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Research Article

Changes in the Anterior Segment and Dry Eye Parameters of People Using Oral Tetracycline

Mehmet Tahir Eski[1], Kuddusi Teberik[2], Taha Sezer[2]

[1]Neon Hospital, Department of Ophtalmology, Erzincan, Türkiye
[2]Düzce University, Faculty of Medicine, Department of Ophthalmology, Düzce, Türkiye

Abstract

Aim: The purpose of the study is to evaluate the effect of anti-inflammatory efficiency of tetracycline on dry eye and anterior segment parameters.

Material and Methods: This prospective study was conducted with 61 people who had been using tetracycline for the past 2 months. Each participant went through a detailed ophthalmological examination where intraocular pressure (IOP), central cornea thickness (CCT), K1 and K2 from keratometry measurements, anterior chamber depth (ACD), axial length (AXL), tear breakup time test (BUT), lissamin green staining (LG), Schirmer's tear test-1 (ST) and ocular surface disease index (OSDI) score were evaluated. Measurements of the patients who would be using a daily dose of 100 mg doxycycline for 2 months were done prior to the medication as well as 1 month and 2 months after the medication. 3 data sets of the participants were compared at the end of 2 months.

Results: When results were compared, it was found that ST and LG parameters gradually increased in the first and second months and this increase was statistically significant ($p<0.001$ and $p=0.018$, respectively). On the other hand, BUT and OSDI scores decreased over time but it was not statistically significant. There were no statistically significant differences in terms of other parameters either ($p>0.05$). When female and male participants were compared in terms of BUT, it was found that the decrease in females at the second month was higher and this was statistically significant ($p=0.01$).

Conclusion: t was concluded that the young individuals using tetracycline displayed an early stage of improvement in dry eye parameters.

Keywords: Dry eye, tetracycline, anterior segment

INTRODUCTION

Chronic blepharitis is an ocular disease widely seen in the society and demands frequent use of doxycycline group in clinical conditions which require oral antibiotic treatment. Furthermore, variable ratios of 3-58% have been reported for the commonly observed ocular rosacea frequency. The symptoms of the disease cover eye lid, conjunctiva and cornea (1-3). The most frequent complaints of the patients who apply to daily clinic with non-specific symptoms are; itching, burning, stinging, watering, redness, feeling of a foreign object, photophobia, pain and blurred vision. The most frequent diagnosis, on the other hand are blepharitis, telangiectasia at the edge of the eye lid, meibomitis, repeated chalazion, hordeolum, superficial punctate keratitis (SPK) and conjunctival hyperemia. In advanced cases, episcleritis, scleritis, keratitis, iritis, corneal vascularization, corneal perforation and vision loss can be seen but with much less frequency. As far as this disease is concerned, it is believed that all findings are generated from eye lid involvement. Tetracycline and derivatives are used in ophthalmology not only for bacterial and chlamydial infections but also for ocular rosacea, causing the remission of symptoms in 2-3 weeks together with an improvement in the ocular findings. Tetracyclines, as a result of their both anti-inflammatory and anti-bacterial effect, are believed to have a major impact on the relevant treatment with enhanced improvement in the ongoing complaints. Apart from rosacea, tetracycline is a commonly used antibiotics in ophthalmology when

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Corresponding Author: Mehmet Tahir Eski, Neon Hospital, Department of Ophtalmology, Erzincan, Türkiye
E-mail: metaes@hotmail.com

diseases such as chalazion, intense blepharitis and hordeolum are concerned (4-7).

In general, the studies conducted with tetracycline are based on the improvement effect of the treatment on ocular findings and symptoms (8-13). Besides, in some studies the comparison of tear parameters of normal individuals verses patients with rosacea are analysed (4, 6,14). But this is the first study that analyses the effect of oral doxycycline treatment on both cornea and tear parameters of chronic blepharitis patients.

