ORIGINAL ARTICLES
PHILIPPINE JOURNAL OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY VOL. 33 NO. 2 JULY – DECEMBER 2018

Efficacy of Clarithromycin Versus Methylprednisolone in the Treatment of Non-Eosinophilic and Eosinophilic Nasal Polyposis: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the efficacy of Clarithromycin versus Methylprednisolone in the treatment of non-eosinophilic and eosinophilic nasal polyposis.

Methods:

Design: Randomized Controlled Trial

Setting: Tertiary Government Training Hospital

Participants: Forty two (42) patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) were grouped into non-eosinophilic and eosinophilic groups after biopsy determination of eosinophil count. Both groups were further randomized into a treatment arm given Clarithromycin (CLA) 500 mg/ day and another arm given Methylprednisolone (METH) 32 mg/ day tapering to 8 mg/ day for 15 days. All participants underwent pre– and post–treatment evaluation via anterior rhinoscopy, Sino-Nasal Outcome Test (SNOT-22) and Endoscopic Appearance (EA) Scoring. Data were encoded and subjected to statistical analysis using Mann-Whitney U test.

Results: For the 9 participants in the non-eosinophilic group, 4 were given CLA and 5 were given METH. The CLA arm showed significant improvement in SNOT-22 scores by the 15th day (p= .007). The METH arm did not demonstrate significant improvement by the 7th (p= .44) or 15th day (p= .22). Comparison of the improvement in SNOT-22 scores between the two arms showed that on both 7th and 15th days, CLA outperformed METH (p= .026 and p= .004, respectively). For the EA scoring, both the CLA and METH groups significantly improved by the 7th (p= .027 and p= 0.017, respectively), and 15th day (p= .013 and p= .027, respectively). Comparison of the improvement in EA scores between the two arms showed significant difference on the 15th day (p= .01) with the CLA performing better than METH. Overall, the results suggest that the CLA arm performed significantly better than the METH arm in the treatment of non-eosinophilic patients.

Of the 33 eosinophilic patients, 17 were given CLA and 16 were given METH. The CLA arm showed significant improvement in SNOT-22 scores by the 15th day (p < .001) while the METH arm on both 7th (p= .033) and 15th day (p< .001). Comparison of the improvement in SNOT-22 results between the two arms showed no significant differences (7th day p= .494; 15th day p= .587). For the EA scoring, both treatment groups showed significant improvement by the 7th and 15th day (p< .001). Comparison of the improvement in EA scores between the two arms showed significant differences (p< .001) on both 7th and 15th day, suggesting that METH was more effective

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Presented at the 10th International Symposium on Recent Advances in Rhinosinusitis and Nasal Polyps, and 61st Annual Convention of the Philippine Society of Otolaryngology Head and Neck Surgery, Philippine Academy of Rhinology "Cesar F. Villafuerte, Sr. Research Contest" (1st Place) November 30, 2017, "Antonio L. Roxas International Research Contest" (Finalist) December 1, 2017, at the Manila Hotel, Manila.

Philipp J Otolaryngol Head Neck Surg 2018; 33 (2): 6-13

than CLA. Overall, the results showed that both CLA and METH were effective in the treatment of eosinophilic nasal polyps. However, METH was significantly better than CLA in terms of superior EA scores.

Conclusion: In terms of improving symptoms and well-being, as well as decreasing nasal polyp size and reducing discharge and edema as reflected in superior SNOT-22 and EA scores, Clarithromycin was significantly more effective than Methylprednisolone in the treatment of non-eosinophilic nasal polyps. While both Clarithromycin and Methylprednisolone were shown to be effective in the treatment of eosinophilic nasal polyps, Methylprednisolone was significantly better than Clarithromycin in terms of superior EA scores. A biopsy for tissue eosinophil cell count prior to treatment is recommended to establish the predominant inflammatory cell in nasal polyps in order to provide appropriate targeted treatment, i.e. Clarithromycin for non-eosinophilic nasal polyps and Methylprednisolone for eosinophilic polyps.

