Efficacy of Oral Doxycycline in Reducing the Size of Pterygium lesions

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ABSTRACT

Objective: To assess the efficacy of oral Doxycycline in reducing the size of pterygium lesions in a Pakistani population
Study Design: Quasi-experimental study.
Place and Duration of Study: Armed Forces Institute of Ophthalmology, Rawalpindi, from Sep 2018 and May 2019.
Methodology: Sixty patients above 20 years of age were enrolled in the study. Oral Doxycycline 200m/day was given for thirty consecutive days. Photographs of the lesions were taken at the time of recruitment and at the end of the study for assessment of pterygium size. Difference between pre-treatment and post-treatment size was analysed and comparison was made with age, gender and initial lesion size.
Results: Twenty-two females and thirty-eight males were examined. The mean age of the participants was 48.8 ± 13.8 years. The mean size of the pterygium lesions before commencing the treatment was 12.24 ± 6.28 mm2. The mean size of the lesions after the treatment was 11.24 ± 5.39 mm^2. The mean difference size was 1.00 ± 1.62 mm2 (p <0.001). The relative change in size (i.e. post-treatment size divided by pre-treatment size) was 0.94 ± 0.09 which was found to be statistically significant (p<0.001). There was correlation between larger initial lesion size and greater relative reduction in size (r = -0.42, p = 0.001).
Conclusion: The change in the size of pterygium lesions produced by Doxycycline was found to be statistically significant but was not deemed clinically significant. Therefore, oral Doxycycline is not recommended for the treatment of pterygium in our population.

Keywords: Doxycycline, Pterygium/pathology, Pterygium/drug therapy.

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INTRODUCTION

The term "pterygium" is derived from the Greek word "pteron", meaning wing. Pterygium is a common fibrovascular proliferative disorder in which the conjunctival tissue grows over the clear cornea in a wing-like configuration. It has a worldwide prevalence of 12% with the highest incidence rate in the "pterygium belt" between 30 degrees north and 30 degrees south of the equator.[1] Patients with pterygium initially present with watering and foreign body sensation. As the lesion grows across the cornea, visual acuity gets compromised due to astigmatism, high-order aberrations and eventually, visual axis involvement.[2-4]

Pterygium has a multifactorial etiology. The various risk factors involved in its development include old age, male gender, UV light exposure, hot dry climate and living in rural environment.[5] In addition to these, immunologic disturbances, genetic mutations and mite infestation are also implicated in its pathogenesis.[6] There is altered expression of factors involved in cell proliferation, migration, extracellular matrix remodelling, fibrosis, and angiogenesis.[7,8]

Over the years, a multitude of clinical studies have been published on the management of pterygium. Most of them are focused on different surgical approaches and invasive techniques. Little attention has been given to conservative treatment of pterygia for patients who are unfit or unwilling for surgery. Recently, systemic Doxycycline has been shown to suppress the activity of many matrix metalloproteinases and reduce the proliferation of pterygia, thereby reducing the lesion size in certain racial groups.[9] Its potential as a treatment option for pterygium has not been previously studied in a Pakistani population. The purpose of this study was to assess the efficacy of oral Doxycycline in reducing the size of pterygium lesions in our population.

METHODOLOGY

This study was conducted at Armed Forces Institute of Ophthalmology, MH Rawalpindi between September 2018 and May 2019 after approval by the ethical committee (Registration number 196/ERC/AFIO). It was a quasi-experimental study assessing the efficacy of oral Doxycycline in reducing the size of primary pterygium lesions and consecutive sampling

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technique was used. A sample size of 60 was obtained using Open Epi calculatorwith confidence interval 95% and power 80%. For group 1, mean and standard deviation were 0.98 ± 0.05 and for group 2 they were 1.01 ± 0.03.[9] All patients attending the out-patient department who met the inclusion criteria were asked to be enrolled in the study. Written informed consent was taken from the patients prior to inclusion in the study.

Inclusion Criteria: Subjects above 20 years of age with primary fleshy pterygium (Tan's classification grade 3),[10] and having at least one of the following complaints: i) foreign body sensation, ii) astigmatism with no other identifiable cause, iii) cosmetic concerns, iv) reduced vision due to corneal involvement threatening the visual axis; were included in the study.

Exclusion Criteria: Pregnant or lactating women, subjects who had allergy or contraindication to Doxycycline, and subjects with recurrent pterygium were excluded from the study.

Ophthalmic examination of the recruited subjects was performed, including uncorrected and corrected distance visual acuity measurement and slit lamp examination; the latterincluded assessment of the length and width of the pterygium from its apex to the limbus. Photographs of the affected eye were taken with a Topcon DC-3 digital camera (Topcon, Japan) and the area of the pterygium lesion encroaching onto the cornea (in mm2) was assessed usingImageJ software (NIH) (Figure-1).

