Original Article

Role of Doxycycline in the Management of Patients with Chronic Rhinosinusitis with Nasal Polyps

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ABSTRACT

Objective/ Hypothesis: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a disease of the nose and paranasal sinuses characterized by mucosal thickening and polyp formation. It is a multifactorial disease with a possible role of infection, allergy, mucociliary dysfunction and swelling of the mucosa. Treatment of CRSwNP can include medical treatment, surgical treatment or both. Doxycycline is a semi-synthetic tetracycline with broad spectrum antibacterial action as well as anti-inflammatory effect. This dual action of doxycycline might give it a role in the treatment of CRSwNP. In this study we have studied a possible role of doxycycline in management of patients with CRSwNP.

Study design: This is a prospective case-study.

Methods: Sixty patients with CRSwNP were included in this study. They were divided into 2 groups. Group (A) received oral prednisolone and oral doxycycline for 3 weeks. Group (B) received only oral prednisolone for the same period. Clinical assessment of both treatment modalities using total symptom score and polyp size score, as well as radiologic assessment using computed tomography of the paranasal sinuses (CT PNS) were compared. Total and absolute eosinophilic counts in complete blood count (CBC) were also compared.

Results: There was no statistically significant difference between the 2 groups in terms of total symptom score, polyp size score, total radiologic score. The absolute eosinophilic count was statistically significantly better in group A than in group B.

Conclusion: In patients with CRSwNP, adding doxycycline to oral prednisolone did not show us any added clinical or radiologic benefit of statistical importance.

Key Words: Chronic rhinosinusitis; doxycycline; nasal polyps; prednisolone.

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INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is defined as inflammation of the nose and paranasal sinus mucosa for at least 12 weeks duration. It is characterized by mucosal thickening and polyp formation. It is a multifactorial disease with a possible role of infection, allergy, mucociliary dysfunction and swelling of the mucosa[1]. The prevalence of CRSwNP in the general population ranges between 1%- 4%. It mostly affects adult individuals[2]. Treatment of CRSwNP can include medical treatment, surgical treatment or both[3]. Recurrence after treatment is relatively high with a recurrence rate of up to 40% 18 months after surgery[4], so repeated surgical intervention is frequently required. According to the European Position Paper on Rhinosinusitis and Nasal Polyp (EPOS) 2020[5], medical treatment with evidence-base of CRSwNP includes local and systemic steroids, antibiotics (tetracycline) and nasal saline irrigation. Other drugs like local and systemic antihistamines, mucolytics, topical and systemic decongestants, topical anticholinergics as well as biologic treatments like antileukotrienes, anti-interleukins and anti-immunoglobulins are either lacking evidence or still under evaluation[6]. Steroids have a multitude of effects, including inhibition of cytokine synthesis, reduction of the number of eosinophils and activated eosinophils, anti-edema effect and reduction of transudation[7]. As a new approach, antibiotics are being used in treatment of CRSwNP particularly in patients with disease exacerbated with Staphylococcus aureus (S aureus) enterotoxins[8]. Doxycycline is a semi-synthetic tetracycline with broad spectrum antibacterial action against S aureus. It also has an anti-inflammatory effect. This dual action of doxycycline might give it a role in the treatment of CRSwNP[9].

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PATIENTS AND METHODS

Patients

This study was conducted in the outpatient clinic of otorhinolaryngology department, Assiut University Hospital, Egypt, from July 2021 to January 2024. Sixty patients with CRSwNP were included in this study. All patients were 18-year or older, having bilateral nasal polyps confirmed by nasal endoscopy and CT PNS according to the EPOS 2020 criteria. Patients with chronic rhinosinusitis without polyps, patients with unilateral polyps, patients younger than 18-years were excluded from the study. Pregnant and lactating women, allergic patients to doxycycline or prednisolone and patients with debilitating diseases were also excluded.

Approval for this study was obtained from institutional review board of faculty of medicine, Assiut University prior to study execution. All participants received & signed a written consent-form indicating the purpose of the study and their freedom to participate in or withdraw from the study at any time without consequences. Participant confidentiality and anonymity were assured. The study itself was in line with the declaration of Helsinki.

