistan Board for Medical Specialties approval taken with order no of 2nd Jan2019.Sixty Patients presented with CRSwN Prefractory to the maximal medical treatment and listed for FESS with informed consent included in the current study. Patient younger than 18 years, with CRSsNP, history of previous FESS or conventional nasal surgeries, polyps of sino-nasal tumor origin, and patients unfollow the postoperative care were excluded from the study. The patients were randomly chosen and divided into two groups, each group included 30 patients, Group A; were Macrolide (clarithromycin 250mg/d/3m) prescribed postoperatively, Group B; without Macrolide. Both groups were topographic data collected preoperatively and clinical assessment pre and post-operatively at 1, 3, 6 months done utilizing the Lund-Kennedy Score (LKS), Lund-Mackay Score (LMS) and Sino-Nasal Outcome Test (SNOT20) scores as follows.

1. Endoscopic LKS (preoperative,1,3,6 months postoperative);The score for each parameter starts from 0 to 2 and collectively ranges from 0 to 20 for both sides. This staging is consisted of Polyp(0=no polyp,1=in middle meatus, 2=beyond middle meatus),edema(0=absent,1=mild, 2=severe),Discharge(0=no discharge, 1=clear, 2=thick),Scaring(0=absent,1=mild, 2=severe), and Crusting(0=absent,1=mild, 2=severe).
2. Radiological LMS (preoperative and 6months postoperative); The CT findings of paranasal sinuses were summarized by above score, the score ranges from 0 to 24. Where 0 (no opacification), 1 (partial opacification), 2 (complete opacification), whereas 0 (no obstructed OMC), 2 (obstructed OMC), and the total score is 12 for each side.
3. SNOT-20(preoperative,1,3,6 months postoperative); This test was applied to all patients and the test score ranged from 0 to 100.

Statistical analysis: Data was collected and coded. The collected data was reviewed and analyzed using the SPSS version 22. Descriptive statistics such as frequency and percentage was calculated. Measures of central tendency and dispersion around the mean were used to describe continuous variables. P value was obtained for the continuous variable using T-independent test and it was considered significant if it was less than 0.05

RESULT

The 60 patients were included in this study, distributed between 40 males (67.8 %) and 20 females (32.2%) with male to female ratio of 2:1, the mean age of the studied population was 42.83 ± 8.46 years and distributed in both groups as follows; group A (42.07±9.26), group B (43.62±7.63).**in** 60 patients15 patients of them have comorbidities such(asthma) 10 cases (16.6%) ,aspirin-exacerbated respiratory disease 5 cases(8.3%) and no case of cystic fibrosis.

Postoperativelya significant noticeable reduction in the mean score of the all SNOT-20 questionnaire items. In additional words, it improves the symptoms mentioned in each item. The outcomes of statistical analysis displayed that use of the macrolide after FESS significantly reduced SNOT-20 with a significant P value between both groups at 3rd, and 6th month postoperatively as shown in table 1.

Table (1) SNOT-20 Score Pre & Postoperatively at 1, 3 ,6 months

	Group A/B	N	Mean ± Std. Deviation	P-value
Pre-operative	Group A	30	76.70 ± 7.69	0.594
	Group B	30	77.76 ± 7.49	
one month after op.	Group A	30	43.50 ± 9.12	0.133
	Group B	30	47.76 ±12.17	
3 months after op.	Group A	30	8.70 ± 2.41	0.00
	Group B	30	11.07 ± 2.28	
6 months after op.	Group A	30	7.47 ± 2.13	0.00
	Group B	30	9.62 ± 1.92	

Table 2: Lund-Mackay Score

	Group A/B	N	Mean ± Std. Deviation	P-value
pre-operative	Group A	30	20.53 ± 2.16	0.166
	Group B	30	19.55 ± 3.14	
6 months after op.	Group A	30	5.90 ± 2.81	0.001
	Group B	30	8.45 ± 2.76	

Table(3) Lund- Kennedy Score (LKS)

	Group A/B	N	Mean ± Std. Deviation	P-value
pre-operative	Group A	30	18.13 ± 1.36	0.10
	Group B	30	17.52 ± 1.46	
one month after op.	Group A	30	7.90 ± 1.37	0.00
	Group B	30	9.00 ± 1.00	
3 months after op.	Group A	30	4.30 ± 0.65	0.33
	Group B	30	4.48 ± 0.79	
6 months after op	Group A	30	2.83 ± 0.79	0.09
	Group B	30	3.21 ± 0.86	

Table (4)Paired T-test for both groups scores (SNOT-20, LKS, LMS)