Keywords: *macrolides, clarithromycin, methylprednisolone, nasal polyps, eosinophils*

Macrolides are known for their immunomodulatory properties. Laboratory and clinical studies have shown that macrolides inhibit mucus hypersecretion, enhance mucociliary activity, reduce mucus secretion and suppress cytokine/chemokine production.[1-4] They have been used as alternative treatment for a host of inflammatory diseases including Chronic Rhinosinusitis (CRS) with and without polyps.[1-4] Roxithromycin and Clarithromycin administered for at least 8 weeks resulted in marked shrinkage of polyps.[5,6] The ability of macrolides to down-regulate neutrophilic activity has been believed to account for its immunomodulatory effect in CRS.[7-9] A significant correlation between decreased nasal lavage levels of IL-8, a potent neutrophil chemotactic factor, and the clinical effect of macrolides on the size of the nasal polyps have been reported.[10]

The therapeutic efficacy of macrolides in improving subjective symptoms decreases in patients with high eosinophil counts in the blood, nasal secretions and nasal mucosa or high serum IgE levels.[9,11,12] While multiple etiopathogeneses have been proposed for CRS in general, nasal polyposis is believed to be primarily IgE-mediated, characterized by Th2 inflammation, local immunoglobulin production and eosinophil infiltration driven by IL-5 and eotaxin.[13] In such so-called eosinophilic patients, corticosteroids have been recommended as first-line management choice. Having been known to suppress the chemotaxis and activation of eosinophils, T cells and mast cells, corticosteroids have also shown beneficial effects in reduction of polyp size, improvement of nasal symptoms and nasal airflow. In conjunction with oral therapy, topical corticosteroids are considered well-tolerated for long term use.[12]

While numerous articles have suggested that macrolides and corticosteroids modulate non-eosinophilic and eosinophilic inflammation, respectively, controversies still exist regarding the use of macrolides in the treatment of CRS.[1-3] Reduction of nasal polyps is often observed but the response is variable and often seen only in smaller polyps. Studies suggest that low dose macrolides provide benefit only when used as an adjunct to topical corticosteroids.[1] A major limitation of these studies was the lack of pretreatment classification based on eosinophilic predominance of nasal polyps which may explain the conflicting responses. Furthermore, an explant model study showed Clarithromycin and Dexamethasone exhibiting similar anti-inflammatory effects on different phenotypes of CRS.[3] These findings have yet to be conclusively reflected outside of the laboratory setting. At present, evidence is still insufficient to warrant concrete recommendations for the use of macrolide therapy in CRS with polyp phenotype.[1]

This clinical study aimed to further investigate the potential beneficial effects of macrolides on both non-eosinophilic and eosinophilic nasal polyps by comparing the efficacy of Clarithromycin against Methylprednisolone. Outcome measures included Sino-Nasal Outcome Test (SNOT-22)[14] and Endoscopic Appearance (EA)[14,15] Scoring.

METHODS

With Institutional Review Board approval, this randomized controlled trial was conducted at the Out-patient Department of a tertiary government training hospital from August 2016 to December 2016. All patients newly diagnosed as having Chronic Rhinosinusitis with nasal polyps (CRSwNP) according to the 2016 Philippine Clinical Practice Guidelines on Chronic Rhinosinusitis[14] were screened for the study. *(Figure 1)* Excluded were patients with unilateral polyps, pregnant patients, immunocompromised patients, those with known hypersensitivity to either macrolides or corticosteroids and patients not amenable to biopsy.

Diagnosis was established via physical examination, anterior rhinoscopy and nasal endoscopy. Patients were asked to evaluate their symptoms using the Sino-Nasal Outcome Test (SNOT-22, Washington University, St. Louis, Missouri).[14] Polyps were evaluated using the Endoscopic Appearance (EA) Score[14,15] as shown below. EA Scoring was done separately for the right and left nasal cavity of each subject, and each side was treated as a separate item for analysis (number of patients multiplied by 2 sides):

Characteristic*	Pre-Test	7th day	15th day
Discharge, right (0,1,2)			
Edema, right (0,1,2)			
Polyp, right (0,1,2,3)			

Characteristic	Pre-Test	7th day	15th day
Discharge, left (0,1,2)			
Edema, left (0,1,2)			
Polyp, left (0,1,2,3)			

* Discharge: 0 – no discharge; 1 – clear, thin discharge; 2 – thick, purulent discharge
Edema: 0 – absent; 1 – mild; 2 – severe
Polyp: 0 – absence of polyps
1 – polyps in the middle meatus only
2 – polyps beyond middle meatus but not blocking the nose completely
3 – polyps completely obstructing the nose

Informed consent was obtained for inclusion in the study and for biopsy of nasal polyps under local anesthesia. Specimens were sent to pathology for eosinophil count. Patients were classified into two groups: non-eosinophilic and eosinophilic, based on the number of eosinophils/ high power field (hpf) at 400x magnification (average of 10 scan fields) as recommended by the 2016 Philippine Clinical Practice Guidelines on Chronic Rhinosinusitis.[14] Presence of <5 eosinophils/hpf was classified as non-eosinophilic while eosinophilic polyps were those with ≥5 eosinophils/hpf by a blinded resident pathologist (co-author).

