The Effects of Topical 0.1% Cyclosporin Treatment on The Corneal Topography, Pachymetry, and Densitometry Values in Severe Pediatric Vernal Keratoconjunctivitis Patients

Umut Dağ[1], Mehtap Çağlayan[2], Hasan Öncül[2], Yusuf Yıldırım[1], Mehmet Fuat Alakuş[2]

ABSTRACT

Purpose: To evaluate the effects of topical 0.1% cyclosporin treatment on topographic, pachymetric, and densitometric maps of the cornea in severe pediatric cases of vernal keratoconjunctivitis (VKC).

Materials and Methods: Thirty eyes of 30 pediatric patients with severe VKC were included in this study. The symptom and sign scores of these VKC patients were calculated and examinations were performed before and 6 months after topical 0.1% cyclosporin treatment. Pre and post-treatment values of flat keratometry (K1), steep K (K2), maximum K (Kmax), central corneal thickness (CCT), corneal volume (CV), anterior, center, posterior and total densitometry values (in two corneal concentric zones: 0-2-mm and 2-6-mm) were compared.

Results: The mean CCT and CV values decreased from 546.85±28.20 to 539.85±25.21 µm and 60.9±3.2 to 60.1±3.0 mm^3, respectively ($p<0.001$, both of them). Keratometry values (K1, K2, and Kmax) did not change after treatment (p:0.787, p:0.464 and p:0.963, respectively). The anterior, center, and total densitometry values in the 0-2-mm and 2-6-mm concentric corneal zones were significantly decreased after treatment ($p<0.001$, for all values).

Conclusions: In severe pediatric VKC patients, topical cyclosporine therapy provides reduction in densitometric (increased corneal transparency), CCT and CV values and also improves symptoms and findings.

Keywords: Vernal keratoconjunctivitis, Topical cyclosporine, Pentacam HR, Corneal thickness, Corneal densitometry.

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is an inflammatory disease that can occur either seasonally or throughout the year with various symptoms and findings, such as itchy eyes, foreign body sensation, light sensitivity, redness, papillary reaction, limbal infiltrates.[1] Although this inflammatory process primarily affects the conjunctiva, this process affects the cornea as well and varying degrees of corneal involvement can be seen.

Some structural changes in the cornea, such as ulcer formation, plaque formation, and ectasia, have been reported in cases of VKC as a result of chronic inflammation.[2-4] In vivo confocal microscopic studies have demonstrated that active VKC cases exhibit increased inflammatory cell density around the sub basal and stromal corneal nerves. In addition, the results showed that VKC affects not only the superficial epithelium, but also the basal epithelium and anterior stroma.[5,6] In addition, it has been suggested that abnormal topography findings, decreased corneal thickness values, and increased corneal densitometry values (indicators of decreased corneal transparency) may result from inflammation and mechanical trauma.[7-9]

Topical steroids are highly effective in suppressing inflammation in VKC patients, but long-term use of such treatments can lead to serious problems, such as cataracts, glaucoma, and ocular infections.[10] For this reason, there

1- MD, Department of Ophthalmology,University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye

2- Assoc. Prof., Department of Ophthalmology,University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye

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Correspondence Address:
Mehtap Çağlayan
Department of Ophthalmology,University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye
Phone:
E-mail: drmehtap85@hotmail.com

is an ongoing search for alternative treatments for VKC, especially cyclosporin. Topical cyclosporin A (CsA) is an immunomodulatory drug that inhibits eosinophil, mast cell, and antigen dependent T cell activation. Previous studies have reported that topical cyclosporins of different concentrations, such as 2%, 1%, 0.1%, and 0.05%, are all effective in improving symptoms and signs of VKC.[11-14] The anti-inflammatory effect of topical cyclosporin treatment on the ocular surface in cases of VKC has also been demonstrated in studies using conjunctival impression cytology, tear cytokine measurement, and in vivo corneal confocal microscopy.[15-17]

The aim of the present study was to investigate the effects of 0.1% topical CsA treatment on the topographic, pachymetric, and densitometric parameters of the cornea in severe pediatric cases of VKC.

MATERIALS AND METHODS

This study was planned according to a prospective observational single-center design. This study was also approved by the local ethics committee and followed the Helsinki Protocol. Written consent was obtained from the parents of the participants. Ethical approval was obtained from the local ethics committee (No:2019/342).