Inflammation is known to be the most frequently seen factor in dry eye etiology. Therefore, we conducted this study to determine whether anti-inflammatory efficiency of tetracycline causes any changes in the dry eye parameters, hence whether it could be used for the purpose of reducing dry eye symptoms.

MATERIAL AND METHOD

Patients who were prescribed to use doxycycline between the dates of June 2022-December 2022 due to systemic reasons were included to the study. This study was conducted by the eye policlinic of our hospital in accordance with the Declaration of Helsinki with a further approval from Institutional Ethics Committee (68/2022-Clinical Trail Protocol). All patients provided informed consent to the protocols and goals of the study prior to each procedure. Only patients without any systemic disease and aged between 18-31 were included. The study initially started with 82 patients but patients who have not arrived for treatment control or abandoned the treatment program were excluded. A total of 61 patients completed the study.

Pregnant or breastfeeding patients, patient with doxycycline, oxibuprokain, lissamin green or fluorescein hypersensitivity, patients who have undergone oral or topical treatment in the last 6 weeks, patients with a previous dry eye diagnosis, contact lens usage or ocular problems such as previous surgery or trauma, were not included to the study.

Patients were tested for corrected best visual acuity, eye movements, pupillary reflex, slit lamp biomicroscopy, fundus examination and intraocular pressure with Goldman applanation tonometry. Patients with corrected best visual acuity of 20/20, no corneal involvement and normal values for all tests are included to the study. Intraocular pressure (IOP), central cornea thickness (CCT), K1 and K2 from keratometry measurements, anterior chamber depth (ACD), axial length (AXL), tear breakup time test (BUT), Lissamin green staining (LG), Schirmer's tear test (ST) and ocular surface disease index (OSDI) scores are analyzed.

Examination started with keratometry measurements on non-contact basis (K1 and K2). It was followed by placing the special filter paper for ST in between the lower eye lid, 1/3 outer section of the eye. ST measurements were taken and recorded after 5 minutes (<10 mm was accepted as significant for the ST result). Eye was stained with fluorescent dye for the BUT and patient was asked to blink a couple of times before the cornea was examined under cobalt blue. Patient was asked not to blink during the examination. Formation of 2 black dots on the cornea are taken as base for BUT value (<10 sec was accepted as significant for BUT).

Sufficient time was taken for conjunctiva to be washed before the cornea was stained (liquid with 1% LG content) and examined for LG. LG results are recorded as 'degree 0' and 'degree 1' in this study (15). OSDI scoring (interval: 0-100), which is a subjective test, is used to determine symptoms related to drug-use and patient comfort (15). After the lissamine green stain is washed, IOP is measured using Goldman applanation tonometry and ACD, AXL and CCT are measured using contact method (NIDEK US-500 Echoscan, Tokyo, Japan) under topical anesthesia with 0.5 % proparacaine (Alcaine, Alcon Laboratories Inc., Fort Worth, TX, USA). All ACD (mm), AXL (mm), IOP (mmHg), K1, K2, ST (mm), BUT (sec), LG, OSDI and CCT (µm) parameters were measured under the same conditions by the same experienced ophthalmologist. All measurements were done during the 9:00-11:00 hour interval in order to avoid any possible diurnal discrepancies. All measurements followed exactly the same procedure and schedule. Measurements of the patients who have been scheduled to undertake oral 100 mg/day doxycycline treatment for 2 months were done before the medication and after the first and second month of medication.

Statistical Analysis

Findings of the study were analyzed by using SPSS 25.0 version software. The distribution of the data was displayed by descriptive analysis parameters (mean, standard deviation, minimum, maximum, frequency and percentage). Kolmogorov-Smirnov test was employed to analyze whether the data is consistent with the normal distribution. Correlation between the categorical variables is analyzed with chi-square test. The mean comparison between two independent groups where the data was non consistent with the normal distribution, was done with Mann Whitney U Test. As for the analysis of discrepancies between the repeated measurements; Cochran's Q Test was used for categorical variables and Friedman Test was used for constant variables. Spearman's Correlation was used for the correlation between constant variables.