After biopsy, all patients were given intranasal fluticasone propionate aqueous nasal spray (50mcg/spray), administered twice daily until such time that the cell count results were released. Thereafter, patients in both groups were randomized via lottery sampling/ fishbowl technique to either Treatment 1 or Treatment 2. Treatment 1 arm was given CLARITHROMYCIN 500mg/day for 15 days. Treatment 2 arm was given METHYLPREDNISOLONE 32mg/day for 5 days, 16mg/day for the next 5 days and 8mg/day for the last 5 days. Treatment regimen was based on the recommendations of the 2016 Philippine Clinical Practice Guidelines on Chronic Rhinosinusitis.[14] Assessors of the nasal polyps before and after treatment were blinded. Patients were not blinded to treatment.

Patients were reevaluated using the SNOT-22 and the EA scores on 7th and 15th day of treatment. Endoscopic evaluation of the nasal polyps was done via review of video recordings by 2 senior residents who did not perform the endoscopies and submitted as a consensus report.

Outcome measure data were encoded and SNOT-22 and EA scores were subjected to statistical analysis using Mann-Whitney U Test (SPSS Version 20, IBM Corp., Armonk, NY, USA).

Patients were informed that should nasal polyps fail to respond to the assigned treatment, they would be shifted to the standard medical treatment for nasal polyposis (oral corticosteroid combined with topical nasal corticosteroid). Patients were also informed of the possible signs and symptoms of the above treatment and were advised that should any adverse drug reaction be experienced during the course of therapy, treatment would be discontinued immediately. Appropriate therapy would be administered and researchers would see to it that patients received appropriate medical attention.

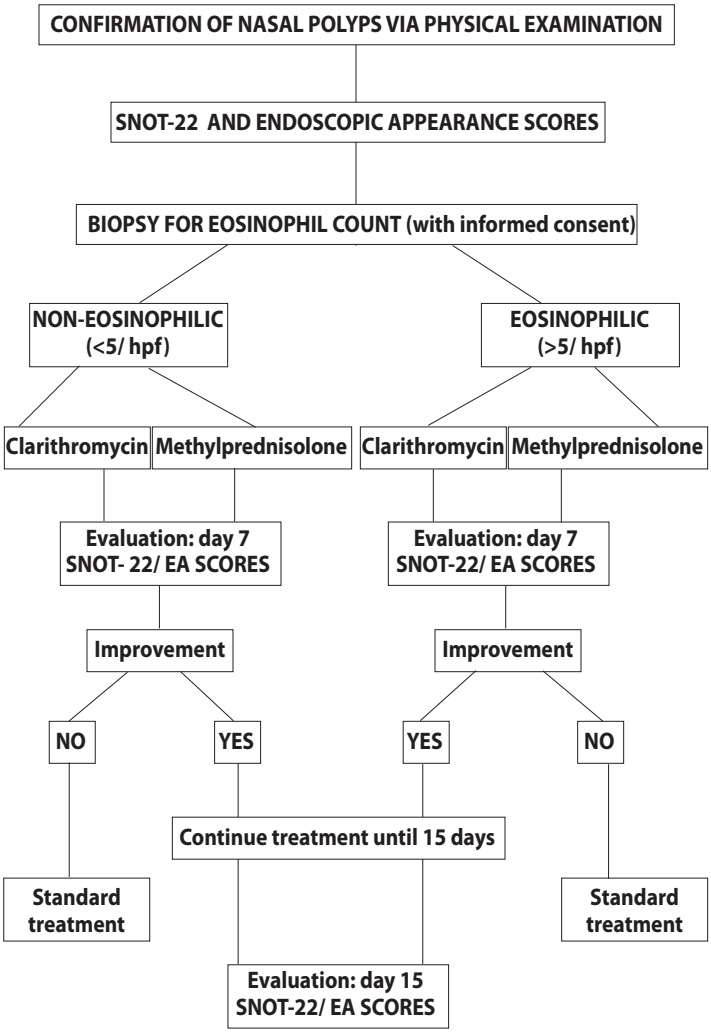

Figure 1. Methodology Flowchart

RESULTS

42 patients participated in the study. 20 were females (47%) and 22 were males (52%) with mean age of 45.25. Nine (21%) were found to be non-eosinophilic and 33 (79%) were classified as eosinophilic.