Thirty eyes of 30 pediatric patients that were started on topical 0.1% CsA treatment for severe VKC and used the drop for six-months were included in this study. Corneal staining value was evaluated with a single-use fluorescein strip after best visual acuity, biomicroscopic anterior segment, and detailed fundus examinations were performed.

The diagnosis of VKC was based on symptoms and clinical findings Disease severity was determined according to a clinical scoring system based on the symptoms and findings. Symptoms included itching, tearing, discomfort (including burning, stinging, and foreign body sensations), discharge, and photophobia. Findings included bulbar conjunctival hyperemia, tarsal conjunctival papillary reaction, punctate keratitis (superficial epithelial keratitis and punctate staining of the cornea with fluorescein), neovascularization of the cornea (new vessel formation crossing the limbus onto the clear cornea by ≥2 mm), cicatrizing conjunctivitis (superficial scarring of the conjunctiva), and blepharitis (hyperemia and edema of the eyelid skin with meibomian gland dysfunction). Each finding was given a value between 0 and 3 (0: absent, 1: mild, 2: moderate, and 3: severe).[15.] If the score was 5 or higher, the eye was classified as severe VKC and topical cyclosporin treatment was started.[15]

Exclusion criteria included topical medication use including topical steroid, antihistamine and mast cell stabilizer up to 1 month before treatment, refractive errors greater than ±1.5D, intraocular pressure (IOP) > 21 mm Hg, previous ocular surgeries, contact lens use, trauma, uveitis, glaucoma, corneal ulcers or scars, suspected or clinical keratoconus (KC), any systemic disease. If the symptoms and findings worsened during topical cyclosporin treatment and required topical corticosteroid therapy, that eyes were also excluded from the study (n=16 eyes). All patients were treated with 0.1% topical CsA (Depores X, Deva, Turkey) four times per day for six months. Pentacam HR measurements were taken in a dark room by the same physician one day after the clinical evaluation. Pentacam measurements were made between 10-12 a.m, taking into account the corneal diurnal changes and use of drops at different times. All of the corneal measurements via the Pentacam HR were performed at least three times.

Flat keratometry (K1), steep K (K2), maximum K (Kmax), central corneal thickness (CCT), and corneal volume (CV) values were recorded. Corneal densitometry values were recorded at four depths of the densitometry map (anterior: 120 microns, center, posterior: 60 microns, and total) at the 0-2-mm and 2-6-mm concentric zones. Densitometry values were graded by gray scale unit (GSU) from 0 (maximum transparency) to 100 (no transparency, opaque cornea).

The data were analyzed with SPSS 20.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). The values of only one eye were used for statistical analysis. Quantitative variables were reported as means and standard deviations. Paired samples t test was used for comparisons. A p value < 0.05 was considered statistically significant.

RESULTS

Eighteen of the 30 patients were male, and 12 of the 30 patients were female. The mean age was 13.1±3.1 years (range: 7-17 years). Limbal-type VKC was found in 12 eyes, palpebral-type VKC was found in 13 eyes, and mixed-type VKC was found in 5 eyes.

The mean of the symptom scores were 10.3±1.43 and 2.5±1.01 ($p<0.001$) while the mean of the sign scores were 9.3±1.37 and 3.4±1.12 ($p<0.001$) before and after treatment. In addition, 10 eyes had punctate keratopathy before treatment, and all of them disappeared after treatment.

The topography, pachymetry, and densitometry values of the severe VKC patients before and after treatment are

summarized in Table 1. When keratometric values were examined, no significant changes were found in the K1 (42.44±1.73 and 42.42±1.36 D), K2 (43.54±1.90 and 43.61±1.67 D), and Kmax (44.46±2.44 and 44.28±2.18 D) values after treatment (p=0.787, p=0.464, and p=0.963, respectively; Table 1). The mean CCT and CV values were 551.85±28.20 µm and 60.9±3.2 mm^3 before treatment and they significantly decreased to 539.85±25.21 µm and 59.1±2.7 mm^3 after treatment (p<0.001 and p<0.001; Table 1).