Parameters		Group A/ Group B	N	Mean ± Std. Deviation	P-value
SNOT 20	Pair 1	pre-operative	76.70	30 ± 7.69	0.00
		one month after op.	43.50	30 ± 9.12	
	Pair 1	pre-operative	71.00	30 ± 4.99	0.00
		3 months after op.	8.70	30 ± 2.41	
	Pair 1	pre-operative	71.00	30 ± 4.99	0.00
		6 months after op.	7.47	30 ± 2.13	
LKS	Pair 1	pre-operative	18.13	30 ± 1.36	0.00
		one month after op.	7.90	30 ± 1.37	
	Pair 1	pre-operative	18.13	30 ± 1.36	0.00
		3 months after op.	4.30	30 ± 0.65	
	Pair 1	pre-operative	18.13	30 ± 1.36	0.00
		6 months after op	2.83	30 ± 0.79	
LMS	Pair 1	pre-operative	20.53	30 ± 2.16	0.00
		6 months after op.	5.90	30 ± 2.81	

The CT scores (LMS) 6 months after FESS for group A (macrolide for 3 months) patients was 5.90 ± 2.81, which was significantly lower than in group B (no antibiotics), with analyses of 8.45 ± 2.76.Statistical analysis displayed that use macrolide after FESS significantly reduced CT-Score (P <0.001) as shown in table 2.

Endoscopic score in group A as follows; 7.90±1.37, 4.30±0.65, 2.83± 0.65 at 1st month, 3rd month and 6 months respectively. The group B was as follows; 9.00±1.00, 4.48±0.79, 3.21± 0.83 at 1st, 3rd and 6th months respectively as shown in table 3.

Using paired T test for both groups scores to compare between a pre and postoperative score (SNOT-20, LKS, LMS) at 1st, 3rd, and 6th months, shows significant difference in all 3 period for both groups collectively as shown in table 4.

DISCUSSION

It is well known that CRS is multifactorial in etiology and globally categorized into subgroups of (CRSsNP) and (CRSwNP)[34]. Although the prevalence of CRS w NP is between 1 and 4% in adults, 0.1% in children, and more common in male 2-4 times than in females[7], the long history of recognition and extensive research and literature, their etiology remains elusive and poorly understood[35].

Despite the adequate measures targeted to treat CRSwNP, still run a chronic and recurrent course which significantly affect quality of life, and places significant financial burden on society[3]. Estimation of cofactors associated with polyp recurrence identified prior ESS and preoperative polyposis severity to be significantly associated with recurrence. This is in contrast to prior cohorts that have identified aspirin-exacerbated respiratory disease and comorbid asthma and incomplete remove the disease are risk factors for recurrence[26].

FESS is used in CRSwNP, that doesn't reply to medications. In the other new literature long-term low-dose macrolide therapy has been described to be effective in CRSwNP or CRSsNP[29,30] .

In this thesis, we study the effect of the Macrolides (Clarithromycin) for 3 months to the control the inflammatory condition and prevent recurrence after FESS in patients with NP, utilizing LM, LK and SNOT-20 scores. Concerning the antibacterial and anti-inflammatory properties of the Macrolides, the action of it comprises increasing mucociliary movement, quickening neutrophils and apoptosis, all were diminished the symptoms of chronic inflammation[2].

In the current study, neither noticeable age, gender relation reported, which is in harmony with a study conducted by Bizarre and Nikakhlagh[9], which needed in the future to stress on it is possible role.

In our study, preoperative baseline LM (CT) score in the A and B patient groups did not differ considerably, being 20.53±2.16 and 19.55±3.14 respectively, which add more strength to the design and patient blind grouping. The

mean CT score 6 months after FESS for group A patients (antibiotics for 3 months) was 5.90 ± 2.81, which was significantly lower than in group B (control no antibiotics) with analyses of 8.45 ± 2.76 (P value= 0.001) as shown in table 1.

In comparison to a study was conducted by Varvyanskaya et al[35], there was no noticeable difference with our report. In their study, patients divided into three groups (control, antibiotic for 12 weeks, and 24 weeks). Although, revealed that CT scores for group 1 (antibiotics 12 weeks) patients was (12.62±4.15), which was significantly lower than in control group(no antibiotics)being (16.66± 2.32), there was no statistical significance between 12 weeks and 24 weeks groups.

This is belong to effect of macrolide can benefit nasal polyps and prevent early recurrence, by which, macrolides considered to contain anti-inflammatory and immune-modulatory capabilities, mainly done the inhibition of cytokine production.

Macrolides have been shown to raise mucociliary transport, diminish goblet cell secretion and cause enhanced apoptosis of neutrophils, altogether of which would diminish the symptoms of chronic inflammation. Anastasia et al. [35] confirmed that a (3 months) antibiotic course reduces the eosinophilic inflammation, thereby preventing early recurrence of nasal polyps, that is why no need to give macrolide for more than(3 months).