For the non-eosinophilic patients, the METH group mean age was slightly younger than that of the CLA group. However, a t-test for two independent samples revealed that the difference was not significant (p= .566). Gender across the groups was also fairly distributed with no significant difference based on Chi-square test (p= .764). Pre-Treatment baseline examination scores were also fairly comparable between both groups. A Mann-Whitney U test on the SNOT-22 scores revealed no significant difference pre-treatment (U= 32.5, Z= -0.696, p= .486 and r= .515). A Mann-Whitney U test on the EA scores also showed no significant difference pre-treatment (U= 4.5, Z= -1.37, p= .171 and r = .190). *(Table 1)*

Table 1. Demographics of Patients with Non-eosinophilic Polyps

Demographic Profile	CLA=4		METH=5	
	Mean	SD	Mean	SD
Age	45.25	9.18	40.8	12.19
Gender:	**Freq**	%	**Freq**	%
Male	2	50.0	2	40.0
Female	2	50.0	3	60.0
Pre-Treatment Evaluation:	**Median**	**Mean Rank**	**Median**	**Mean Rank**
SNOT-22	2.5	8.56	3.5	10.25
EA	3.4	6.38	2.8	3.9

For the eosinophilic patients, the METH group mean age was slightly older than that of the CLA group. However, a t-test for two independent samples revealed that the difference was not significant (p= .649). Likewise, gender was fairly distributed between both groups as computed on Chi-square test (p= .611). Pre-Treatment examination scores were also fairly similar between both groups. A Mann-Whitney U test on the SNOT-22 scores showed no significant difference pre-treatment (U= 517.5, Z= -0.354, p= .723 and r= .727). A Mann-Whitney U test on the EA scores revealed no significant pre-treatment difference either (U= 128, Z= -0.294, p=.769 and r= .790). *(Table 2)*

Non-Eosinophilic polyps

For the 9 participants in the non-eosinophilic group, 4 were given Clarithromycin (CLA) and 5 were given Methylprednisolone (METH).

A. SNOT-22 of Pre-Treatment versus 7th day and versus 15th day *(Figure 2)*

Table 2. Demographics of Patients with Eosinophilic Polyps

Demographic Profile	CLA=17		METH=16	
	Mean	SD	Mean	SD
Age	42	10.012	43.81	12.59
Gender:	**Freq**	%	**Freq**	%
Male	10	58.8	8	50.0
Female	7	41.2	8	50.0
Pre-Treatment Evaluation:	**Median**	**Mean Rank**	**Median**	**Mean Rank**
SNOT-22	3	34.32	3	32.68
EA	3.2	17.47	3	16.5

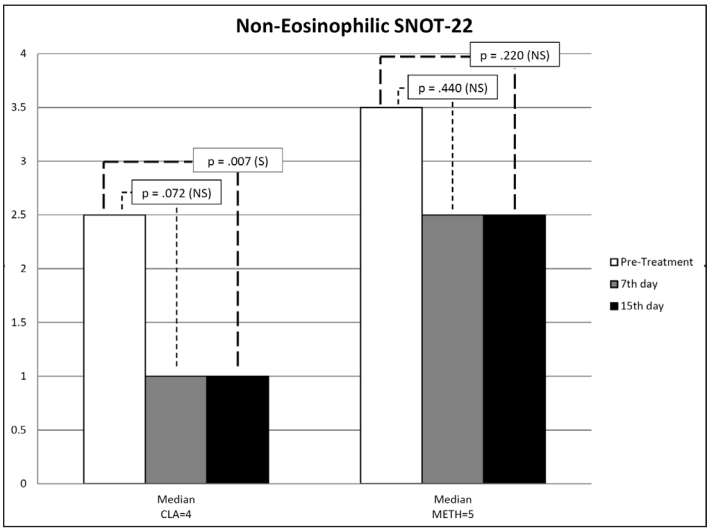

Figure 2. Mann-Whitney U Test Comparison of SNOT-22 scores for Non-eosinophilic nasal polyps: CLA (Clarithromycin); METH (Methylprednisolone); Median in White bar (Pre-Treatment); Median in Gray bar (7th day); Median in Black bar (15th day); Small dashed line (p-value of Pre-Treatment versus 7th day); Big dashed line (p-value of Pre-Treatment versus 15th day); S (Significant); NS (Nonsignificant)

A1. Clarithromycin

Medians of Pre-Treatment and 7th day were 2.5 and 1, respectively, with no significant difference (Mean ranks were 10.56 and 6.44, respectively; U= 15.5, Z= -1.8, p= .072 and r= .083). The medians of Pre-Treatment and 15th day were 2.5 and 1, respectively. There was a significant difference by the 15th day (Mean ranks were 11.5 and 5.5, respectively; U = 8, Z = -2.677, p= .007 and r = .010) suggesting a significant effect of Clarithromycin on the 15th day.