RESULTS

Demographical specifications of the participants are shown in the table (Table 1).

Table 1. Demografic features

	X±SD	Min-Max
Age	21.7±3.6	18-31
Gender	**n**	**%**
Female	23	37.7
Male	38	62.3

Table 2. Change of parameters by gender over time

Variable	Time	Stage	Male	Female	Statistics	p
Lissamine Green [n(%)]	0.Month	0.Stage	19 (31.1)	32 (52.5)	0.027[a]	0.870
		1.Stage	4 (6.6)	6 (9.8)		
	1.Month	0.Stage	20 (32.8)	35 (57.4)	0.428[a]	0.513
		1.Stage	3 (4.9)	3 (4.9)		
	2.Month	0.Stage	20 (32.8)	35 (57.4)	0.428[a]	0.513
		1.Stage	3 (4.9)	3 (4.9)		
BUT (sec) [X±SD]	0.Month		21.7±7.7	31.4±16.3	-2.580[b]	**0.010***
	1.Month		24.9±10.1	27.4±11.5	-1.094[b]	0.274
	2.Month		23.2±12.8	27.9±14.1	-1.539[b]	0.124
Schirmer (mm) [X±SD]	0.Month		6.5±2.6	6.1±2.9	-1.085[b]	0.278
	1.Month		10.3±7.0	11.3±5.8	-0.897[b]	0.370
	2.Month		11.5±6.3	12.8±5.1	-1.220[b]	0.223
OSDI [X±SD]	0.Month		23.3±16.6	20.4±23.4	-1.209[b]	0.227
	1.Month		16.9±22.9	21.1±25.2	-1.371[b]	0.170
	2.Month		16.7±21.6	20.7±23.2	-1.551[b]	0.121
IOP (mmHg) [X±SD]	0.Month		16.7±2.3	15.5±1.4	-1.997[b]	**0.046***
	1.Month		15.5±1.6	15.6±1.5	-0.808[b]	0.419
	2.Month		15.8±1.5	15.7±1.4	-0.457[b]	0.647
Central corneal thickness (µm) [X±SD]	0.Month		547.6±16.4	545.5±20.3	-0.895[b]	0.173
	1.Month		539.9±16.9	557.6±22.6	-3.134[b]	**0.002***
	2.Month		544.3±9.5	550.7±18.0	-1.674[b]	0.094
K1 [X±SD]	0.Month		42.2±0.7	43.0±1.6	-1.761[b]	0.078
	1.Month		42.2±0.7	43.0±1.6	-1.467[b]	0.142
	2.Month		42.1±0.7	42.9±1.6	-1.093[b]	0.274
K2 [X±SD]	0.Month		43.1±0.8	43.5±1.8	-0.030[b]	0.976
	1.Month		43.0±0.9	43.4±1.7	-0.060[b]	0.952
	2.Month		43.0±0.9	43.5±1.8	-0.464[b]	0.642
ACD (mm) [X±SD]	0.Month		3.0±0.3	3.0±0.4	-1.070[b]	0.285
	1.Month		3.1±0.5	3.1±0.5	-0.464[b]	0.642
	2.Month		3.1±0.5	3.1±0.5	-1.088[b]	0.277
AXL (mm) [X±SD]	0.Month		22.7±0.5	22.6±0.6	-0.517[b]	0.605
	1.Month		22.6±0.7	22.7±0.8	-0.979[b]	0.328
	2.Month		22.7±0.8	22.8±0.7	-2.334[b]	**0.020**

a: Chi-Square Test; b: Mann Whitney U Test, *p<0.05
BUT: Break Up Time; IOP: Intraocular Pressure; ACD: Anterior Chamber Depth; AXL: Axial Length

There is a total of 63 participants in the group, of which 38 are male (62.3%) and 23 are female (37.7%). The age average of the group is 21.7±3.6.