In the current study, endoscopic score achieves better outcome at 1st month visit in group A in comparison to group B with a P value= 0.00.as shown in fig.(1a, f) However, at 3rd and last visit at 6th month postoperative, did not showed significant difference between both groups, due to the scar formation occurred leading to discharge, collection of secretion and inflammation. as shown in fig.(1c, d, g, h)

In comparison to other studies were conducted by Dabirmoghaddam etal·[34] and Nakamura et al.[31], although similar results were achieved at 1stmonth postoperative visitwith a p < 0.05 for each study, Dabirmoghaddam etal·[34,36]showed a noticeable improvement in the 2nd visit at 6 months postoperatively with a *p value*<0.05). aforementioned discrepancy is related to the severity of the disease and associated comorbidities in our series studied patients, were selected randomly without exclusion of the CRSwNP associated comorbidities from the study, such as (asthma16.6%), aspirin-exacerbated respiratory disease (8.3%) and no case of cystic fibrosis. which excluded by Dabirmoghaddam et al[34] in their study.

Regarding SNOT-20 score, generally all items were decreased more in group A in comparison to group B, especially nasal discharge, nasal obstruction and improved sense of smell at endpoint in last visit at 6th month postoperatively, that was reach a significant analysis with (p value=0.00) it is due to reduced inflammatory process, decrease edema and scar formation. However, in first visit at the 1st month postoperatively, there was no noticeable difference between both groups with a p value=0.13, which is due to the early persistence of the edema, inflammation, clot and crust formation despite utilizing macrolide. From reviewing literature, we noted our report is in harmony with Nikakhlagh et al[32] and Oliveira et al. [9], were follow their series for 6 months postoperatively and reported significant changes in SNOT 20 score with (p < 0.05).

Despite the advantage of clarithromycin drug, it has some adverse reactions, in this study some patients have mild abdominal patient, nausea, dyspepsia and one patient had hyperhidrosis. These reactions are usually mild and adapted without need for stop the drug in this study.

Unfortunately, we did not culture from middle meatus for bacterial resistance related macrolide because we use it as anti-inflammatory, but according to a study conducted by Anastasia et al[35], there was no resistance increased for macrolide use for six months. In addition, we did not investigate Eosinophil Cationic Protein levels in our study for patients because not available, however in a study conducted by Oliveira et al[9] shows the reduction of ECP levels in the nasal secretions after FESS and in the postoperative period with clarithromycin.

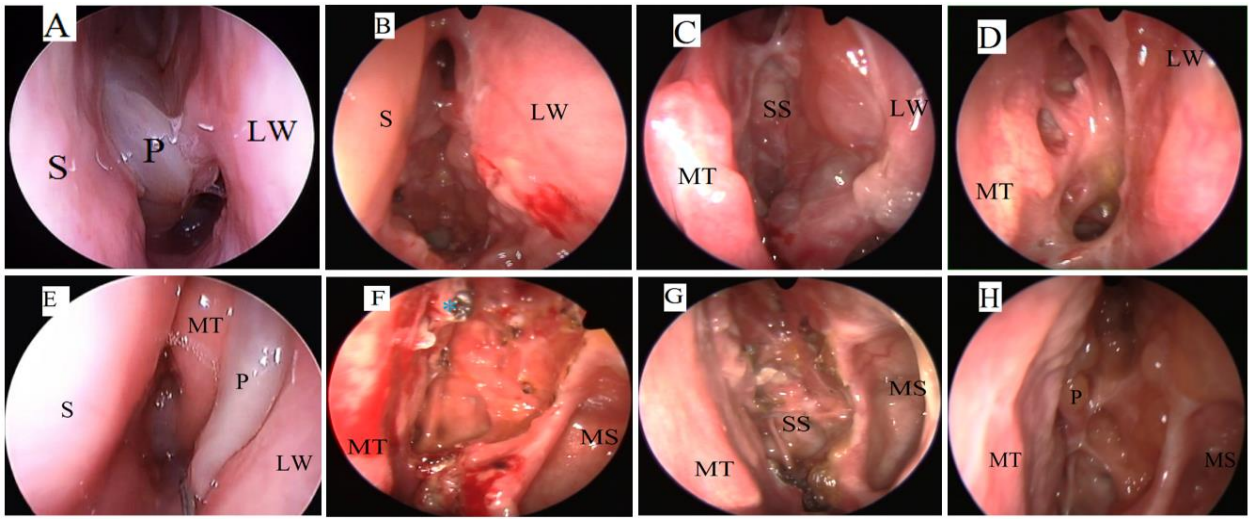

Fig.(1)Pre, and postoperative endoscopic images of patient underwent FESS.1st row group A and 2nd row group B (pre op, postop, 1st, 3rd, 6th months) respectively.(S) septum, (p) polyps, (LW)lateral wall, (MT)middle turbinate, (SS)sphenoid sinus,(MS) maxillary sinus,(blue*)clot.

CONCLUSION

The results of our study confirmed the efficacy and safety of 3 months low-dose (250 mg/day) (clarithromycin) treatment for patients with CRSwNP after FESSsignificantly associated with improvement in quality of life, according to (SNOT-20, LMS and LKS), it can inhibit early recurrence of NP.The key to effective implementation of macrolide therapy, in CRS, is patient selection. Our study recommended to use the macrolide especially for CRS patients associated with comorbidities like (Asthma, AFRS, Cystic fibrosis) for 3 months in low dose postoperatively.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: For this type of study formal consent is obtained.

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