A2. Methylprednisolone

The medians of Pre-Treatment and 7th day were 3.5 and 2.5, respectively, with no significant difference (Mean ranks were 11.45 and

9.55, respectively; U= 40.5,Z= -0.772, p= .44 and r= .481). Medians of Pre-Treatment and 15th day were 3.5 and 2.5, respectively, with no significant difference (The mean ranks were 12.05 and 8.95, respectively; U = 34.5, Z = -1.226, p = .22 and r = .247) suggesting there was no improvement with Methylprednisolone on both days.

B. EA Score of Pre-Treatment versus 7th day and versus 15th day *(Figure 3)*

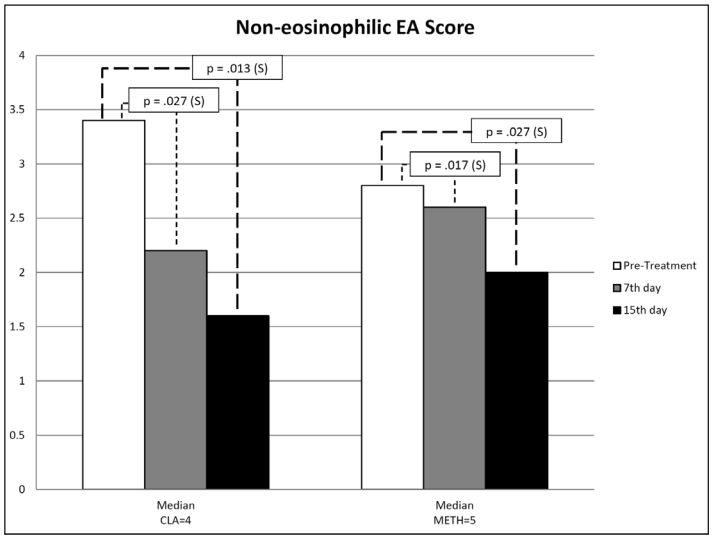

Figure 3. Mann-Whitney U Test Comparison of EA scores for Non-eosinophilic nasal polyps: CLA (Clarithromycin); METH (Methylprednisolone); Median in White bar (Pre-Treatment); Median in Gray bar (7th day); Median in Black bar (15th day); Small dashed line (p-value of Pre-Treatment versus 7th day); Big dashed line (p-value of Pre-Treatment versus 15th day); S (Significant); NS (Nonsignificant)

B1. Clarithromycin

The medians of Pre-Treatment and 7th day were 3.4 and 2.2, respectively, with a significant difference (The mean ranks were 6.38 and 2.63, respectively; U= 0.5, Z= -2.205, p= .027 and r= .029). The medians of Pre-Treatment and 15th day were 3.4 and 1.6, respectively, with a significant difference (The mean ranks were 6.5 and 2.5, respectively; U= 0, Z= -2.477, p= .013 and r= .029) suggesting there was significant improvement with Clarithromycin on both the 7th and 15th days.

B2. Methylprednisolone

The medians of Pre-Treatment and 7th day were 2.8 and 2.6, respectively, with a significant difference (Mean ranks were 7.7 and 3.3, respectively; U= 1.5, Z= -2.386, p= 0.017 and r= 0.016). Medians of Pre-Treatment and 15th day were 2.8 and 2, respectively, with a significant difference (Mean ranks were 6.38 and 2.63, respectively; U= .5, Z= -2.205, p= .027 and r= .029) suggesting there was improvement by the 7th and 15th day.

C. Clarithromycin versus Methylprednisolone Improvement in SNOT-22 and EA Scores on the 7th and 15th day

C1. SNOT-22

For the 7th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 1 and 2.5, respectively, with a significant difference (The mean ranks were 6.5 and 11.9, respectively; U= 16, Z= -2.221, p= .026 and r= .034). For the 15th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 1 and 2.5, respectively, with a significant difference (The mean ranks were 5.63 and 12.6, respectively; U= 9, Z= -2.902, p= .004 and r= .004) showing that on both 7th and 15th days, CLA outperformed METH.

C2. EA Score

For the 7th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 2.2 and 2.6, respectively, with no significant difference (The mean ranks were 4.25 and 5.6, respectively; U= 7, Z= -0.786, p= .432 and r= .556). For 15th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 1.6 and 2, respectively, with a significant difference on the 15th day (The mean ranks were 2.5 and 7, respectively; U= 0, Z= -2.582, p= .01 and r= .016) suggesting the CLA arm results were better than the METH arm on the 15th day.

Overall, the results suggest that the CLA arm performed significantly better than the METH arm in the treatment of non-eosinophilic patients.

Eosinophilic polyps

Of the 33 eosinophilic patients, 17 were given Clarithromycin (CLA) and 16 were given Methylprednisolone (METH).