Study Scheme

Patients were randomly assigned into two groups (A) and (B) using numerical method where even numbers were assigned to group (A) and Odd ones to group (B).

In group (A): Patients have received oral prednisolone in tablet form for 3 weeks in decreasing doses. In the 1st week the dose was 20 mg in the morning and 20 mg in the evening. The dose was reduced to 20 mg in the morning in the 2nd week and to 10 mg in the morning in the 3rd week. In addition to prednisolone, patients in this group have received oral doxycycline (200 mg as a loading dose in the 1st day followed by 100 mg every day for the next 20 days). Doxycycline was taken one hour after mid-day meal.

In group (B): Patients have received oral prednisolone as a sole therapy with the same dose and duration as group A.

In both groups, -twice daily- isotonic saline nasal irrigation was prescribed after the 3rd week till the end of the study.

Before starting the study, full history taking and full clinical assessment including ear, nose -including nasal endoscopy- and throat examination were accomplished. All patients had a CBC and a CT PNS -axial and coronal cuts without contrast- done too. After starting treatment, patients were asked to come for assessment by the end of the 3rd, 8th and 12th week. Patients were also asked to come back at any point should they notice any adverse reactions either nasal or systemic.

Outcomes and assessments:

1. **Symptomatology:** using a questionnaire, all patients were asked to evaluate five major symptoms (nasal obstruction, rhinorrhea, postnasal discharge, hyposmia and facial pain) from 0-4 where 0 means having no symptom and 4 means having intolerable one. Total symptom score (TSS) is the sum of the five individual symptoms.

2. **Polyp size score:** through nasal endoscopic evaluation using 0° Karl Storz HOPKINS rigid telescope, 4 mm in diameter and by using modified Lildholdt grading system[10], total polyp size score (TPSS) was calculated as the sum of the scores from both sides.

3. **Eosinophilic count:** Through CBC, the absolute eosinophilic count was calculated with a reference range of 0 - 0.6 $\times 10^3$ /uL. The relative eosinophilic count was recorded as % ratio of the eosinophilic count to the total leucocytic count.

4. **Radiologic evaluation:** by the end of the study, another CT PNS was obtained. Using Lund-Mackay scoring system[11], radiologic score of both sides was calculated. The total radiologic score is the sum of the scores of both sides.

Follow up

- At the end of the 3rd week: patients were assessed for total symptom score, total polyp size score as well as absolute and relative eosinophilic count.
- At the end of the 8th week: Assessment of total symptom score and total polyp size score was done.
- At the end of the 12th week: Assessment of total symptom score, total polyp size score and total radiologic score was done.

Statistical analysis

Data were collected and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Appropriate tests were utilized. A *P-value* was considered significant when it is <0.05.

RESULTS

The mean age of patients in group (A) was 38.80 with a range (25.4 – 52.2). In group (B) the mean age was 40.47 with a range (27.37 – 53.57). There was 20 males and 10 females in group (A). In group (B), there was 13 males and 17 females. Allergic rhinitis was present in about 80 % in both groups and asthma was present in about half of them (13 patients in group A and in 15 patients in group B).

Table 1: Comparison between the 2 groups in terms of TSS at different visits

Total Symptoms Score	Group A(*n*=30)	Group B(*n*=30)	*P-value*
1st Visit			
• Mean ± SD	11.93 ± 1.9	12.47 ± 1.4	= 0.218*
• Median (Range)	12 (9 – 15)	13 (10 – 14)	
2nd Visit			
• Mean ± SD	7.27 ± 1.0	7.80 ± 1.2	= 0.070*
• Median (Range)	7 (6 – 9)	8 (5 – 9)	
3rd Visit			
• Mean ± SD	8.90 ± 0.9	8.47 ± 1.5	= 0.174*
• Median (Range)	9 (7 – 10)	9 (5 – 10)	
4th Visit			
• Mean ± SD	9.93 ± 1.1	9.73 ± 1.6	= 0.572*
• Median (Range)	10 (7 – 12)	10 (7 – 13)	
• *P-value***	< 0.001	< 0.001	

*Independent t-test was used to compare the differences in Mean between groups
**RM-ANOVA was used to compare the differences in Mean within group

(Table 1) showed that there was statistically significant improvement in TSS between pre-treatment values and the 3 post treatment values in both groups. There was however no statistically significant difference between the 2 groups at any of the evaluated time.

