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Research Article

How do Functional Tear Tests and Corneal and Anterior Chamber Parameters Change After Topical Cyclosporine -A 0.05% Treatment in Dry Eye Diagnosed Women?

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Abstract

Objectives: To report the effects of cyclosporine-A 0.05% on functional tear tests, corneal thickness and anterior chamber parameters in dry eye (DED) diagnosed women.

Methods: Thirty-eyes of 30 women with DED symptoms and Schirmer test scores of ≤5 mm/ 5 min with tear break-up-time (BUT) <10 sec were included. Only the right eyes of the subjects were included. All patients were treated with topical cyclosporine-A 0.05% (b.i.d) and sodium hyaluronate 0.15% (q.i.d). The baseline and 3rd-month results of Schirmer, BUT and topographical central corneal thickness (CCT) and thinnest corneal thickness (TCT), anterior chamber depth (ACD) and volume (ACV) were used for the statistical significance.

Results: After topical cyclosporine-A 0.05% treatment, the median of the baseline Schirmer score of 4 mm (range, 0-5) increased to 6 mm (range, 3-5), and the median of the baseline BUT of 3 seconds (range, 1-9) increased to 4.5 seconds (range, 2-13) with a statistical significance. No significant difference was observed on the evaluated parameters of CCT, TCT, ACD, and ACV.

Conclusion: Three months' use of topical cyclosporine-A with an artificial tear of topical sodium-hyaluronate has a favorable effect on functional tear tests without any change of corneal and anterior chamber topographical parameters.

Keywords: Anterior chamber, cornea, cyclosporine, dry eye, tear tests

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Dry eye disease (DED) is one of the most frequent (5 to 35%) causes of patient visits to ophthalmology services.[1] Recently, Tear Film & Ocular Surface Society (TFOS) DEWS II Definition and Classification Subcommittee created an evidence-based definition. DED is defined as loss of homeostasis of the tear film and is a multifactorial disease of the ocular surface accompanied by ocular findings and symptoms in which ocular surface inflammation, hyperosmolarity, neurosensory abnormalities play a critical role in etiology.[2]

The decrease in tear production causes chronic inflammation on the ocular surface. The inflammation leads to further inflammatory cell infiltration, increased expression of adhesion molecules and inflammatory cytokines, increased activity of matrix metalloproteinases in the tear fluid and corneal epithelium and increased apoptosis in the ocular surface epithelium. Also, these inflammatory mediators are responsible for reduced ocular surface sensitivity and a decrease in the sensitivity of stimulated reflex tearing. This self-perpetuating cycle is responsible for the pathogenesis of DED.[3, 4]

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Pharmacological approaches for the management of DED are artificial tears and anti-inflammatory and immunomodulatory agents such as oral tetracyclines, topical corticosteroids, and topical cyclosporine-A.[5, 6] Although most dry eye disease treatments have a palliative effect, topical cyclosporine A is an anti-inflammatory agent and currently, the only disease-modifying agent.[7]

Cyclosporine-A primarily suppresses activation and proliferation of T-lymphocytes, reduces inflammatory and apoptotic markers, and increases goblet cell density which provides an increase in the quality and quantity of the tear.[7] Also, it decreases the damage to lacrimal gland tissue and the ocular surface.[8] A cyclosporine 0.05% ophthalmic emulsion was approved by the United States Food and Drug Administration for the treatment of moderate to severe dry eye disease in 2003. There are several studies reporting significant improvement in dry eye with topical cyclosporine-A treatment.[7, 9, 10] A significant improvement was demonstrated in blurred vision, Schirmer score, BUT, and impression cytologic findings in patients with DED.[7, 9] The effect of the treatment on symptoms and signs of DED has been shown to persist after 1 year.[10]

The changes of functional tear tests of Schirmer and tear break-up time (BUT) associated with topical cyclosporine-A treatment were investigated before, however little is known about the changes ofthe cornea and anterior chamber measurements related to the topical cyclosporine- Atreatment in DED. It was aimed to report the effects of topical cyclosporine-A 0.05% on functional tear tests with corneal thickness and anterior chamber parameters obtained by topography.