A. SNOT-22 of Pre-Treatment versus 7th day, and versus 15th day *(Figure 4)*

A1. Clarithromycin

Medians of Pre-Treatment and 7th day were 3 and 2, respectively. A Mann-Whitney U test revealed no significant difference (The mean ranks were 39.15 and 27.85, respectively; U= 517.5, Z= -0.352, p= .723 and r= .727). The medians of Pre-Treatment and 15th day were 3 and 2, respectively, with a significant difference (The mean ranks were 44.36 and 22.64, respectively; U= 186, Z= -4.793, p< .001 and r< .001) suggesting there was significant improvement on the 15th day.

A2. Methylprednisolone

The medians of Pre-Treatment and 7th day were 3 and 2, respectively, with a significant difference (Mean ranks were 38.36 and 28.64,

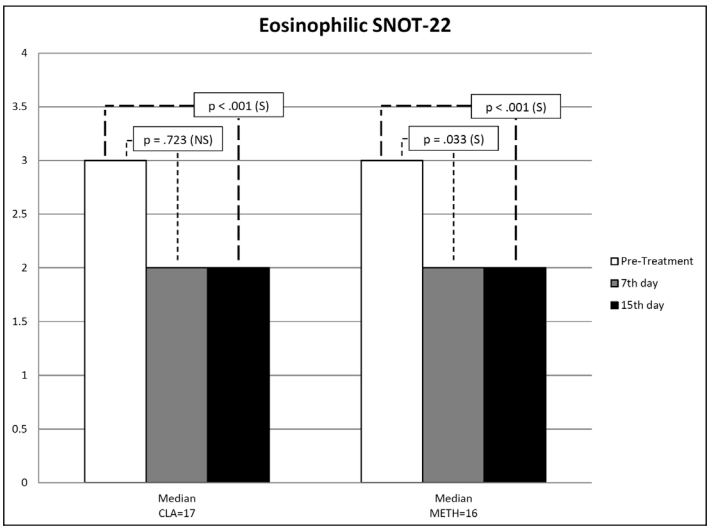

Figure 4. Mann-Whitney U Test Comparison of SNOT-22 scores for Eosinophilic nasal polyps: CLA (Clarithromycin); METH (Methylprednisolone); Median in White bar (Pre-Treatment); Median in Gray bar (7th day); Median in Black bar (15th day); Small dashed line (p-value of Pre-Treatment versus 7th day); Big dashed line (p-value of Pre-Treatment versus 15th day); S (Significant); NS (Nonsignificant)

respectively; U= 384, Z= -2.133, p= 0.033 and r= 0.033). Medians of Pre-Treatment and 15th day were 3 and 2, respectively, with a significant difference (Mean ranks were 42.88 and 24.12, respectively; U= 235, Z= -4.152, p< .001 and r< .001) suggesting there was significant improvement on both the 7th and 15th day.

B. EA Score of Pre-Treatment versus 7th day, and versus 15th day *(Figure 5)*

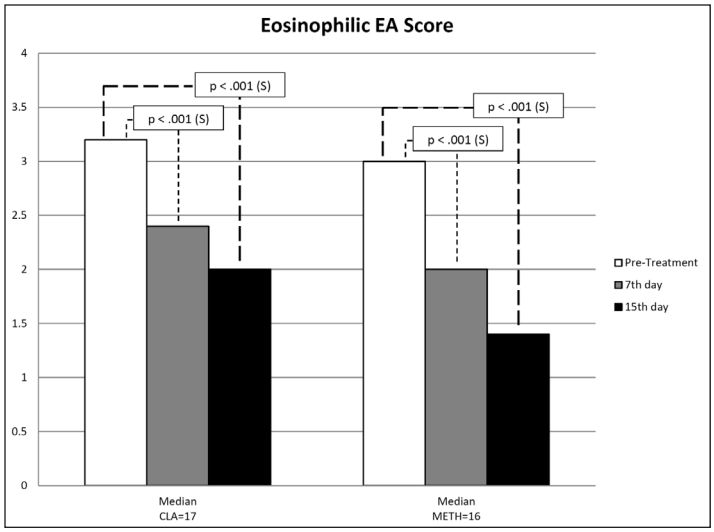

Figure 5. Mann-Whitney U Test Comparison of EA scores for Eosinophilic nasal polyps: CLA (Clarithromycin); METH (Methylprednisolone); Median in White bar (Pre-Treatment); Median in Gray bar (7th day); Median in Black bar (15th day); Small dashed line (p-value of Pre-Treatment versus 7th day); Big dashed line (p-value of Pre-Treatment versus 15th day); S (Significant); NS (Nonsignificant)

B1. Clarithromycin

The medians of Pre-Treatment and 7th day were 3.2 and 2.4, respectively, with a significant difference (Mean ranks were 24.35 and 10.65, respectively; U= 28, Z= -4.083, p< .001 and r< .001). Medians of Pre-Treatment and 15th day were 3.2 and 2, respectively, with a significant difference (Mean ranks were 25.82 and 9.18, respectively; U= 3, Z= -4.922, p< .001 and r< .001) suggesting a significant improvement with Clarithromycin on both the 7th and 15th day.