The distribution of the changes in the parameters over time based on gender was examined in tabular form (Table 2). There was no statistically significant difference in the LG tests results over time based on gender (p=0.870, p=0.513 and p=0.513, respectively). BUT results, on the other hand, were higher and statistically significant for males compared to females for the pre-medication period whereas there was no statistically significant difference after the medication (p=0.010, p=0.274 and p=0.124, respectively). There were no statistically significant differences over time based on gender for ST and OSDI results (p=0.278, p=0.370 and p=0.223; p=0.227, p=0.170 and p=0.121, respectively). IOP results were higher and statistically significant for males compared to females for the pre-medication period however, there was no statistically significant difference after the medication (p=0.046, p=0.419 and p=0.647, respectively). CCT results were higher and statistically significant for females compared to males 1 month after the medication started however, there was no statistically significant difference in the other periods (p=0.002, p=0.173 and p=0.094, respectively). There was no statistically significant difference over time based on gender in terms of K1, K2 and ACD results (p=0.078, p=0.142 and p=0.274; p=0.976, p=0.952 and p=0.642; p=0.285, p=0.642 and p=0.277, respectively). AXL results were statistically higher and statistically significant for males compared to females at the end of the 2 months medication period however, there was no statistically significant difference among the other parameters (p=0.020, p=0.605 and p=0.328, respectively).

The distribution of the changes in the parameters over time are shown in the table (Table 3). LG test displayed a improvement in the number of patients in Stage 1 over time whereas the number of patients in Stage 0 improved, concluding that there is a statistically significant difference (p=0.018). It was found that ST and K2 values increase over time after the medication and this difference is statistically significant (p=0.018 and p=0.032, respectively). No statistically significant difference was found in terms of BUT, OSDI, IOP, CCT, K1, K2, ACD and AXL (p=0.172, p=0.051, p=0.600; p=0.124, p=0.061, p=0.694 and p=0.285, respectively).

Table 3. Change of parameters over time

	Stage	Time			Statistics	p
		0.Month	1.Month	2.Month		
Lissamine Green [n(%)]	0.Stage	51	55	55	8.000[a]	0.018*
	1.Stage	10	6	6		
BUT [X±SD]		27.7±14.4	26.4±11.0	26.1±13.7	3.520[b]	0.172
Schirmer (mm) [X±SD]		6.2±2.8	10.9±6.2	12.3±5.6	72.120[b]	<0.001*
OSDI [X±SD]		21.5±21.0	19.5±24.3	19.1±22.5	5.940[b]	0.051
IOP (mmHg) [X±SD]		15.9±1.9	15.6±1.5	15.8±1.4	1.022[b]	0.600
CCT (µm) [X±SD]		546.3±18.8	550.9±22.2	548.3±18.7	4.172[b]	0.124
K1 [X±SD]		42.7±1.4	42.7±1.3	42.6±1.4	5.583[b]	0.061
K2 [X±SD]		43.3±1.5	43.2±1.5	43.3±1.5	6.898[b]	0.032*
ACD (mm) [X±SD]		3.0±0.4	3.1±0.5	3.1±0.5	0.731[b]	0.694
AXL (mm) [X±SD]		22.7±0.5	22.6±0.7	22.8±0.7	2.510[b]	0.285

a: Cochran's O Test; b: Friedman Test, *p<0.001
BUT: Break Up Time; CCT: Central Corneal Thickness; IOP: Intraocular Pressure; ACD: Anterior Chamber Depth; AXL: Axial Length

DISCUSSION

We found that oral doxycycline use improves the dry eye parameters in individuals with chronic eye disease.