Table 2: Comparison between the 2 groups in terms of TPSS at different visits.

Polyp Size Total Score	Group A(*n*=30)	Group B(*n*=30)	*P-value*
1st Visit			
• Mean ± SD	6.27 ± 1.1	6.73 ± 1.2	= 0.129*
• Median(Range)	6 (5 – 8)	7 (5 – 8)	
2nd Visit			
• Mean ± SD	3.87 ± 1.1	4.20 ± 1.1	= 0.239*
• Median(Range)	4 (2 – 6)	5 (3 – 6)	
*P-value***	< 0.001	< 0.001	
3rd Visit			
• Mean ± SD	4.83 ± 1.3	5.13 ± 1.4	= 0.346*
• Median(Range)	5 (3 – 7)	5 (3 – 8)	
*P-value***	= 0.021	= 0.044	
4th Visit			
• Mean ± SD	5.33 ± 1.2	6.01 ± 1.6	= 0.676*
• Median(Range)	5 (4 – 8)	7 (4 – 8)	
*P-value***	= 0.121	= 0.301	

*Independent t-test was used to compare the differences in Mean between groups
**RM-ANOVA was used to compare the differences in Mean within group

(Table 2) showed that there was high statistically significant improvement in TPSS between pre-treatment levels and those at 3rd-week and 8th -week post-treatment levels in both groups. This improvement faded away at the 12th -week visit in both groups. There was no statistically significant difference between both groups at any of the 3 post treatment evaluation times.

Table 3: Comparison between the 2 groups in terms of eosinophilic counts.

	Group A(*n*=30)	Group B(*n*=30)	*P-value*
Absolute Eosinophilic count			
1st Visit			
• Mean ± SD	0.38 ± 0.08	0.45 ± 0.03	=0.116*
• Median (Range)	0.3(0.2–0.4)	0.44(0.1–1.3)	
2nd Visit			
• Mean ± SD	0.23 ± 0.08	0.33 ± 0.02	=0.022*
• Median (Range)	0.2 (0.1 – 0.4)	0.28(0.1–0.9)	
*P-value***	< 0.001	< 0.001	
Relative Eosinophilic count			
1st Visit			
• Mean ± SD	4.48 ± 1.1	5.08 ± 1.3	=0.413*
• Median (Range)	5 (3 – 6)	5 (8 – 17)	
2nd Visit			
• Mean ± SD	3.66 ± 1.8	3.83 ± 1.4	=0.711*
• Median (Range)	3.4 (2 – 8)	3.8 (1 – 6)	
*P-value***	= 0.057	= 0.055	

*Independent t-test was used to compare the differences in Mean between groups
**RM-ANOVA was used to compare the differences in Mean within group

(Table 3) showed that the absolute eosinophilic count was decreased significantly in both groups at the 3rd-week visit relative to the pre-treatment levels. Statistically significant lower counts were noticed in group (A) when compared to those of group (B). In contrary to the absolute eosinophilic counts, the relative eosinophilic counts haven't shown such significant changes with any of the 2 treatment modalities tested or when the 2 groups were compared with each other.

Table 4: Comparison between the 2 groups in terms of radiologic findings.

	Group A(*n*=30)	Group B(*n*= 30)	*P-value*
1st Visit			
• Mean ± SD	21.97 ± 2.3	20.73 ± 3.1	= 0.112*
• Median (Range)	22.5 (16 – 24)	20 (13 – 24)	
4th Visit			
• Mean ± SD	19.47 ± 2.8	18.50 ± 3.7	= 0.267*
• Median (Range)	20 (12 – 24)	17 (11 – 24)	
*P-value***	< 0.001	< 0.001	

*Independent t-test was used to compare the differences in Mean between groups
**RM-ANOVA was used to compare the differences in Mean within group.