B2. Methylprednisolone

The medians of Pre-Treatment and 7th day were 3 and 2, respectively. A Mann-Whitney U test showed a significant difference (The mean ranks were 24.47 and 8.53, respectively; U= 0.5, Z= -4.856, p< .001 and r< .001). Medians of Pre-Treatment and 15th day were 3 and 1.4 respectively, showing a significant difference (The mean ranks were 24.5 and 8.5, respectively; U= 0, Z= -4.858, p< .001 and r< .001). There was significant improvement on 7th and 15th day respectively with methylprednisolone showing more improvement on the 15th day.

C. Clarithromycin versus Methylprednisolone Improvement in SNOT-22 and EA Scores on the 7th and 15th day

C1. SNOT-22

For 7th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 2 and 2, respectively. There was no significant difference (The mean ranks were 35.03 and 31.97, respectively; U= 494, Z= -0.684, p= .494 and r= .503). For the 15th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 2 and 2, respectively, also with no significant difference (The mean ranks were 34.65 and 32.35, respectively; U= 506.5, Z= -0.544, p= .587 and r= .607). Both treatments were found to be equally effective in improving SNOT-22 scores.

C2. EA Score

For the 7th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 2.4 and 2, respectively, with a significant difference (The mean ranks were 23.29 and 10.31, respectively; U= 29, Z= -3.933, p< .001 and r< .001). For the 15th day, medians of treatment arm 1 (CLA) and treatment 2 (METH) were 2 and 1.4, respectively, also with a significant difference (The mean ranks were 23.26 and 10.34, respectively; U= 29.5, Z= -3.894, p< .001 and r< .001) suggesting that methylprednisolone performed better than clarithromycin.

Overall, the results showed that both Clarithromycin and Methylprednisolone were effective in the treatment of eosinophilic nasal polyps. However, Methylprednisolone was significantly better than Clarithromycin in terms of superior EA scores.

DISCUSSION

In this study, Clarithromycin performed better than Methylprednisolone in the treatment of non-eosinophilic nasal polyps. This is in congruence with most studies comparing macrolides and corticosteroids in the treatment of nasal polyps, suggesting that corticosteroids perform poorly in the absence of eosinophilic predominance.[5,6,10,16] In an investigation comparing responses of neutrophil-positive and neutrophil-negative nasal polyps to oral prednisone treatment, Wen and colleagues noted that neutrophil-mediated inflammation negatively affected the efficacy of oral corticosteroid therapy.[16] The result of this study was further supported by a double-blind study by Wallwork *et al.* in which patients treated with Roxithromycin (compared to placebo) who demonstrated significant improvement in both subjective and objective outcome measures exhibited low levels of IgE, suggesting that low levels of eosinophils in nasal polyps may respond better to macrolide treatment.[6] By the same token, a study done by Haruna *et al.* noted that poor responders to macrolide therapy had a statistically significant increase in the percentage of eosinophils in the sampled polyp tissue, further emphasizing the preferential response to therapy of both nasal polyp phenotypes.[9]

Macrolides are better known for their capacity to inhibit neutrophilic rather than eosinophilic function. Reduced numbers of neutrophils and inhibition of neutrophilic function lead to lower concentrations of neutrophil elastase and IL-8, and ultimately to a decrease in tissue injury.[7] However, some studies revealed macrolides also contribute to eosinophil reduction. A study done by Fan *et al.* revealed clarithromycin decreased both IL-8 and IL-5 concentrations in nasal discharges, implying its effect in both neutrophil and eosinophil mediated inflammation.[17] An in vitro study done by Lin *et al.* revealed macrolide Azithromycin can down regulate IL-5 production suggesting effectivity in other eosinophil mediated diseases such as asthma.[17]