Blepharitis is an ocular disease widely seen in the society independent of patient age and is known as the inflammation of the eyelids. Blepharitis can be acute due to various reasons such as bacterial, viral or even parasitic or it can be chronic with a repeating or idle pattern. Chronic blepharitis, which is classified under seborrheic, staphylococcal and meibomian gland disfunction, can be treated with certain type and amount of antibiotics depending on the relevant clinical practice. As such, oral tetracycline and doxycycline might serve as an effective treatment in cases of not only posterior blepharitis but also when topical medications and eyelid sanitation are not sufficient, which might be the case with most meibomian gland disfunction patients (2).

Ocular rosacea progress with non-specific symptoms like itching, burning, stinging, watering, redness, feeling of a foreign object, photophobia, pain and blurred vision. Although ocular rosacea is a commonly seen condition, it can be easily overlooked due to the non-specificity of the symptoms and the limited diagnostic criteria (15).

Before the study, BUT was found to be high in females and IOP was found to be high for males. It is assumed that the found differences are generating form the relatively limited number of participating patients. Furthermore, CCT was found to be high in females in the first month. No further comparison was done since there was no previous literature related to the effect of tetracycline on eyes. However, it is a known fact that there is cornea involvement in acne rosacea and chronic blepharitis cases (6,8,11,16). The reason for this might be neutrophil chemotaxis, lymphocyte proliferation and matrix metalloproteinase activity (3,17-19).

As a result of previous literature review, it was seen that there was very limited amount of study related to the effect of tetracycline on dry eye and that there was no complete consensus among the existing studies. The doxycycline comparison study conducted by Arman A et al. and Bilgin B et al. showed a statistically significant increase in the ST score (8,20). Andrade FMX et al., did not find any statistically significant difference in their study with 39 participants (16). In our study, we found that ST increased in a statistically significant manner after the treatment. Kashkouli et al. found that there was no statistically significant difference in terms of BUT (11). Andrade FMX et al. found statistically significant increase in terms of BUT in their study (16). In the study conducted by Arman A et al. with patients using doxycycline, no statistically significant difference was found compared to pre-treatment in terms of OSDI (8). Similarly, in our study, we found no statistically significant difference in terms of BUT and OSDI scores. Additionally, as a result of LG staining results of our study, we found that there was a statistically significant decrease in the number of patients in stage 1 after tetracycline use. Further comparison studies were not done since there was no other study on LG analysis in the literature.

Previous studies suggested that in cases of meibomian gland inflammation, eyelid sanitation and topical medication have an improving effect but not completely sufficient for the ocular surface. Hence, these primary treatments are reinforced with short-term topical steroid, long-term topical cyclosporine and oral doxycycline providing a much more desired solution to patients' complaints. Doxycycline, with its antibacterial quality and anti-inflammatory effect is commonly used in rosacea treatment and is capable of not only inhibiting neutrophil chemotaxis, angiogenesis, lymphocyte proliferation but also of blocking matrix metalloproteinase activity and collagenase and lipase production. Therefore, it has been preferred to be used in ocular rosacea and chronic blepharitis cases together with exiting topical treatments (2,3,17-19).

The limiting aspect of our study is being mono-centered and having relatively small number of participating patients. On the other hand, we have seen that although

there were a few studies on acne rosacea patients, there was no study done on chronic blepharitis patients. Therefore, the strength of our study lies in the fact that this is the first study in literature on the effects of tetracycline on cornea and dry eye parameters when used by chronic blepharitis patients.

CONCLUSION

Chronic blepharitis is a commonly seen ocular condition in ophthalmology. Additionally, dry eye is another ocular condition considerably seen in patients. Various agents are being tested for chronic blepharitis treatment. As a result of our study, we have found an improvement in the dry eye parameters of chronic blepharitis patients. Therefore, we suggest that tetracycline will be more favorable with patients suffering from chronic blepharitis and dry eye. Considering that our study is one of the first studies done on this subject, it is our belief that it would serve as an example to many more to follow. We also believe that further studies should be conducted based on multi-centered and wide spread patient participation.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Düzce Univercity ethical committee (68/2022-Clinical Trail Protocol).*

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