Methods

Study Group

This prospective observational study enrolled a total of thirty-two eyes of 32 patients of women who were referred to Ankara Numune Education and Research Hospital with dry eye symptoms of itching, watery eyes, burning, stinging, foreign body sensation and dryness. A power analysis was performed to justify the minimum study population. Assuming 33.3% of the alterations from the baseline Schirmer test results, we determined that a sample of ≥30 eyes of 30 patients would provide a study power of 80%. Only the right eyes were selected for randomization.

Ethics

Informed consent was obtained from all patients and the study was in compliance with the Declaration of Helsinki and was approved as an observational drug study by the local Ethics Committee. Topical cyclosporine-A 0.05% is the first accepted topical agent for modification of the DED by the FDA in 2003 due to the positive contribution to the disease-associated inflammation and tear parameters.[11] Thus, a control group (with similar clinical features and without topical cyclosporine treatment) could not be adapted in the study because of the clinical severity of our DED cases and breaching the Good Clinical Practice Guidelines.

Inclusion Criteria

The inclusion criteria included; the presence of at least one of the dry eye symptoms (burning, itching, tearing, redness, foreign body sensation, etc.), being over the age of 18 and having ≤5 mm/5 minutes of Schirmer test score and BUT under 10 seconds both.

Totally, 32 eyes of 32 dry-eye diagnosed women were included in the study. Two patients were excluded related to the data gaps of the Pentacam scanning.

Exclusion Criteria

The patients with a history of infectious and allergic diseases, glaucoma, ocular trauma, ocular surgery or laser treatment, refractive surgery and contact lens wear, eye-lid disorders, any type of periorbital or lacrimal gland malformations, punctum or nasolacrimal duct obstructions, periorbital tumors, any type of topical ophthalmic medications or systemic medications affecting the ocular surface used in the last one month were excluded.

Study Design and Materials

Thirty eyes of 30 women, with Schirmer test result of ≤5 mm in 5 minutes and BUT <10 sec on more than one occasion were included in this prospective observation. All participants were questioned about demographic data and clinical history. Each subject underwent a complete ophthalmological examination including best-corrected visual acuity, slit-lamp examination, fundus examination in addition to corneal fluorescein staining, tear BUT, and Schirmer test without any topical anesthetic eye drop. Schirmer strip was placed behind the lower eyelid at the part between the middle and outer third of the lid after the routine assessment. After 5 minutes, the wet portion of the strip was measured in millimeters. The BUT was performed by a fluorescein strip that was applied to the fornix of the lower eyelid. The patients were instructed to look forward without blinking. The time interval between the last blink and the first appearance of the dry spot on the precorneal tear film was measured while examining by slit-lamp biomicroscopy under cobalt blue light. Pentacam is a non-invasive and objective device that allows a detailed evaluation of the corneal structure. It's based on a rotating Scheimpflug camera, that scans and measures the cornea and anterior chamber parameters.[12] All patients underwent baseline corneal

Table 1. Alterations of the functional tear tests after the topical cyclosporine- A and artificial eye drop treatment

	Schirmer Test (mm) Mean/Median	Tear Break Up Time (BUT) (sec) Mean/Median
Baseline	4.35±2.28/4 (range, 0–5)	3.7±2.04/3 (range, 2–9)
3rd month	7.13±4.00/6 (range, 3–15)	4.62±2.34/4.5 (range, 2–13)
Pa	**<0.001**	**<0.001**

a: Wilcoxon Signed Ranks Test for the statistical significance of the Schirmer and BUT measurements (p<0.05).

topographical evaluation by Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany) imaging. Corneal topography was used to obtain corneal and anterior chamber parameters. Central corneal thickness (CCT), the corneal thickness at the thinnest location (TCT), anterior chamber volume (ACV), anterior chamber depth (ACD), and corneal volume (CV) were measured by Pentacam Scheimpflug imaging. All Pentacam measurements were obtained under standard mesopic dim light conditions in non-dilated eyes at between 08:00 and 10:00 a.m. to avoid diurnal variations. Only reliable scans that marked the "quality specification" of Pentacam were included in the analysis.