(Table 4) showed that there was no statistically significant difference between the 2 groups in terms of radiologic scoring at 12th -week evaluation when compared to the initial visit. Both groups showed the same improvement levels.

DISCUSSION

The high prevalence of CRSwNP, the highly negative impact of the disease on the patient's quality of life and the strong burden of the problem on healthcare costs (estimated cost around 6 $ billion / year in the USA in 2019[12] encourage researchers to evaluate new drugs and new modalities of treatment to help patients with this problem.

In this study we have evaluated doxycycline for a possible role in management of CRSwNP. We have chosen to add doxycycline to prednisolone which is the drug commonly used for short time to control symptoms of these patients. Evaluation was focused upon any added benefit of doxycycline when combined with prednisolone in terms of symptom control, polyp size control, radiologic changes, as well as eosinophilic count.

This study showed that there was high statistically significant improvement in TSS in both groups when the pre-treatment values were compared with the 3 post-treatment ones. When both groups were compared together, there was no statistically significant difference between them. (Table 1)

When evaluating the TPSS, there was high statistically significant reduction in TPSS in both groups early in the treatment (at the 3rd week). However, on the 8th week visit, the reduction in TPSS was just significant and by the end of the 12th week, this improvement faded away in both groups. Again, there was no statistically significant difference noticed between both groups at any of the 3 post-treatment visits. (Table 2)

From both (Tables 1 and 2), we found that doxycycline added very little -if any- to the degree of symptom control. It did not prolonged the duration of the therapeutic effect of prednisolone. The reason behind that could probably be because the therapeutic effect of prednisolone was so strong and marked that it absorbed any similar effect of doxycycline.

The discrepancy between improvement in TSS and absence of such improvement in TPSS at the 3rd post-treatment visit, could be explained by the fact that a minimal change in the polyp size might cause remarkable improvement in a symptom like nasal obstruction which is the most troublesome symptom in all patients.

The changes in the absolute eosinophilic count were highly significant in both groups at 1st post-treatment visit and the reduction was statistically significant in group (A) when compared with group (B). We couldn't pick up an explanation for that difference. The relative eosinophilic count changes were insignificant between pre-treatment and 1st post-treatment visit as well as between both groups when compared together. (Table 3)

The CT scan evaluation of both groups by the 12th week revealed similar results with no statistically significant differences. (Table 4)

One of the early studies about value of doxycycline in CRSwNP was performed by Van Zele *et al* in 2010[9]. It separately compared oral prednisolone and doxycycline with placebo for 20 days. The study found that both drugs did well in symptom and polyp size control. There was however strong shorter improvement with prednisolone compared with moderate longer lasting one with doxycycline.

De Schryver *et al.* in 2015 reported similar longer-term improvement symptom and polyp size control with doxycycline when compared with oral prednisolone. The study also evaluated mepolizumab and omalizumab[13].

In 2017, Pinto *et al.* compared the possible value of adding doxycycline to local saline douches and nasal steroids. They reported better control of symptoms and polyp sizes. The reported improvement was less remarkable in asthmatic patients and those with aspirin sensitivity[14]. About half of our patients were asthmatic, this might explain why our results with doxycycline were unfavorable.

The single study combining doxycycline with oral steroid was done by Parasher *et al* in 2019. It concluded a limited benefit of adding doxycycline to oral prednisolone in patients with moderate to severe CRSwNP[15].

Nabavi *et al.* in 2023 found that doxycycline for 6 weeks added to a base-line treatment with nasal fluticasone, and saline irrigation plus oral montelucast significantly improved the quality of life of patients with CRSwNP[16].

CONCLUSION

The combination of oral doxycycline to oral prednisolone showed us no statistically significant better results over oral prednisolone alone. However, the frequently released publications (more than 20 papers in the last decade) testing different ways and combinations for using doxycycline in patients with CRSwNP reflect increasing interest in this drug and how to hire it to benefit the most from its antibacterial and immune-modulatory effects to help patients with CRSwNP.

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