The corneal densitometry values of the patients are summarized in Table 2. The corneal densitometry values in the anterior 0-2 mm and 2-6 mm corneal concentric zones were 22.73±1.18 and 21.06±1.60 GSU, and they decreased to 20.52±1.21 and 18.69±1.54 GSU after treatment. The corneal densitometry values in the center 0-2 mm and 2-6 mm corneal concentric zones were 14.22±1.19 and 12.50±1.01 GSU before treatment, respectively, and they decreased to 12.85±0.88 and 11.39±0.61 GSU after treatment.

Anterior, center, and total corneal densitometry values significantly decreased in the 0-2-mm concentric zone after treatment, but no significant changes were observed in the posterior densitometry values (p<0.001, p<0.001, p<0.001 and p=0.495, respectively). Similarly, while the anterior, center, and total densitometry values significantly decreased in the 2-6-mm concentric zone after treatment, there were no significant changes in the posterior densitometry values (p<0.001, p<0.001, p<0.001 and p=0.192, respectively).

DISCUSSION

Corneal health is very important in VKC as it has much impact on visual performance. Serious involvement can be seen in the cornea, ranging from mild punctate epitheliopathy to macro erosion, ulcer formation, and plaque formation.[18] Clinically, corneal health is frequently

Table 1: *Topography and pachymetry values before and after 0.1% topical cyclosporin treatment in severe pediatric vernal keratoconjunctivitis patients*

	Pretreatment	After treatment	p*
K1 (D)	42.44±1.73	42.42±1.36	0.787
K2 (D)	43.54±1.90	43.61±1.67	0.464
Kmax (D)	44.46±2.44	44.28±2.18	0.963
CCT (µm)	546.85±28.20	539.85±25.21	**<0.001**
CV (mm^3)	60.9±3.2	60.1±3.0	**<0.001**

K1: Flat keratometry; K2: Steep keratometry; Kmax: Maximum keratometry; CCT: Central corneal thickness; CV: Corneal volume; D: Dioptri; µm: micron; mm^3: cubic millimeter
*Paired sample test

Table 2: *The changes in corneal densitometry values after topical 0.1% cyclosporine treatment in severe pediatric vernal keratoconjunctivitis patients*

Variables		Pretreatment	After treatment	p*
Anterior 120µm	**0-2 mm**	22.73±1.18	20.52±1.21	**<0.001**
	2-6 mm	21.06±1.60	18.69±1.54	**<0.001**
Center	**0-2 mm**	14.22±1.19	12.85±0.88	**<0.001**
	2-6 mm	12.50±1.01	11.39±0.61	**<0.001**
Posterior 60µm	**0-2 mm**	10.75±0.66	10.69±0.81	0.495
	2-6 mm	9.91±0.63	9.82±0.66	0.192
Total thickness	**0-2 mm**	16.14±1.5	14.62±0.89	**<0.001**
	2-6 mm	14.91±1.66	13.22±0.74	**<0.001**

*Paired sample test

evaluated by measuring the amount of epithelial surface damage through biomicroscopic examination and corneal staining methods. It is now possible to evaluate corneal health through more objective parameters due to recent developments in corneal imaging systems.

Pentacam HR is a device that includes a Scheimpflug camera system, can rotate 180 degrees, and provides data regarding corneal curvature, height, pachymetry, and corneal densitometry, which is an indicator of corneal health.[19,20] All of these values are affected by population variations such as age, gender, and refractive error, but they provide valuable information concerning corneal health in many diseases.

Improvement of VKC symptoms after topical cyclosporin treatment have been reported in many studies.[11-15] In the present study, symptoms and findings of VKC improved in all patients after six months of treatment with 0.1% topical cyclosporine treatment.

There are few studies that have examined the effects of topical cyclosporin treatment on the morphological features of the cornea. Kara et al. investigated the effects of 0.05% topical CsA treatment for dry eye syndrome and found no significant differences in the morphological and functional parameters of the cornea (K1, K2, the surface asymmetry index score, CCT, endothelial cell density, corneal hysteresis, and the corneal resistance factor) after six months of treatment with topical cyclosporin treatment.[21] Due to the increased risk of KC in VKC, the topographic and pachymetric properties of the cornea have been evaluated in many studies.[7,8,22,23] However, only one study has investigated the densitometric properties of the cornea in cases of VKC.[9] Further, there is not any study that have investigated the effects of cyclosporine therapy on corneal topographic, pachymetric, and densitometric parameters in severe pediatric VKC patients.