All patients were prescribed topical cyclosporine-A 0.05% (Restasis; Allergan, Irvine, CA) bis in die (b.i.d, twice in a day) in addition to sodium-hyaluronate 0.15% based non-preserved artificial tears (Eyestil; SIFI S.P.A. Catania, Italy) quarter in die (q.i.d, four times in a day).[7] After a 3-month therapy, the Schirmer test without anesthesia, BUT, and topographical evaluation were performed again without any topical medication usage in the examination morning.

Statistical Analysis

SPSS for Windows version 12.0 (SPSS Inc., Cary, NC) was used for statistical calculations. Statistical analysis was performed by Wilcoxon signed-rank tests after the normality test with Shapiro-Wilk to compare the Schirmer results, BUT values, and topographical parameters both before and after 3 months of the treatment. The confidence interval level was set to 95% where a corresponding P value threshold was identified as 0.05 where any output P below 0.05 is interpreted as an indicator of statistical significance.

Results

The mean age of the patients was 52.36±6.4 years. All the included patients have consulted also to the Rheumatology Service and 9 and 4 of the 30 patients were diagnosed as primary and secondary Sjögren's Syndrome, respectively. The rest of the DED patients were interpreted to have an idiopathic etiology.

The changes in the functional tear tests after the topical treatment are given in Table 1. All the observed positive alterations were statistically and clinically significant.

The Schirmer test and BUT alterations of the patients after 3 months topical treatment were about 50% for the median values.

The cornea and anterior chamber parameters (CCT, TCT, CV, ACV, ACD) evaluated by the Pentacam are summarized in Table 2. None of these parameters showed a statistically significant change after 3 months of topical cyclosporine-A and artificial-tear therapy.

Discussion

There are several studies evaluating the changes in corneal thickness, volume, and densitometry in some dry eye-related diseases and therapies. An increase in corneal densitometry and a decrease in corneal thickness and corneal volume have been reported in patients with rheumatoid arthritis due to stromal proteolytic activity and increased tangential forces on corneal epithelium.[13–15] A reversible decrement at thinnest corneal thickness values was observed after isotretinoin therapy which causes dry eye symptoms and signs.[16] Contrary to the studies that found a significant decrease in corneal thickness in DED,[17–21] some reported no change.[22, 23]

Table 2. Cornea and anterior chamber parameters obtained by pentacam imaging at baseline and after 3 months of topical cyclosporine-A treatment

Cornea and Anterior Segment Parameters	Baseline (Mean±SD/Median)	After Topical Treatment (3 months) (Mean±SD/Median)	pb
CCT	545.66±35.89/538	545.27±31.94/541	0.826
TCT	540.40±35.98/534.5	540.11±32.32/536.5	0.881
CV	60.61±3.17/60.65	60.49±2.98/60.2	0.763
ACD	2.64±0.52/2.57	2.65±0.54/2.57	0.288
ACV	120.88±0.52/126	117.05±37.03/124	0.345

SD: Standard deviation; CCT: Central corneal thickness; TCT: Thinnest corneal thickness; CV: Corneal volume; ACD: Anterior chamber depth; ACV: Anterior chamber volume; b: Wilcoxon Signed Ranks Test for statistical significance (p<0.05).