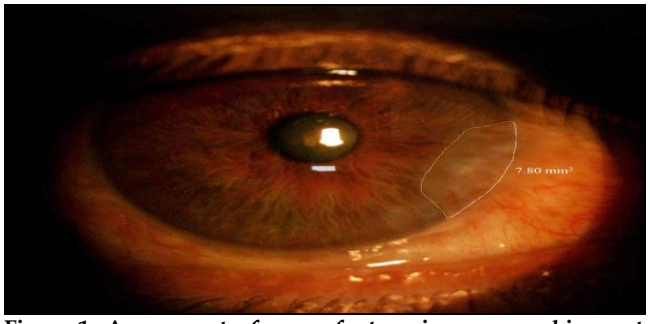

Figure-1: Assessment of area of pterygium encroaching onto the cornea using Image J software.

Patients were prescribed oral Doxycycline (Capsule Vibramycin) for 30consecutive days in a dose of 200mg/day.They were instructed to take two 100mg capsules every day, one in the morning and one in the evening. They were called for follow-up after 30 days when a second photograph was taken and any side-effects of treatment were recorded. The primary endpoint was change in lesion size after 30 days of treatment. Thus, the photographs taken during the first and second visit were compared and the variation in the surface area occupied by the pterygium was calculated. Data collection proforma was filled for record keeping. All measurements/examinations were carried out by single person to exclude observer bias.

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) version 22.0. Normality of data were checked using Shapiro-Wilk test. Since the data was not normally distributed, Wilcoxon signed ranks test (two-tailed) was usedfor analysis of the difference between pre-treatment and post-treatment values. Spearman correlation method was applied to compare age, genderand initial size of the lesion with the response to treatment. The *p*-value of ≤0.05 was considered significant.

RESULTS

During the nine-month study period, there were 80 patients who met the inclusion criteria and agreed to be enrolled in the study. However,[19] of these patients were lost to follow-up and were thus excluded from the study. One patient presented with a mild rash on his forearms within the first week of starting treatment and thence forth dropped out of the study. Three more patients presented with the complaint of mild nausea which resolved once they started taking the medicine with a meal. These 3 patients did not withdraw consent for the treatment.

There were 60 patients who completed the study. The mean age of the participants was 48.8 ± 13.8 years (range 21-90 years). There were 22 females (36.7%) and 38 males (63.3%). The most common presenting complaint was foreign body sensation 28 (46.7%), followed by reduced vision due to astigmatism 14 (23.3%), cosmesis 11 (18.3%) and reduced vision due to visual axis involvement 7 (11.7%). The mean astigmatism produced by the lesions was 2.1 DC (range 0.00 to 9.25 DC). The mean area of the pterygium lesions recorded before commencing the treatment was 12.24 ± 6.28 mm^2. The mean area of the lesions after the treatment was 11.24 ± 5.39 mm^2. During treatment, 43 patients experienced a decrease in size of the lesion, 5 patients experienced an increase in size of the lesion and in 12 patients there was no change in size of the lesion. The mean difference in pre-treatment and post-treatment area was 1.00 ± 1.62 mm2 (p <0.001). The relative change in size (i.e. post-treatment size divided by pre-treatment size) was 0.94 ± 0.09 which was found to be statistically significant (p<0.001). Table-I showed the clinical characteristics of the subjects.

Table-I: Clinical characteristics of the patients enrolled in the study.

	Median	Interquartile Range	*p*-value
Size Before Treatment (mm²)	10.78	5.62	
Size after Treatment (mm²)	10.00	5.57	
Difference in Pre- and Post-Treatment Size (mm²)	0.44	1.37	<0.001
Relative Change in Surface Area (Post-treatment size/pre-treatment size))	0.97	0.11	<0.001

The change in area of the lesions was compared with the age, gender and initial size of the lesions, as shown in Table-II.

Table-II: Correlation of demographic and clinical characteristics of the patients with the relative change in surface area of lesions after treatment.

	n	Correlation with Relative Change in Surface Area	
		r	*p*-value
Age	60	-0.08	0.55
19-44 years	19	0.10	0.70
45-64 years	31	0.07	0.70
65+ years	10	-0.49	0.15
Gender	60	0.00	0.98
Initial size of lesion	60	-0.42	0.001

No significant correlation was found with age or gender. The comparison with the formerwas further studied by dividingthe subjects into three age groups and repeating the analysis but no significant correlation was found in any subgroup. However, there was a positive correlation between higher initial size and larger reduction of the pterygium lesion (r=-0.42, *p*= 0.001) as shown in Figure-2.

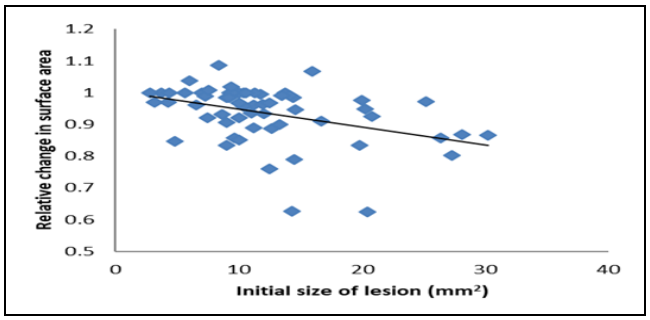

Figure-2: Correlation plot between initial size of lesion and relative change in size in response to treatment. Lesions that were small at the time of presentation showed a lower response to treatment (in terms of change in surface area) whereas lesions that were initially larger in area showed a greater reduction in size after treatment.