In the present study, no significant changes were found in K1, K2, and Kmax values of VKC patients after topical cyclosporin treatment; while there was a significant decrease in CCT and CV values. Pekel et al. found that CCT values were significantly higher in children with active allergic conjunctivitis than in healthy subjects; CV values were also higher in the active allergic conjunctivitis patients than in the healthy subjects, but this difference was not significant.[24] In a study by Yeter et al., CCT and central nonepithelial corneal thickness decreased significantly after topical steroid treatment in patients with seasonal allergic conjunctivitis.[25] Yeter et al. suggested that the stroma may have been thickened by the effects of the inflammatory process or inflammatory mediators during the active period of the disease and that the cornea may have been thinned as the inflammatory state improved after steroid treatment.[25] It can be hypothesized that the decreases in CCT and CV values after topical cyclosporin treatment in VKC may have occurred due to the same mechanism.

It has been reported that corneal densitometry values, which indicate corneal transparency, can be affected even in the silent and early stages of VKC.[9] In addition, factors such as the number, diameter, and alignment of collagen fibrils can disrupt tear stability and may cause changes in the corneal epithelium, stromal keratocytes, and the extracellular matrix, thus impairing corneal transparency.[26-9] Chan et al. evaluated corneal transparency in the silent and mild stages of VKC and found that anterior, posterior, and total corneal densitometry values were significantly higher in the eyes with VKC than in healthy eyes, most prominently in the anterior layer including the epithelium and the anterior stroma.[9] Chan et al. suggested that this decrease in corneal transparency may have developed secondary to inflammation, the activation of inflammatory cells in the cornea or swelling of the collagen matrix.[9] They also suggested that the repeated mechanical microtrauma and eye friction of the thickened eyelid on the corneal epithelium could have contributed to a reduction in corneal transparency by altering the corneal microarchitecture.[9] However, Chan et al. excluded cases with corneal involvement and dry eyes, as these factors might have affected densitometry values. In the present study, we examined the effects of topical CsA treatment on corneal densitometry values in cases of severe VKC. Corneal densitometry values in the central 6-mm concentric zone significantly decreased in the anterior, center, and total depths in severe VKC patients after topical CsA treatment. Unlike the cases examined by Chan et al., all the cases in the present study were severe VKC cases. The staging methods used to determine the severity of the disease in the present study were also different from those of Chan et al. While Chan et al. used a staging system that classifies cases with corneal involvement as severe VKC, we used a staging system that utilizes a clinical scoring method based on symptom and finding severity. In the present study, only 10 eyes exhibited punctate keratitis. Punctate keratitis were mild, and none of them were within the central 6-mm zone. Although punctate keratopathy had completely healed in all of these cases after treatment, we believe that the observed changes in corneal densitometry values were not related to epithelial healing because the observed corneal involvement was not located within the 6-mm central zone. Anterior corneal densitometry values reflect the corneal densitometry of the anterior stroma as

well as the corneal epithelium. Center corneal densitometry values significantly decreased after topical cyclosporin treatment compared to the pretreatment values. We believe that these improvements in anterior and center corneal densitometry values may have developed secondary to the anti-inflammatory effect of the topical cyclosporin. Using corneal confocal microscopy, Modugno et al. recently examined microstructural changes in the central cornea of patients with VKC after topical cyclosporin treatment and reported that epithelial and stromal cell reflectivity was an indicator of post-treatment metabolic activity.[17] They also reported that the number of the inflammatory cells in the anterior stroma decreased after treatment, although was not statistically significant.[17] Finally, they found that corneal stromal nerve thickness and tortuosity decreased after treatment, but this change was also non-significant. The results of the present study may be the clinical reflection of the confocal microscopic findings that were evaluated by Modugno et al.

The present study had some limitations. First, this study used a small sample size and a short follow-up period. Second, the contrast sensitivity evaluation would be better in understanding the effects of the corneal densitometric changes on optical quality.

In conclusion, this study revealed significant decreases in CCT and CV values after topical cyclosporin treatment in severe pediatric cases of VKC. Topical cyclosporin treatment also had a positive effect on corneal transparency. Pentacam HR may help clinicians evaluating the corneal health and monitoring the topical CsA treatment effect in VKC cases. These results should be supported by future studies with larger sample sizes and longer follow-up periods using in vivo confocal microscopy with the Pentacam HR.

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