Thinner corneal epithelial thickness has been reported in different parts of the cornea.[24–28] Erdelyi et al.[27] attributed thinner corneal epithelium according to the destruction of stem cells at the limbus. Cui et al.[24] demonstrated that the superior corneal epithelium was thinner in patients with the DED than normal subjects and the average superior corneal thickness achieved by optical coherence tomography (OCT) was correlated positively with Schirmer test scores. The corneal thinning in the dry eye results from hyperosmolarity of the tear fluid and a decrease in tear film thickness. Hyperosmolarity of the tear fluid contributes to the inflammatory cascade that induces the production of cytokines and matrix metalloproteinase-9.[2] Inflammation leads to apoptotic death of epithelial cells of the cornea including goblet cells.[29] This cascade may be responsible for decreasing in corneal thickness. Matrix metalloproteinase-1 (MMP-1) is responsible for the degradation of the extracellular matrix in the corneal stroma. Elevated levels of cytokines cause an imbalance between MMP-1 and the tissue inhibitors of MMP-1 leads to destructive keratolysis. This can be another mechanism that explains corneal thinning in the dry eye.[30, 31]

Çakır et al.[25] investigated the early effect of artificial tears on corneal thickness and central corneal epithelial thickness in dry eye patients. They revealed mid-peripheral corneal thickness measured by topography and central corneal epithelial thickness obtained by anterior segment OCT were significantly higher after artificial tear treatment of 1 month. The central and peripheral corneal thickness values didn't change significantly after treatment. Karadayı et al.[32] demonstrated an increase in CCT after the treatment of artificial tears for 1 week.

Cyclosporine-A prevents synthesis and secretion of several proinflammatory cytokines including tumor necrosis factor-α and interleukin-6. A significant decrease in the immune activation markers HLA-DR, CD11a, and interleukin-6 levels were demonstrated after 6 months of treatment with cyclosporine-A 0.05%.[33–35] A number of studies reported that significant improvement in tear production and cytological grades and an increase in goblet cell density occurred compared with the other therapies in patients with dry eye.[7, 8, 10]

The effects of topical cyclosporine A on functional tests such as Schirmer and BUT and cytological findings were well demonstrated but the effect of cyclosporine A on anterior chamber parameters has not been evaluated, before. This is also the first study that evaluates CCT change by using Pentacam Scheimpflug imaging after topical cyclosporine-A treatment.

Guzey et al.[36] investigated the effect of cyclosporine-A on corneal thickness and reported a significant increase in corneal thickness measured by ultrasound pachymetry after topical cyclosporine treatment of 6 months.

Kara et al.[37] compared the topographical findings of dry eye patients at baseline and after treatment of topical cyclosporine-A, and found no significant difference in the thinnest pachymetry, keratometry values and surface asymmetry index obtained by Orbscan II, and in CCT measured with ultrasonic pachymetry.

The dry eye seems to affect CCT values, but it is not clear if it affects anterior chamber depth. To our knowledge, there is only one study that evaluates anterior chamber depth in DED in the literature. Sanchis-Gimeno et al.[18] compared CCT, ACD, lens thickness, vitreous depth, and axial length values of dry eye patients and normal subjects and didn't find any significant differences in these parameters except CCT. We investigated the change with topical cyclosporine A use in CCT, TCT, CV as well as ACD and ACV. We didn't find any significant difference in the corneal and anterior chamber parameters after 3 months.

The limitations of our study were lack of tear osmolarity values, failure to include a control group due to ethical reasons and lack of a pure observation for cyclosporine 0.05% effect without any artificial tear drop. However, an artificial tear was a necessity for those patients related to their mild to severe dry eye symptoms and findings. Also, we couldn't find any short-term or long-term regarding data of sodium hyaluronate 0.15% on the functional tear tests and anterior chamber parameters. Also, it would be advantageous to classify the patients as pre-menopausal and post-menopausal according to the role of sex hormones in DED.[38] The other limitations of the current study are the short follow-up time and limited sample size. Further long-term prospective studies with a larger sample size should be done to better define the effects of topical cyclosporine A treatment on corneal and anterior chamber parameters.

In conclusion, 3 months of topical cyclosporine-A 0.05% with an artificial tear of sodium hyaluronate 0.15% has a favorable effect on functional tear tests of Schirmer and BUT, without any changes of topographical corneal and anterior chamber parameters.

Disclosures

Ethics Committee Approval: Informed consent was obtained from all patients and the study was in compliance with the Declaration of Helsinki and was approved as observational drug study by the local Ethics Committee of Ankara Numune Education and Research Hospital with the number of E-18-2095.

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