At the end of the study, up to 86% of the patients reported subjective improvement in symptoms in terms of decreased redness and foreign body sensation. However, this outcome was not expected and therefore not objectively documented.

DISCUSSION

Pterygium is notorious for being difficult to treat and the only definitive treatment is surgery which is also complicated by frequent recurrences. The numerous factors involved in its pathogenesis have been targeted by novel treatment strategies with some showing promising results. Of note, Doxycycline is an antimicrobial drug thatbeen recently studied for its role in reducing the size of pterygium lesions.[9,11,12] It has already been approved by FDA for other ocular diseases. In this study, the efficacy of Doxycycline as a potential systemic treatment option for primary fleshy pterygia was evaluated.

Clinically, pterygium is a bulky vascular tissue that is believed to originate from the corneal limbus and uses the Bowman's membrane as a leading structure to advance onto the corneal surface.[13,14] UV radiation has been known to play a key role in this process by altering the limbal stem cells and fibroblasts that contribute to the initiation of pterygium and inducing various cytokines, growth factors and matrix metalloproteinases that promote its progression.[7,14,15] Mutations in the *p*-53 gene produced by the UV radiation cause an upregulation of various growth factors, including vascular endothelial growth factor which is responsible for rampant angiogenesis in the growth.[14,16]

The overexpression of matrix metallo proteinases and extensive angiogenesis, both are targets of Doxycycline which has been shown to decrease the levels of pterygial cell migration and vascular growth at a daily dose of 200mg. Cox *et al* studied the effect of Doxycycline in murine models and found that it inhibits ocular angiogenesis.[11] Larrayoz *et al,* identified 332 genes which altered their expression in a dose-dependent manner upon exposure to Doxycycline, including those involved in production of extracellular matrix components.[12] Rua *et al,* conducted a randomized controlled trial and concluded that systemic Doxycycline was effective in reducing the size of pterygia in people of Caucasian descent and older age.[9]

The results of our study demonstrated that oral Doxycycline in a dose of 200 mg/day produced a statistically significant difference in pterygium lesions in up to 71% of the studied population. A greater reduction in areawas seen in lesions that were larger at the time of initial presentation. However, in contrast to the previous study, no correlation was found between

increasing age and relative reduction in size.[9] No difference in response was seen between males and females, either. Similar to the previous study, only a few number of patients reported side-effects to the treatment which were mild and resolved with discontinuation of the medicine. The compliance rate in this study was better than expected at the outset.

It was interesting to note that, although the pterygium size did not reduce in all the patients, majority of them reported improvement in their symptoms in terms of decreased redness and foreign body sensation. This may be explained by Doxycy-cline's effect in reducing the vascularity of these lesions. Several studies in the past have shown that the vascular density of the pterygium is positively correlated with its dimensions,[17] and both these factors, in turn, are related to the various manifestations of pterygium including astigmatism, high-order aberrations, dry eyes and meibomian gland dysfunction, erroneous biometry and high rate of recurrence.[3,4,18-20] Therefore, the dec-rease in vascularity may be regarded as a significant outcome and further studies are recommended to objectively document this result.

Although oral Doxycycline was well tolerated in our subjects, there were a few limitations of this study. First, even though the results from our study demonstrated that the relative change in pterygium lesions after treatment was statistically significant, the difference may not be perceived as clinically significant. For a patient with a large pterygium encroaching onto the visual axis, the decrease in size of a few millimetres may not be enough to justify this treatment. A longer duration of treatment may have yielded better results. Second, only primary fleshy pterygia were included in this study. The efficacy of this treatment in recurrent pterygia and those with a lower grade of vascularity (according to Tan's classification),[10] was not studied. Third, although the Image J software used in this study for the calculation of pterygium size has been shown to have good reproducibility,[21] the possibility of a measurement error and observer bias cannot be entirely ruled out because it is dependent on user experience.

However, in view of the statistically significant change in size and subjective improvement of symptoms, further studies are recommended to assess the efficacy and safety profile of topical Doxycycline formulation which may achieve better drug concentrations in the ocular tear film and may result in a better outcome.

In conclusion, the reduction in the size of pterygium lesions produced by short-term oral Doxycycline was found to be statistically significant but was not deemed clinically significant. Therefore, oral Doxycyclineis not recommended for the treatment of pterygium in our population.

Conflict of Interest: None.

Authors' Contribution

SR: Data collection/analysis, article writing, AA: Reviewed the article, AY: Concept and design, reviewed the article, AA: Data collection, analysis, FK: Abstract writing.

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