In our study, Clarithromycin was as effective as Methylprednisolone in improving SNOT-22 and EA scores of eosinophilic patients although statistically significant difference was only noted in the EA scores. These results were similar to an explant study by Zeng *et al.* which found that Clarithromycin and Dexamethasone exerted similar anti-inflammatory effects on both non-eosinophilic and eosinophilic polyp tissues which had distinctly different inflammatory pathways.[3] Both Clarithromycin and Dexamethasone up-regulated the production of anti-inflammatory mediators and down-regulated the production of Th2 response and eosinophilia promoting molecules, Th1 response and neutrophilia-promoting molecules.[3] While the effect of macrolides on eosinophils has been less commonly investigated, these findings indicate that Th2 cytokines are more frequently reduced than Th1 cytokines, suggesting that the role of macrolides in eosinophilic inflammatory disease should not be ignored.[7]

Most trials and reviews promoted long-term, low dose macrolide therapy for chronic rhinosinusitis.[4-6,8-10,16,18-20] Nakamura *et al.* advocated the use of low dose macrolide therapy for up to 6 months to allow regeneration and persistence of healthy mucosa even after discontinuation of treatment.[8] His investigation revealed that treatment of macrolides for 3 months still did not allow full recovery of nasal mucosa and submucosal glands, however, long term administration of macrolide for up to 9 months improved ciliary clearance causing decrease in mucus gland secretions allowing restoration of healthy mucosa.[8] Wallwork *et al.* noted that significant clinical improvement was seen by the 12th week of macrolide treatment.[9] However, this prolonged course of treatment can lead to emergence of resistance and potential adverse drug effects. Wong *et al.* noted that longer courses of Clarithromycin were associated with more cardiovascular events.[21] The increased risk may persist well beyond even after clarithromycin is stopped. While long term, low dose macrolide treatment has been suggested, effects of long term macrolide therapy such as antibiotic resistance and cardiac events should not be ignored.

In our study, Clarithromycin was given at 500mg once daily for 15 days to closely simulate the standard duration of oral steroid therapy, in contrast to the suggested 250mg/day for at least 8 weeks. Two weeks course of macrolides have been reported to show significant reduction in eosinophils, macrophages, Il-6, Il-8 and TNF-alpha, which however, lasted only for two weeks after discontinuation of treatment.[4] A more recent study done by Fan *et al.* noted that short-term, high-dose macrolide was effective in the treatment of chronic rhinosinusitis.[17] Endoscopic appearance and SNOT-20 scores, as well as inflammatory markers (IL-5 and IL-8), decreased by the 7th day of Clarithromycin 500 mg twice daily, suggesting that dosage, rather that duration of treatment, offers greater importance in the treatment of nasal polyps.[17] However, the question of how long lasting the improvement observed in just 2 weeks of Clarithromycin treatment remains unclear.

The value of determining polyp tissue eosinophil count should also be highlighted. As numerous studies reflect the different responses to either macrolide or oral corticosteroid, determination of nasal polyp phenotype can prove to be cost effective and safe for the patient. Since Clarithromycin performed better than Methylprednisolone in the treatment of non-eosinophilic polyps, establishing the low eosinophil count prior to treatment would spare the patient unnecessary corticosteroid medication. Pretreatment cell count will also decrease

incidence of resistance hence we recommend initial nasal polyp biopsy in order to provide a more targeted treatment. Further studies may be done to address cost-effectiveness and safety issues.

An interesting side note in this study was that our study population predominantly exhibited the eosinophilic phenotype (79%). Eosinophilic inflammation has been considered a cardinal feature of CRSwNP in Caucasians, and in contrast, around half of Asians present with eosinophilic inflammation, indicating a more heterogeneous feature of CRSwNP in Asians.[21-25] Our findings closely mirrors the study of Wen *et al.* wherein the sample Chinese population was determined to be predominantly eosinophilic (76%).[16]

We acknowledge the limitations of our study in terms of sample size and follow-up period. A multi-institutional study involving a larger sample size and a longer follow-up is currently under development. A larger sample size would mean larger subset population of non-eosinophilic polyps. A longer duration of follow-up would determine how long the improvement will last with only 2 weeks of treatment. Blinding of patients might also help diminish research bias.

In summary, our study showed that in terms of improving symptoms and well-being, as well as decreasing nasal polyp size and reducing discharge and edema as reflected in superior SNOT-22 and EA scores, Clarithromycin performed better than Methylprednisolone in the treatment of non-eosinophilic nasal polyps. While both Clarithromycin and Methylprednisolone were shown to be effective in the treatment of eosinophilic nasal polyps, Methylprednisolone was significantly better than Clarithromycin in terms of superior EA scores. A biopsy for tissue eosinophil cell count prior to treatment is recommended to establish the predominant inflammatory cell in nasal polyps in order to provide appropriate targeted treatment, i.e. Clarithromycin for non-eosinophilic nasal polyps and Methylprednisolone for eosinophilic polyps.

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